Why molecules move along a temperature gradient

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Molecules drift along temperature gradients, an effect called thermophoresis, the Soret effect, or thermodiffusion. In liquids, its theoretical foundation is the subject of a long-standing debate. By using an all-optical microfluidic fluorescence method, we present experimental results for DNA and polystyrene beads over a large range of particle sizes, salt concentrations, and temperatures. The data support a unifying theory based on solvation entropy. Stated in simple terms, the Soret coefficient is given by the negative solvation entropy, divided by *kT*. The theory predicts the thermodiffusion of polystyrene beads and DNA without any free parameters. We assume a local thermodynamic equilibrium of the solvent molecules around the molecule. This assumption is fulfilled for moderate temperature gradients below a fluctuation criterion. For both DNA and polystyrene beads, thermophoretic motion changes sign at lower temperatures. This thermophilicity toward lower temperatures is attributed to an increasing positive entropy of hydration, whereas the generally dominating thermophobicity is explained by the negative entropy of ionic shielding. The understanding of thermodiffusion sets the stage for detailed probing of solvation properties of colloids and biomolecules. For example, we successfully determine the effective charge of DNA and beads over a size range that is not accessible with electrophoresis.

DNA | fluorescence | microfluidic | Soret | thermodiffusion

Thermodiffusion has been known for a long time (1), but its theoretical explanation for molecules in liquids is still under debate. The search for a theoretical understanding is motivated by the fact that thermodiffusion in water might lead to powerful all-optical screening methods for biomolecules and colloids. Equally well, thermodiffusion handles and moves molecules all-optically and therefore can complement well established methods: for example, electrophoresis or optical tweezers. For the latter, forces of optical tweezers scale with particle volume and limit this method to particles of only >500 nm. Electrophoresis does not suffer from force limitations but is difficult to miniaturize because of electrochemical reactions at the electrodes.

On the other hand, thermodiffusion allows the microscale manipulation of small particles and molecules. For example, 1,000-bp DNA can be patterned arbitrarily in bulk water (Fig. 1). The temperature pattern "DNA," heated by 2 K, was written into a water film with an infrared laser scanning microscope. The concentration of 1,000-bp DNA was imaged by using a fluorescent DNA tag. In an overall cooled chamber at 3°C, DNA accumulates toward the heated letters "DNA" (negative Soret effect), whereas at room temperature DNA is thermophobic (positive Soret effect) as seen by the dark letters.

In the past, the apparent complexity of thermodiffusion prevented a full theoretical description. As seen for DNA in Fig. 1, molecules characteristically deplete from regions with an increased temperature, but they can also show the inverted effect and accumulate (2, 3). Moreover, the size scaling of thermodiffusion recorded by thermal field flow fractionation showed fractional power laws with a variety of exponents that are hard to interpret (4, 5). The latter effect might be resolved by revealing nonlinear thermophoretic drift for the strong thermal gradients used in thermal field flow fractionation (our unpublished observations).

A variety of methods were used to measure thermodiffusion, mostly in the nonaqueous regime, ranging from beam deflection (2, 3, 6), holographic scattering (7–9), electrical heating (10), to thermal lensing (11). Recently we have developed a fluorescence microfluidic imaging technique (12, 13) that allows the measurement of thermodiffusion over a wide molecule size range without artifacts induced by thermal convection. Highly diluted suspensions can be measured; therefore, particle–particle interactions do not have an influence. We only apply moderate temperature gradients. In the following study, we used this method to confirm a straightforward theoretical explanation of thermodiffusion.

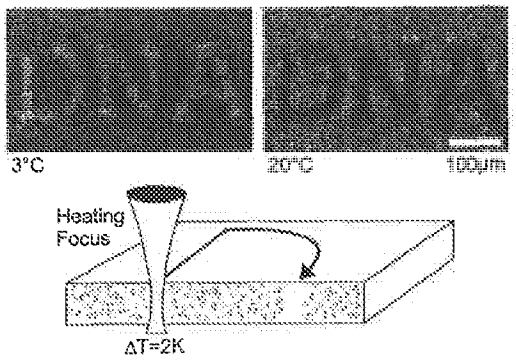

Fig. 1. Thermodiffusion manipulates the DNA concentration by small temperature differences within the bulk solution. A thin water film is heated by 2 K along the letters "DNA" with an infrared laser. For a cooled chamber at 3°C, fluorescently tagged DNA accumulates at the warm letters. However, at room temperature, DNA moves into the cold, showing reduced fluorescence. The chamber is 60 μm thin, containing 50 nM DNA in 1 mM Tris buffer. Every 50th base pair is labeled with TOTO-1 (for details, see supporting information).

Theoretical Approach

For diluted concentrations, it is generally assumed (14) that the thermodiffusive drift velocity $\vec{v}$ depends linearly on the temperature gradient ∇T with a proportionality constant which equals the thermodiffusion coefficient D_T: $\vec{v} = -D_T \nabla T$. In steady state, thermodiffusion is balanced by ordinary diffusion. Constant diffusion and thermodiffusion coefficients both lead to an exponential depletion law (15) $c/c_0 = \exp[-(D_T/D)(T - T_0)]$, with the concentration c depending on the temperature difference $T - T_0$ only. The concentration c is normalized by the boundary condition of the concentration c_0 with temperature T_0. The Soret coefficient is defined as ratio $S_T = D_T/D$, which determines the magnitude of thermodiffusion in the steady state. Although the above exponential distribution could motivate an approach based on Boltzmann equilibrium statistics, it is commonly argued that thermodiffusion without exception is a local nonequilibrium effect that requires fluid dynamics, force fields, or particle–solvent potentials (16–20). However, in a previous paper (15), we demonstrated that for moderate temperature

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gradients the thermal fluctuations of the particle are the basis for a local equilibrium. This allows the description of the thermodiffusive steady state by a succession of local Boltzmann laws, yielding $c/c_0 = \exp[-(G(T) - G(T_0))/kT]$, with G being the Gibbs-free enthalpy of the single particle–solvent system. Such an approach is valid only if the temperature gradient ∇T is below a threshold $\nabla T < (aS_T)^{-1}$, which is given by the particle fluctuations with the hydrodynamic radius a and Soret coefficient S_T, as shown recently (15). In the present study, temperature gradients below this limit were used so that thermodiffusion is measured at local thermodynamic equilibrium conditions.

Local thermodynamic equilibrium allows the derivation of a thermodynamic foundation of the Soret coefficient. The local Boltzmann distribution relates small concentration changes δc with small Gibbs-free energy differences: $\delta c/c = -\delta G/kT$. We equate this relation with a locally linearized thermodiffusion steady state given by $\delta c/c = -S_T \delta T$ and thus find the Soret coefficient by the temperature derivative of G:

$$S_T = D_T/D = (kT)^{-1} \times \partial G/\partial T. \qquad [1]$$

Whereas the above relation is sufficient for the following derivation, it can be generalized by locally applying the thermodynamic relation $dG = -SdT + Vdp + \mu dN$. For single particles at a constant pressure we find that the Soret coefficient equals the negative entropy of the particle–solvent system S according to $S_T = -S/kT$. This relation is not surprising given that the entropy is by definition related with the temperature derivative of the free enthalpy.

The above general energetic treatment is inherent in previously described approaches based on local equilibrium (14, 21, 22), including the successful interpretation of thermoelectric voltages of diluted electrolytes (23, 24), which are described by energies of transfer. Recently, the nonequilibrium approach by Ruckenstein (25) was applied to colloids (26) with the characteristic length l assigned to the Debye length λ_{DH}. If instead one would assign the characteristic length according to $l = 2a/3$ with the particle radius a, the Ruckenstein approach would actually confirm the above local equilibrium relation (1) for the Soret coefficient. Measurements on SDS micelles (26) appeared to confirm this nonequilibrium approach, but for the chosen particles the competing parameter choices $l = 2a/3$ and $\ell = \lambda_{DH}$ yielded comparable values. Thus, the experiments could not distinguish between the competing theories.

We will use the above local equilibrium relations to derive the Soret coefficient for particles larger than the Debye length in aqueous solutions and put the results to rigorous experimental tests. Two contributions dominate the particle entropy S in water (Fig. 2*a*): the entropy of ionic shielding (Fig. 2a *Left*) and the temperature-sensitive entropy of water hydration (Fig. 2*a Right*). The contribution from the entropy of ionic shielding is calculated with the temperature derivative of the Gibbs-free enthalpy (26, 27) $G_{ionic} = Q_{eff}^2 \lambda_{DH}/[2A\varepsilon\varepsilon_0]$ with the effective charge Q_{eff} and particle surface A. Alternatively, this enthalpy can be interpreted as an electrical field energy $G_{ionic} = Q_{eff}^2/[2C]$ in the ionic shielding capacitor C. We neglect the particle–particle interactions because the fluorescence approach allows the measurement of highly diluted systems. To obtain the Soret coefficient, temperature derivatives consider the Debye length $\lambda_{DH}(T) = \sqrt{\varepsilon(T)\varepsilon_0 kT/(2e^2 c_S)}$ and the dielectric constant $\varepsilon(T)$. Both temperature derivatives give rise to a factor $\beta = 1 - (T/\varepsilon)\partial\varepsilon/\partial T$. The effective charge Q_{eff} is largely temperature-insensitive, which was confirmed by electrophoresis independently (28). Such a dependence would be unexpected because the strongly adsorbed ions dominate the value of the effective charge. Experimentally, we deal with colloids exhibiting flat surfaces, i.e., the particle radius is larger than λ_{DH}. In this case, charge renormalization does not play a role and we can introduce an effective surface charge density $\sigma_{eff} = Q_{eff}/A$ per molecule area A. From the temperature derivation according to Eq. 1, the ionic contribution to the Soret coefficient is $S_T^{(ionic)} = (A\beta\sigma_{eff}^2\lambda_{DH})/(4\varepsilon\varepsilon_0 kT^2)$. A similar relation was derived for charged micelles recently (22), although without considering the temperature dependence of the dielectric coefficient ε. Next, the contribution to the Soret coefficient from the hydration entropy of water can be directly inferred from the particle-area-specific hydration entropy $s_{hyd} = S_{hyd}/A$, namely $S_T^{(hyd)} = -As_{hyd}(T)/kT$. Finally, the contribution from the Brownian motion is derived as $S_T = 1/T$ by inserting the kinetic energy of the particle $G = kT$ into Eq. 1. However, this contribution is very small ($S_T = 0.0034$/K) and can be neglected for the molecules under consideration. The contributions from ionic shielding and hydration entropy add up to

$$S_T = \frac{A}{kT}\left(-s_{hyd} + \frac{\beta\sigma_{eff}^2}{4\varepsilon\varepsilon_0 T} \times \lambda_{DH}\right). \qquad [2]$$

The Soret coefficient S_T scales linearly with particle surface A and Debye length λ_{DH}. We tested Eq. 2 by measuring S_T versus salt concentration, temperature, and molecule size. In all cases, thermodiffusion is quantitatively predicted without any free parameters. We used fluorescence single-particle tracking to follow carboxyl-modified polystyrene beads (catalog no. F-8888, Molecular Probes, Eugene, OR) with diameters of 1.1 and 0.5 at 25 aM dialyzed into 0.5 mM Tris·HCl at pH 7.6. Thermodiffusion of particles ≤ 0.2 μm is measured by the fluorescence decrease that reflects the bulk depletion of the particles (12). The chamber thickness of 20 μm damped the thermal convection to negligible speeds (15). The experimental design also excludes thermal lensing and optical trapping (15). Debye lengths λ_{DH} were titrated with KCl (see the supporting information, which is published on the PNAS web site).

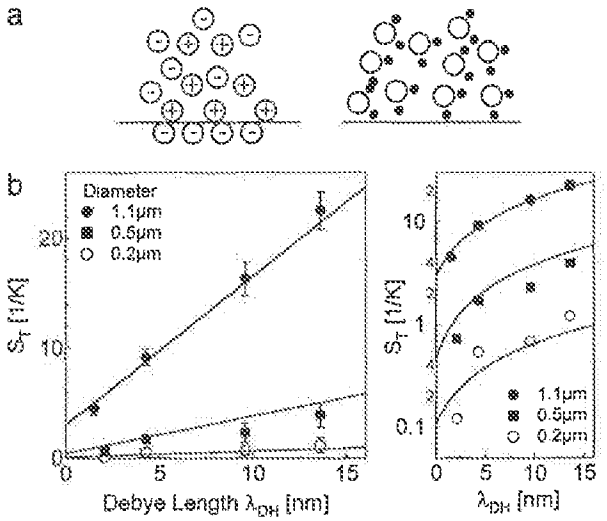

Fig. 2. Salt dependence. (*a*) Thermodiffusion in water is dominated by ionic shielding (*Left*) and water hydration (*Right*). (*b*) Soret coefficient S_T versus Debye length for carboxyl-modified polystyrene beads of diameter 1.1, 0.5, and 0.2 μm. Linear plot (*Left*) and logarithmic plot (*Right*). The Soret coefficients are described by Eq. 2 with an effective surface charge of $\sigma_{eff} = 4{,}500$ e/μm^2 known from electrophoresis. The intercept $S_T(\lambda_{DH} = 0)$ is fitted with a hydration entropy per particle surface of $s_{hyd} = -1{,}400$ J/(mol·K·μm^2).

Salt Dependence. Fig. 2*b* shows the Soret coefficients of polystyrene beads with different sizes versus λ_{DH}. The Soret coefficients

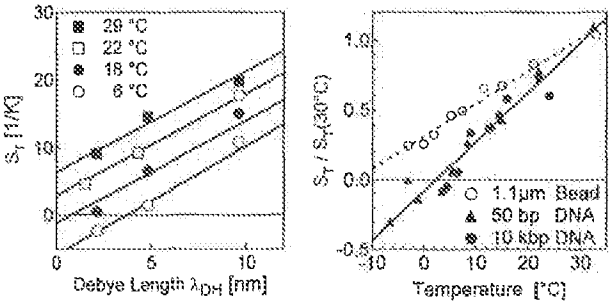

Fig. 3. Temperature dependence. (*a*) The temperature dependence is dominated by the linear change in the hydration entropy S_{hyd}. It shifts the salt-dependent thermodiffusion $S_T(\lambda_{DH})$ to lower values. The particle size is 1.1 µm. (*b*) The Soret coefficient S_T increases linearly with the temperature as expected for a hydration entropy S_{hyd}(7). It depends on the molecule species, not its size, as seen from the rescaled Soret coefficients for DNA with different lengths.

scale linearly with a small intercept at $\lambda_{DH} = 0$ and confirm the λ_{DH}-dependence of Eq. 2. For smaller-diameter beads, the Soret coefficients scale with the particle surface area A (Fig. 2), as expected from Eq. 2. To check whether Eq. 2 also quantitatively explains the measured Soret coefficients, we inferred the effective charge of the beads by electrophoresis (see supporting materials). By using 40-nm beads with identical carboxyl surface modifications at $\lambda_{DH} = 9.6$ nm, we fluorescently observed free-flow electrophoresis and corrected for electroosmosis, finding an effective surface charge density of $\sigma_{eff} = 4{,}500 \pm 2{,}000$ $e/\mu m^2$. This value is virtually independent from the used salt concentrations (28). With this inferred effective charge, Eq. 2 fits the Soret coefficient for various bead sizes and salt concentrations well (Fig. 2*b*, solid lines).

The intercept $S_T(\lambda_{DH} = 0)$, where ionic contributions are zero, also scales with particle surface and is described by a hydration entropy per particle surface of $s_{hyd} = -1{,}400$ J/(mol·K·µm²). The value matches the literature values for similar surfaces reasonably well (29–31). For example, dansyl-alanine, a molecule with surface groups comparable with polystyrene beads, was measured to have a hydration entropy (29) of −0.13 J/(mol·K) at a comparable temperature. Linear scaling with its surface area by using a radius of $a = 2$ nm results in a value of $s_{hyd} = -2{,}500$ J/(mol·K·µm²), in qualitative agreement with our result. The hydration entropy is a highly informative molecule parameter that is notoriously difficult to measure, yielding an interesting application for thermodiffusion.

Temperature Dependence. Hydration entropies S_{hyd} in water are known to increase linearly with decreasing temperatures (29–31). Because the slope of the ionic contribution of S_T versus λ_{DH} is with high-precision temperature insensitive for water [$\beta(T)/(\varepsilon T^2) \approx$ const], only the intercept is expected to decrease as the overall temperature of the chamber is reduced. This is indeed the case, as seen from the temperature dependence of beads with diameters of 1.1 µm ($T = 6$–29°C) (Fig. 3*a*). We infer from the intercept $S_T(\lambda_{DH} = 0)$ that the hydration entropy changes sign at ≈20°C. As seen for DNA in Fig. 1, hydration entropy can dominate thermodiffusion at low temperatures and move molecules toward the heat ($D_T < 0$).

The properties of hydration entropy lead to a linear increase of S_T over temperatures at a fixed salt concentration as measured for 1.1-µm beads and DNA (Fig. 3*b*). We normalized S_T by dividing by S_T(30°C) to compensate for molecule surface area. The slopes of S_T over temperature differ between beads and DNA. However the slope does not differ between DNA of different size (50 bp versus 10,000 bp). Based on Eq. 2, this is to be expected because the temperature dependence of the hydration entropy depends only on the type of surface of the molecule, not its size. We measured the diffusion coefficients of the DNA species at the respective temperature independently. Within experimental error, changes in the diffusion coefficient D match with the change of the water viscosity without the need to assume conformational changes of DNA over the temperature range. Please note that the change of the sign of the DNA Soret coefficient is situated near the point of maximal water density only by chance. There, the two entropic contributions balance. For polystyrene beads at $\lambda_{DH} = 2$ nm for example, the sign change is observed at 15°C (Fig. 3*a*). An increased Soret coefficient over temperature was reported for aqueous solutions before (3), however with a distinct nonlinearity that we attribute to remnant particle–particle interactions.

Size Dependence of the Beads. The Soret coefficient was measured for carboxyl-modified polystyrene beads in diameters ranging from 20 nm to 2 µm. Beads with diameters of 0.2, 0.1, 0.04, and 0.02 µm were diluted to concentrations of 10 pM, 15 pM, 250 pM, and 2 nM, and their bulk fluorescence was imaged over time to derive D_T and D (12, 15) from the depletion and subsequent back-diffusion. Larger beads with diameters of 1.9, 1.1, and 0.5 µm were diluted to concentrations of 3.3 aM, 25 aM, and 0.2 pM and measured with single-particle tracking. The solutions were buffered in 1 mM Tris (pH 7.6) with $\lambda_{DH} = 9.6$ nm. In all cases, interactions between particles can be excluded. Care was taken to keep the temperature gradient in the local equilibrium regime.

We find that the Soret coefficient scales with particle surface over four orders of magnitude (Fig. 4*a*). The data are described well with Eq. 2 with an effective surface charge density of $\sigma_{eff} = 4{,}500$ $e/\mu m^2$ and neglected hydration entropy contribution. The 5-fold too-low prediction for the smallest particle (20 nm in diameter) can be explained by charge renormalization because its radius is smaller than λ_{DH}.

The diffusion coefficient D for spheres is given by the Einstein relation and scales inversely with radius $D \propto 1/a$. Inserting Eq. 2 into $S_T = D_T/D$, the thermodiffusion coefficient D_T is expected to scale with particle radius a. This is experimentally confirmed over two orders of magnitude (Fig. 4*b*). These findings contradict several theoretical studies claiming that D_T should be independent of particle size (16–20, 26), based on ambiguous experimental results from thermal field flow fractionation (4) that were probably biased by nonlinear thermodiffusion in large thermal gradients (15).

Size Dependence of DNA. Whereas polystyrene beads share a very narrow size distribution as a common feature with DNA molecules, beads are a much less complicated model system. Beads are rigid spheres that interact with the solvent only at its surface. In addition, the charges reside on the surface, where the screening takes place. Thus, the finding that thermodiffusion of flexible and homogeneously charged DNA is described equally well with Eq. 2 is not readily expected and quite interesting (Fig. 4 *c* and *d*).

We measured DNA with sizes of 50–48,502 bp in 1 mM Tris buffer ($\lambda_{DH} = 9.6$ nm) at low molecule concentrations between 1 µM (50 bp) and 1 nM (48,502 bp). Only every 50th base pair was stained with the TOTO-1 fluorescent dye. The diffusion coefficient was measured by back-diffusion after the laser was turned off and depends on the length L of the DNA in a nontrivial way. The data are well fitted with a hydrodynamic radius scaling $a \propto L^{0.75}$. This scaling represents an effective average over two DNA length regimes. For DNA molecules longer than ≈1,000 bp, a scaling of 0.6 is found (32), whereas shorter DNA scales with an exponent of ≈1 (see the supporting information).

We can describe the measured Soret coefficient over three

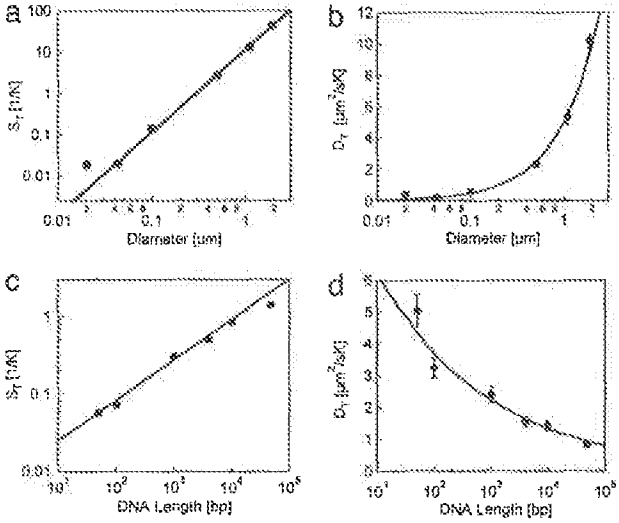

Fig. 4. Size dependence. (*a*) For polystyrene beads, the Soret coefficient scales with the particle surface over four orders of magnitude. Measurements are described by Eq. 2 with an effective surface charge density of $\sigma_{eff} = 4{,}500$ e/μm^2 (2) and negligible hydration entropy. The deviation for the bead with a diameter of 20 nm can be understood from an increased effective charge due to the onset of charge normalization for $a \approx \lambda_{DH}$. (*b*) Accordingly, the thermodiffusion coefficient D_T scales linearly with bead diameter. (*c*) The Soret coefficient of DNA scales according to $S_T \propto \sqrt{L}$, with the length L of the DNA based on Eq. 2 with an effective charge per base pair of 0.12 e. (*d*) Thermodiffusion coefficient D_T decreases over DNA length with $D_T \propto L^{-0.25}$, caused by the scaling of diffusion coefficient $D \propto L^{-0.75}$.

orders of magnitude of DNA lengths with Eq. 2 if we assume that effective charge of the DNA is shielded at the surface of a sphere with the hydrodynamic radius a. Because of the low salt concentration ($\lambda_{DH} = 9.6$ nm), such globular shielding is reasonable. Not only is the experimentally observed scaling of the Soret coefficient with the square root of its length correctly predicted based on Eq. 2 ($S_T \propto Q_{eff}^2/a^2 \propto L^2/L^{1.5} \propto L^{0.5}$), but the Soret coefficient also is fully described in a quantitative manner (Fig. 4*c*, solid line), with an effective charge of 0.12 e per base, matching well with literature values (33) ranging from 0.05 e/bp to 0.3 e/bp.

As shown in Fig. 4*d*, the thermodiffusion coefficient for DNA drops with DNA length according to $D_T = DS_T \propto Q_{eff}^2/a^3 \propto L^2/L^{2.25} \propto L^{-0.25}$. Thus, shorter DNA actually drifts faster in a temperature gradient than longer DNA. It is important to point out that this finding is in no way contradictory to experimental findings of a constant D_T over polymer length in nonaqueous settings (8). According to Eq. 1, the thermodynamic relevant parameter is the Soret coefficient, which is determined by the solvation energetics. The argument (19) that polymers have to decouple into monomers to show a constant D_T merely becomes the special case where the solvation energetics determine both S_T and D with equal but inverted size scaling. In accordance with our local energetic equilibrium argument, S_T and not D_T dominates thermodiffusion also for nonaqueous polymers near a glass transition (8). Here, S_T is constant, whereas D_T and D scale according to an increased friction. However, for a system of DNA in solution, for which long-ranging shielding couples the monomers, a constant D_T over polymer length cannot be assumed *a priori* (Fig. 4*d*).

Effective Charge. The effective charge Q_{eff} is a highly relevant parameter for colloid science, biology, and biotechnology. So far it only could be inferred from electrophoresis, restricted to

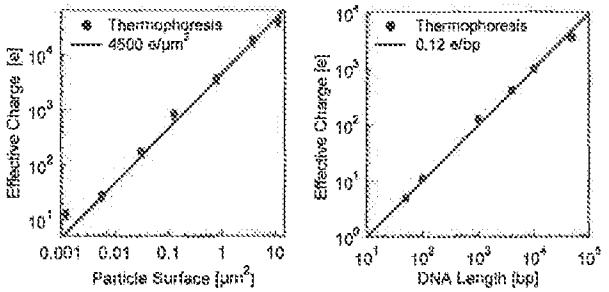

Fig. 5. Effective charge from thermodiffusion. Effective charge is inferred from thermodiffusion using Eq. 3. Polystyrene beads (20–2,000 nm) (*a*) and DNA (50–50,000 bp) (*b*) were measured over a large size range, which is impossible with electrophoresis. As expected, the effective charge of the beads scales with particle surface and linearly with the length of DNA.

particles smaller than the Debye length ($a \leq 3\lambda_{DH}$) (34). Unfortunately, many colloids are outside this regime. As shown before, a similar size restriction does not hold for thermodiffusion. In many cases, the hydration entropy s_{hyd} contributes <15% (Fig. 2) and can be neglected at moderate salt levels. Thus, we can invert Eq. 2 to obtain the effective charge Q_{eff} for spherical molecules from

$$Q_{eff} = \frac{2T^2}{3\eta D}\sqrt{\frac{\varepsilon\varepsilon_0\kappa^3 S_T}{\beta\pi\lambda_{DH}}}. \qquad [3]$$

The effective charge derived from thermodiffusion measurements of polystyrene beads and DNA is plotted in Fig. 5 over several orders of magnitude in size. The effective charge of beads scales linearly with particle surface, with a slope confirming the effective surface charge density of $\sigma_{eff} = 4{,}500$ e/μm^2, which was inferred from electrophoresis only for small particles. Average deviations from linear scaling are <8% (Fig. 5*a*). The effective charge inferred from thermodiffusion measurements of DNA using Eq. 3 scales linearly with DNA length with an effective charge of 0.12 e/bp. The length scaling is confirmed over four orders of magnitude with an average error of 12% (Fig. 5*b*). Thus, thermodiffusion can be used to infer the effective charge with low errors for a wide range of particle sizes. This is even more interesting for biomolecule characterization because measurements of thermodiffusion can be performed all-optically in picoliter volumes.

Conclusion

We describe thermodiffusion, the molecule drift along temperature gradients, in liquids with a general, microscopic theory. Applied to aqueous solutions, this theory predicts thermodiffusion of DNA and polystyrene beads with an average accuracy of 20%. We experimentally validate major parameter dependencies of the theory: linearity against screening length λ_{DH} and molecule hydrodynamic area A, quadratic dependence on effective charge, and linearity against temperature. Measurements of thermodiffusion can be miniaturized to the micrometer scale with the all-optical fluorescence technique and permit microscopic temperature differences to manipulate molecules based on their surface properties (Fig. 1). The theoretical description allows the extraction of solvation entropy and the effective charge of molecules and particles over a wide size range.

Materials and Methods

Infrared Temperature Control. The temperature gradients used to induce thermodiffusive motions were created by aqueous absorption of an infrared laser (Furukawa Electric, Tokyo, Japan) at a wavelength of 1,480 nm and 25 mW of power. Water strongly

absorbs at this wavelength with an attenuation length of $\kappa = 320$ μm. The laser beam was moderately focused with a lens of 8-mm focal distance. Typically, the temperature in the solution was raised by 1–2 K in the beam center with a $1/e^2$ diameter of 25 μm, measured with the temperature-dependent fluorescence signal of the dye 2′,7′-bis(carboxyethyl)-5(6)-carboxyfluorescein (12). Thin chamber heights of 10–20 μm and moderate focusing removed possible artifacts from optical trapping, thermal lensing, and thermal convection (12). For temperature-dependent measurements, both the objective and the microfluidic chip were tempered with a thermal bath. Imaging was provided from an AxioTech Vario fluorescence microscope (Zeiss, Oberkochen, Germany), illuminated with a high-power light-emitting diode (Luxeon, Calgary, Canada), and recorded with the CCD camera SensiCam QE (PCO, Kelheim, Germany).

Molecules. Highly monodisperse and protein-free DNA of 50, 100, 1,000, 4,000, 10,000, and 48,502 bp (Fast Ruler fragments and λ-DNA; Fermentas, St. Leon-Rot, Germany) were diluted to 50 μM base pair concentration, i.e., the molecule concentration was between 1 μM (50 bp) and 1 nM (48,502 bp). DNA was fluorescently labeled by the intercalating TOTO-1 fluorescent dye (Molecular Probes) with a low dye/base pair ratio of 1:50. Carboxyl-modified polystyrene beads with diameters of 2, 1, 0.5, 0.2, 0.1, 0.04, and 0.02 μm (catalog nos. F-8868, F-8823, F-8827, F-8888, F-8795, F-8823, and F-8827; Molecular Probes) were dialyzed (Eluta Tube mini; Fermentas) in distilled water and diluted in 1 mM Tris (pH 7.6) to concentrations between 3.3 aM (2 μm) and 2 nM (0.02 μm).

Concentration Imaging Over Time. Either the method of concentration imaging (12) or single-particle tracking was used to measure thermodiffusion at low concentrations, namely <0.03 g/liter for DNA and 10^{-5} g/liter for beads. At higher concentrations, we found profound changes of thermodiffusion coefficients. DNA and polystyrene beads of <0.5 μm in diameter were imaged over time (12) by bright-field fluorescence with a ×40 oil-immersion objective. Concentrations inferred after correcting for bleaching, inhomogeneous illumination, and temperature-dependent fluorescence (12) were fitted with a finite element theory. The model captures all details of both thermodiffusive depletion and back-diffusion to measure D_T and D independently (see supporting information). Measurements were performed in microfluidic chips 10 μm in height with polydimethylsiloxane on both sides.

Single-Particle Tracking. Polystyrene particles of >0.5 μm in diameter were measured by single-particle tracking due to the slow equilibration time and risk that steady-state depletion is disturbed by thermal convection. The thermodiffusive drift was imaged with a ×32 air objective at 4 Hz at an initial stage of depletion in a 20-μm-thick chamber. Averaging over the z position of the particles removed effects from thermal convection. The drift velocity versus temperature gradient of 400 tracks were linearly fitted by $v = -D_T \nabla T$ to infer D_T. The diffusion coefficients D of the particles were evaluated based on their squared displacement, matching within 10% the Einstein relationship.

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1. Ludwig C (1856) *Sitzungber Bayer Akad Wiss Wien Math-Naturwiss Kl* 20:539.
2. Giglio M, Vendramini A (1977) *Phys Rev Lett* 38:26–30.
3. Iacopini S, Piazza R (2003) *Europhys Lett* 63:247–253.
4. Jeon SJ, Schimpf ME, Nyborg A (1997) *Anal Chem* 69:3442–3450.
5. Shiendu PM, Liu G, Giddings JC (1995) *Anal Chem* 67:2705–2713.
6. Piazza R, Guarino A (2002) *Phys Rev Lett* 88:208302.
7. de Gans BJ, Kita R, Müller B, Wiegand S (2003) *J Chem Phys* 118:8073–8081.
8. Rauch J, Köhler W (2002) *Phys Rev Lett* 88:185901.
9. Wiegand S, Köhler W (2002) in *Thermal Nonequilibrium Phenomena in Fluid Mixtures* (Springer, Berlin), p 189.
10. Putnam SA, Cahill DG (2005) *Langmuir* 21:5317–5323.
11. Rusconi R, Isa L, Piazza R (2004) *J Opt Soc Am B* 21:605–616.
12. Duhr S, Arduini S, Braun D (2004) *Eur Phys J E* 15:277–286.
13. Braun D, Libchaber A (2002) *Phys Rev Lett* 89:188103.
14. de Groot SR, Mazur P (1969) *Nonequilibrium Thermodynamics* (North-Holland, Amsterdam).
15. Duhr S, Braun D (2006) *Phys Rev Lett* 96:168301.
16. Emery AH, Jr, Drickamer HG (1955) *J Chem Phys* 23:2252–2257.
17. Ham J (1960) *J Appl Phys* 31:1853–1858.
18. Morozov KI (1999) *J Exp Theor Phys* 88:944–946.
19. Schimpf ME, Semenov SN (2000) *J Phys Chem B* 104:9935–9942.
20. Voit A, Krekhov A, Enge W, Kramer L, Köhler W (2005) *Phys Rev Lett* 92:214501.
21. Dhont JKG (2004) *J Chem Phys* 120:1632–1641.
22. Fayolle S, Bickel T, Le Bolteux S, Würger A (2005) *Phys Rev Lett* 95:20830.
23. Agar JN, Turner JCR (1960) *Proc R Soc London Ser A* 255:307–329.
24. Snowdon PN, Turner JCR (1960) *Trans Faraday Soc* 56:1409–1418.
25. Ruckenstein E (1981) *J Colloid Interface Sci* 83:77–85.
26. Piazza R, Guarino A (2002) *Phys Rev Lett* 88:208302.
27. Israelachvili J (1992) *Intermolecular and Surface Forces* (Academic, New York), 2nd Ed.
28. Lin W, Galletto P, Borkovec M (2004) *Langmuir* 20:7465–7473.
29. Haidacher D, Vailaya A, Horváth C (1996) *Proc Natl Acad Sci USA* 93:2290–2295.
30. Southall NT, Dill KA, Haymet ADJ (2002) *J Phys Chem B* 106:521–533.
31. Kronberg B, Costas M, Silveston R (1995) *Pure Appl Chem* 67:897–902.
32. Pluen A, Netti PA, Jain RK, Berk DA (1999) *Biophys J* 77:542–552.
33. Smith SB, Bendich AJ (1990) *Biopolymers* 29:1167–1173.
34. O'Brien RW, White LR (1978) *J Chem Soc Faraday Trans 2* 74:1607–1626.

EXHIBIT B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
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Signed: Michael I. Chakansky /Michael I Chakansky/

REPLY BY PATENTEE TO A NON-FINAL OFFICE ACTION PURSUANT TO 37 C.F.R. §1.111

Madame:

In compliance with the Notice Re Defective Paper in *Inter Partes* Reexamination, mail date February 26, 2013, Patent owner MonoSol Rx, LLC ("Patentee" and/or "MonoSol") hereby presents its re-drafted response to the Office Action in the above-identified *Inter Partes* Reexamination, dated November 29, 2012 ("Office Action"), a reply to which is due March 13, 2013. Please amend U.S. Patent No. 7,897,080 ("the '080 Patent") in reexamination as set forth hereinbelow. The present amendments are being made in accordance with 37 C.F.R. §1.530(d)–(j). Patentee has previously paid fees for the addition of 4 new independent claims and 324 new dependent in connection with this reexamination. Accordingly, no claim fees are believed to be due with this submission. If, however, there are any fees due in connection with this submission, authorization to charge such fees, including any claim fees, and authorization to credit any overpayments, to Deposit Account No. 08-2461 are hereby provided.

Amendment to the Claims begins on page 2 of this paper.

Remarks begin on page 42 of this paper.

Amendment to the Claims

1. (Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less; [and]

(e) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(f) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

2. (Original) The process of claim 1, wherein said pre-determined amount of master batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.

3. (Original) The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.

4. (Original) The process of claim 1, wherein said water-soluble polymer comprises polyethylene oxide.

5. (Original) The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

6. (Original) The process of claim 5, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl

cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

7. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

8. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

9. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

10. (Original) The process of claim 1, wherein said solvent is selected from the group

consisting of water, polar organic solvent, and combinations thereof.

11. (Original) The process of claim 10, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

12. (Cancelled)

13. (Amended) The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-

spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

14. (Amended) The process of claim 1, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

15. (Original) The process of claim 1, wherein said active is a bioactive active.

16. (Cancelled)

17. (Original) The process of claim 1, wherein said active is an opiate or opiate-derivative.

18. (Original) The process of claim 1, wherein said active is an anti-emetic.

19. (Original) The process of claim 1, wherein said active is an amino acid preparation.

20. (Original) The process of claim 1, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

21. (Original) The process of claim 1, wherein said active is a protein.

22. (Original) The process of claim 1, wherein said active is insulin.

23. (Original) The process of claim 1, wherein said active is an anti-diabetic.

24. (Original) The process of claim 1, wherein said active is an antihistamine.

25. (Original) The process of claim 1, wherein said active is an anti-tussive.

26. (Original) The process of claim 1, wherein said active is a non-steroidal anti-inflammatory.

27. (Original) The process of claim 1, wherein said active is an anti-asthmatics.

28. (Amended) The process of claim 1, wherein said active is an anti-diarrhea preparation.

29. (Original) The process of claim 1, wherein said active is an alkaloid.

30. (Original) The process of claim 1, wherein said active is an anti-psychotic.

31. (Original) The process of claim 1, wherein said active is an anti-spasmodic.

32. (Original) The process of claim 1, wherein said active is a biological response modifier.

33. (Original) The process of claim 1, wherein said active is an anti-obesity drug.

34. (Original) The process of claim 1, wherein said active is an H_2-antagonist.

35. (Original) The process of claim 34, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

36. (Original) The process of claim 1, wherein said active is a smoking cessation aid.

37. (Original) The process of claim 1, wherein said active is an anti-parkinsonian agent.

38. (Original) The process of claim 1, wherein said active is an anti-depressant.

39. (Original) The process of claim 1, wherein said active is an anti-migraine.

40. (Original) The process of claim 1, wherein said active is an anti-Alzheimer's agents.

41. (Original) The process of claim 1, wherein said active is a dopamine receptor agonist.

42. (Original) The process of claim 1, wherein said active is a cerebral dilator.

43. (Original) The process of claim 1, wherein said active is a psychotherapeutic agent.

44. (Original) The process of claim 1, wherein said active is an antibiotic.

45. (Original) The process of claim 1, wherein said active is an anesthetic.

46. (Original) The process of claim 1, wherein said active is a contraceptive.

47. (Original) The process of claim 1, wherein said active is an anti-thrombotic drug.

48. (Original) The process of claim 1, wherein said active is diphenhydramine.

49. (Original) The process of claim 1, wherein said active is nabilone.

50. (Original) The process of claim 1, wherein said active is albuterol sulfate.

51. (Original) The process of claim 1, wherein said active is an anti-tumor drug.

52. (Original) The process of claim 1, wherein said active is a glycoprotein.

53. (Original) The process of claim 1, wherein said active is an analgesic.

54. (Original) The process of claim 1, wherein said active is a hormone.

55. (Original) The process of claim 1, wherein said active is a decongestant.

56. (Original) The process of claim 1, wherein said active is a loratadine.

57. (Original) The process of claim 1, wherein said active is dextromethorphan.

58. (Original) The process of claim 1, wherein said active is chlorpheniramine maleate.

59. (Original) The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

60. (Original) The process of claim 1, wherein said active is an appetite stimulant.

61. (Original) The process of claim 1, wherein said active is a gastrointestinal agent.

62. (Original) The process of claim 1, wherein said active is a hypnotic.

63. (Original) The process of claim 1, wherein said active is taste-masked.

64. (Original) The process of claim 1, wherein said active is taste-masked using a flavor.

65. (Original) The process of claim 1, wherein said active is coated with a controlled release composition.

66. (Original) The process of claim 65, wherein said controlled release composition provides an immediate release.

67. (Original) The process of claim 65, wherein said controlled release composition provides a delayed release.

68. (Original) The process of claim 65, wherein said controlled release composition provides a sustained release.

69. (Original) The process of claim 65, wherein said controlled release composition provides a sequential release.

70. (Original) The process of claim 1, wherein said active is a particulate.

71. (Original) The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.

72. (Original) The process of claim 1, further comprising a step of providing a second film layer.

73. (Original) The process of claim 72, wherein said second film layer is coated onto said resulting film.

74. (Original) The process of claim 72, wherein said second film layer is spread onto said resulting film.

75. (Original) The process of claim 72, wherein said second film layer is cast onto said resulting film.

76. (Original) The process of claim 72, wherein said second film layer is extruded onto said resulting film. .

77. (Original) The process of claim 72, wherein said second film layer is sprayed onto said resulting film.

78. (Original) The process of claim 72, wherein said second film is laminated onto said resulting film.

79. (Original) The process of claim 72, further comprising laminating said resulting film to another film.

80. (Original) The process of claim 72, wherein said second film layer comprises an active.

81. (Amended) The process of claim [72]80, wherein said active in said second film is different than said active in said resulting film.

82. (Amended) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives[, drugs, medicaments] and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%; [and]

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

83. (Original) The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.

84. (Original) The process of claim 82, wherein said polymer comprises a polymer selected

from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

85. (Original) The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

86. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

87. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

88. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol

copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

89. (Original) The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

90. (Original) The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

91. (Cancelled)

92. (Amended) The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management

agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

93. (Amended) The process of claim 82, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

94. (Original) The process of claim 82, wherein said active is a bioactive active.

95. (Cancelled)

96. (Original) The process of claim 82, wherein said active is an opiate or opiate-derivative.

97. (Original) The process of claim 82, wherein said active is an anti-emetic.

98. (Original) The process of claim 82, wherein said active is an amino acid preparation.

99. (Original) The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

100. (Original) The process of claim 82, wherein said active is a protein.

101. (Original) The process of claim 82, wherein said active is insulin.

102. (Original) The process of claim 82, wherein said active is an anti-diabetic.

103. (Original) The process of claim 82, wherein said active is an antihistamine.

104. (Original) The process of claim 82, wherein said active is an anti-tussive.

105. (Original) The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.

106. (Original) The process of claim 82, wherein said active is an anti-asthmatics.

107. (Amended) The process of claim 82, wherein said active is an anti-diarrhea preparation.

108. (Original) The process of claim 82, wherein said active is an alkaloid.

109. (Original) The process of claim 82, wherein said active is an anti-psychotic.

110. (Original) The process of claim 82, wherein said active is an anti-spasmodic.

111. (Original) The process of claim 82, wherein said active is a biological response modifier.

112. (Original) The process of claim 82, wherein said active is an anti-obesity drug.

113. (Original) The process of claim 82, wherein said active is an H_2-antagonist.

114. (Amended) The process of claim [82]113, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

115. (Original) The process of claim 82, wherein said active is a smoking cessation aid.

116. (Original) The process of claim 82, wherein said active is an anti-parkinsonian agent.

117. (Original) The process of claim 82, wherein said active is an anti-depressant.

118. (Original) The process of claim 82, wherein said active is an anti-migraine.

119. (Original) The process of claim 82, wherein said active is an anti-Alzheimer's agents.

120. (Original) The process of claim 82, wherein said active is a dopamine receptor agonist.

121. (Original) The process of claim 82, wherein said active is a cerebral dilator.

122. (Original) The process of claim 82, wherein said active is a psychotherapeutic agent.

123. (Original) The process of claim 82, wherein said active is an antibiotic.

124. (Original) The process of claim 82, wherein said active is an anesthetic.

125. (Original) The process of claim 82, wherein said active is a contraceptive.

126. (Original) The process of claim 82, wherein said active is an anti-thrombotic drug.

127. (Original) The process of claim 82, wherein said active is diphenhydramine.

128. (Original) The process of claim 82, wherein said active is nabilone.

129. (Original) The process of claim 82, wherein said active is albuterol sulfate.

130. (Original) The process of claim 82, wherein said active is an anti-tumor drug.

131. (Original) The process of claim 82, wherein said active is a glycoprotein.

132. (Original) The process of claim 82, wherein said active is an analgesic.

133. (Original) The process of claim 82, wherein said active is a hormone.

134. (Original) The process of claim 82, wherein said active is a decongestant.

135. (Original) The process of claim 82, wherein said active is a loratadine.

136. (Original) The process of claim 82, wherein said active is dextromethorphan.

137. (Original) The process of claim 82, wherein said active is chlorpheniramine maleate.

138. (Original) The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

139. (Original) The process of claim 82, wherein said active is an appetite stimulant.

140. (Original) The process of claim 82, wherein said active is a gastrointestinal agent.

141. (Original) The process of claim 82, wherein said active is a hypnotic.

142. (Original) The process of claim 82, wherein said active is taste-masked.

143. (Original) The process of claim 82, wherein said active is taste-masked using a flavor.

144. (Original) The process of claim 82, wherein said active is coated with a controlled release composition.

145. (Original) The process of claim 144, wherein said controlled release composition provides an immediate release.

146. (Original) The process of claim 144, wherein said controlled release composition provides a delayed release.

147. (Original) The process of claim 144, wherein said controlled release composition provides a sustained release.

148. (Original) The process of claim 144, wherein said controlled release composition provides a sequential release.

149. (Original) The process of claim 82, wherein said active is a particulate.

150. (Original) The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.

151. (Original) The process of claim 82, further comprising a step of providing a second film layer.

152. (Original) The process of claim 151, wherein said second film layer is coated onto said resulting film.

153. (Original) The process of claim 151, wherein said second film layer is spread onto said resulting film.

154. (Original) The process of claim 151, wherein said second film layer is cast onto said resulting film.

155. (Original) The process of claim 151, wherein said second film layer is extruded onto said resulting film.

156. (Original) The process of claim 151, wherein said second film layer is sprayed onto said resulting film.

157. (Original) The process of claim 151, wherein said second film layer is laminated onto said resulting film.

158. (Original) The process of claim 151, further comprising laminating said resulting film to another film.

159. (Original) The process of claim 151, wherein said second film comprises an active.

160. (Amended) The process of claim [151]159, wherein said active in said second film is different than said active in said resulting film.

161. (Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said[making a] film capable of being administered to a body surface and having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; [and]

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration, and

[(e)](f) administering said resulting film to a body surface.

162. (Original) The process of claim 161, wherein said body surface is a mucous membrane.

163. (Original) The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.

164. (Original) The process of claim 161, wherein said body surface is the surface of a wound.

165. (Original) The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.

166. (Original) The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

167. (Original) The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

168. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic

acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

169. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

170. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

171. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

172. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

173. (Cancelled)

174. (Amended) The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

175. (Amended) The process of claim 161, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,

]vitamins and combinations thereof.

176. (Original) The process of claim 161, wherein said active is a bioactive active.

177. (Cancelled)

178. (Original) The process of claim 161, wherein said active is an opiate or opiate-derivative.

179. (Original) The process of claim 161, wherein said active is an anti-emetic.

180. (Original) The process of claim 161 wherein said active is an amino acid preparation.

181. (Original) The process of claim 161, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

182. (Original) The process of claim 161, wherein said active is a protein.

183. (Original) The process of claim 161, wherein said active is insulin.

184. (Original) The process of claim 161, wherein said active is an anti-diabetic.

185. (Original) The process of claim 161, wherein said active is an antihistamine.

186. (Original) The process of claim 161, wherein said active is an anti-tussive.

187. (Original) The process of claim 161, wherein said active is a non-steroidal anti-inflammatory.

188. (Original) The process of claim 161, wherein said active is an anti-asthmatics.

189. (Amended) The process of claim 161, wherein said active is an anti-diarrhea preparation.

190. (Original) The process of claim 161, wherein said active is an alkaloid.

191. (Original) The process of claim 161, wherein said active is an anti-psychotic.

192. (Original) The process of claim 161, wherein said active is an anti-spasmodic.

193. (Original) The process of claim 161, wherein said active is a biological response modifier.

194. (Original) The process of claim 161, wherein said active is an anti-obesity drug.

195. (Original) The process of claim 161, wherein said active is an H_2-antagonist.

196. (Original) The process of claim 195, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

197. (Original) The process of claim 161, wherein said active is a smoking cessation aid.

198. (Original) The process of claim 161, wherein said active is an anti-parkinsonian agent.

199. (Original) The process of claim 161, wherein said active is an anti-depressant.

200. (Original) The process of claim 161, wherein said active is an anti-migraine.

201. (Original) The process of claim 161, wherein said active is an anti-Alzheimer's agents.

202. (Original) The process of claim 161, wherein said active is a dopamine receptor agonist.

203. (Original) The process of claim 161, wherein said active is a cerebral dilator.

204. (Original) The process of claim 161, wherein said active is a psychotherapeutic agent.

205. (Original) The process of claim 161, wherein said active is an antibiotic.

206. (Original) The process of claim 161, wherein said active is an anesthetic.

207. (Original) The process of claim 161, wherein said active is a contraceptive.

208. (Original) The process of claim 161, wherein said active is an anti-thrombotic drug.

209. (Original) The process of claim 161, wherein said active is diphenhydramine.

210. (Original) The process of claim 161, wherein said active is nabilone.

211. (Original) The process of claim 161, wherein said active is albuterol sulfate.

212. (Original) The process of claim 161, wherein said active is an anti-tumor drug.

213. (Original) The process of claim 161, wherein said active is a glycoprotein.

214. (Original) The process of claim 161, wherein said active is an analgesic.

215. (Original) The process of claim 161, wherein said active is a hormone.

216. (Original) The process of claim 161, wherein said active is a decongestant.

217. (Original) The process of claim 161, wherein said active is a loratadine.

218. (Original) The process of claim 161, wherein said active is dextromethorphan.

219. (Original) The process of claim 161, wherein said active is chlorpheniramine maleate.

220. (Original) The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

221. (Original) The process of claim 161, wherein said active is an appetite stimulant.

222. (Original) The process of claim 161, wherein said active is a gastrointestinal agent.

223. (Original) The process of claim 161, wherein said active is a hypnotic.

224. (Original) The process of claim 161, wherein said active is taste-masked.

225. (Original) The process of claim 161, wherein said active is taste-masked using a flavor.

226. (Original) The process of claim 161, wherein said active is coated with a controlled release composition.

227. (Original) The process of claim 226, wherein said controlled release composition provides an immediate release.

228. (Original) The process of 226, wherein said controlled release composition provides a delayed release.

229. (Original) The process of claim 226, wherein said controlled release composition

provides a sustained release.

230. (Original) The process of claim 226, wherein said controlled release composition provides a sequential release.

231. (Original) The process of claim 161, wherein said active is a particulate.

232. (Original) The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.

233. (Original) The process of claim 161, further comprising a step of providing a second film layer.

234. (Original) The process of claim 233, wherein said second film layer is coated onto said resulting film.

235. (Original) The process of claim 233, wherein said second film layer is spread onto said resulting film.

236. (Original) The process of claim 233, wherein said second film layer is cast onto said resulting film.

237. (Original) The process of claim 233, wherein said second film layer is extruded onto said resulting film.

238. (Original) The process of claim 233, wherein said second film layer is sprayed onto said resulting film.

239. (Original) The process of claim 233, wherein said second film layer is laminated onto said resulting film.

240. (Original) The process of claim 233, further comprising laminating said resulting film to another film.

241. (Original) The process of claim 233, wherein said second film comprises an active.

242. (Amended) The process of claim [233]241, wherein said active in said second film is different than said active in said resulting film.

243. (Original) The process of claim 1, said active is an anti-nauseant.

244. (Amended) The process of claim 1, said active is an erectile dysfunction drug.

245. (Original) The process of claim 1, said active is a vasoconstrictor.

246. (Original) The process of claim 1, said active is a stimulant.

247. (Original) The process of claim 1, said active is a migraine treatment.

248. (Original) The process of claim 1, said active is granisetron hydrochloride.

249. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

250. (Original) The process of claim 1, wherein said resulting film provides administration of said active through gingival application of said individual.

251. (Original) The process of claim 1, wherein said resulting film provides administration of said active through sublingual application of said individual.

252. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

253. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

254. (Cancelled)

255. (Cancelled)

256. (Original) The method of claim 1, wherein said resulting film contains less than about 6% by weight solvent.

257. (Cancelled)

258. (Original) The method of claim 1, wherein said resulting film is orally administrable.

259. (Original) The method of claim 1, wherein said active is in the form of a particle.

260. (Original) The method of claim 1, wherein said matrix comprises a dispersion.

261. (Original) The process of claim 82, said active is an anti-nauseant.

262. (Amended) The process of claim 82, said active is an erectile dysfunction drug.

263. (Original) The process of claim 82, said active is a vasoconstrictor.

264. (Original) The process of claim 82, said active is a stimulant.

265. (Original) The process of claim 82, said active is a migraine treatment.

266. (Original) The process of claim 82, said active is granisetron hydrochloride.

267. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

268. (Original) The process of claim 82, wherein said resulting film provides administration of said active through gingival application of said individual.

269. (Original) The process of claim 82, wherein said resulting film provides administration of said active through sublingual application of said individual.

270. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

271. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

272. (Cancelled)

273. (Cancelled)

274. (Original) The method of claim 82, wherein said resulting film contains less than about 6% by weight solvent.

275. (Cancelled)

276. (Original) The method of claim 82, wherein said resulting film is orally administrable.

277. (Original) The method of claim 82, wherein said active is in the form of a particle.

278. (Original) The method of claim 82, wherein said matrix comprises a dispersion.

279. (Original) The process of claim 161, said active is an anti-nauseant.

280. (Amended) The process of claim 161, said active is an erectile dysfunction drug.

281. (Original) The process of claim 161, said active is a vasoconstrictor.

282. (Original) The process of claim 161, said active is a stimulant.

283. (Original) The process of claim 161, said active is a migraine treatment.

284. (Original) The process of claim 161, said active is granisetron hydrochloride.

285. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

286. (Original) The process of claim 161, wherein said resulting film provides administration of said active through gingival application of said individual.

287. (Original) The process of claim 161, wherein said resulting film provides administration of said active through sublingual application of said individual.

288. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

289. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

290. (Cancelled)

291. (Cancelled)

292. (Original) The method of claim 161, wherein said resulting film contains less than about 6% by weight solvent.

293. (Cancelled)

294. (Original) The method of claim 161, wherein said resulting film is orally administrable.

295. (Original) The method of claim 161, wherein said active is in the form of a particle.

296. (Original) The method of claim 161, wherein said matrix comprises a dispersion.

297. (Original) The method of claim 1, wherein said matrix comprises an emulsion, a colloid or a suspension.

298. (Original) The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.

299. (Original) The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.

300. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

301. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

302. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

303. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

304. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

305. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

306. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

307. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

308. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

309. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

310. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

311. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

312. (New) The process of claim 1, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

313. (New) The process of claim 82, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

314. (New) The process of claim 161, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

315. (New) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes

by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%;

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of said active as indicated by said analytical chemical tests.

316. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

317. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus using air currents, which have forces below a yield value of said flowable polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by no more than 10%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling drying by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said

active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

318. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus at a temperature of about 60 °C and using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-

elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by less than 5%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by less than 5% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

REMARKS

I. Description of the Patent and the Applicant's Reply

The above-identified U.S. Patent No. 7,897,080 (" '080 Patent") is presently under reexamination. Claims 1-299 were issued in the '080 Patent. Claims 1-299, subject to reexamination, were rejected in the Office Action. Claims 16, 95 and 177, have been canceled herein as they are identical to claims 32, 111 and 193, respectively. See Office Action, p. 7. Claims 12, 91, 173, 254, 255, 257, 272, 273, 275, 290, 291, and 293 have also been canceled purely for clarity. Claims 300 through 318 are new.

While the Examiner's rejection of all the claims is respectfully traversed in all respects, claims 1, 82 and 161 of the '080 Patent have been amended in an effort to advance the prosecution of the present reexamination. Claims 1, 82 and 161 are hereby amended in accordance with 37 C.F.R. §1.530(d) (2) and (f). In accordance with 35 U.S.C. § 314(a), the amendments to claims 1, 82 and 161, new independent claims 315-318, and new dependent claims 300-314 do not enlarge the scope of the claims of the '080 Patent. Explanation of the support for these claims appears below. Entry of this amendment and reconsideration is respectfully requested.

II. Status of Claims and Support for Claim Changes Pursuant to 37 C.F.R. §1.530(e)

The status of the claims as of the date of this amendment is as follows: Claims 1-299 were issued in the '080 Patent and are subject to reexamination. Claims 1-299, subject to reexamination, were rejected in the Office Action. Claims 300 through 318 are new and are subject to examination. Please cancel claims 16, 95 and 177, as they are identical to claims 32, 111 and 193, respectively. See Office Action, p. 7. Please cancel Claims 12, 91, 173, 254, 255, 257, 272, 273, 275, 290, 291, and 293, for clarity, including some limitations which now appear in the independent claims from which some depend.

In compliance with 37 C.F.R. § 1.530(j), the amendments to claims 1, 82 and 161 do not enlarge their scope or the scope of the original claims or introduce new matter, nor do the

amendments adding new claims 300 through 318 enlarge the scope of the original claims or introduce new matter.

Support for the amendments to claims 1, 82 and 161 and new claims 300 through 318 may be found throughout the '080 Patent, including, the Abstract, Specification, Figures and Claims, for example, at col. 13, ll. 23-36, col. 16, l. 62 through col. 17, l. 3, col. 28, l. 66 through col. 29, l. 6; col. 29, ll. 20-35 and 38; col. 32, ll. 34-41; col. 2, ll. 27-46; col. 15, ll. 28-43, and the Abstract; quoted in detail below; col. 3, ll. 58-60 ("the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval"); col. 19, l. 30 through col. 21, l. 31 (actives including pharmaceutical actives, bioactive actives, and combinations thereof); col. 6, ll. 49-52 ("These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process."); Figures 6, 7, 8, 35 and 36 and col. 14, ll. 20-25 ("drying" and "drying apparatus"); col. 11, ll. 17-19 ("Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition"); col. 11, ll. 21-23 ("yield values . . . force"); col. 12, ll. 20-36, col. 13, ll. 37-38 ("After mechanical mixing, the film may be placed on a conveyor"); col. 29, ll. 11-13 ("As the film is conveyed through the manufacturing process, for example on a conveyor belt apparatus"); col. 33, l. 10 through col. 34, l. 24 (example M); col. 44, 11. 9-13 ("the controlled drying process of the present invention allows for uniform drying to occur, whereby evaporative cooling and thermal mixing contribute to the rapid formation of viscoelastic film and the 'locking-in' of uniformity of content throughout the film"); col. 4, l. 8; col. 6, ll. 46-52; col. 13, ll. 36-43; col. 26, ll. 9-27; col. 28, ll. 24-58; col. 29, ll. 8-10; col. 20, ll. 65-66 ("Erectile dysfunction . . . drugs"); col. 19, l. 55 ("anti-diarrhea preparations"); col. 6, ll. 52-60 ("Examples of controlled drying processes include . . . hot air impingement across the bottom substrate and bottom heating plates . . . controlled radiation drying . . . such as infrared and radio frequency radiation . . . ."); col. 7, lines 5 through 16 ("This may be achieved by applying heat to the bottom surface of the film . . . or alternatively by the introduction of controlled microwaves to evaporate the water . . . . air currents directed at the bottom of the film should desirably be controlled"); col. 27, ll. 53-55 ("The temperature at which the films are dried is about 100°C. or less"); col. 41, ll. 49-50 ("films were dried in an oven at approximately 60° C."). Support for new claims may also be found throughout the '080 Patent, including, the Figures, Tables and

Claims, for example at col. 19, ll. 10-25, col. 19, l. 30 through col. 22, l. 28, col. 25, ll. 53-60, col. 22, ll. 24-28; col. 28, ll. 1-2; col. 14, ll. 63-65; Tables 17 and 18; Figures 6-8, 33, 34 and 35. Many of the claim elements of the new independent claims can be found in original independent claims 1, 82, and 161 of the '080 patent.

> "Temperatures that approach 100° C. will generally cause degradation of proteins as well as nucleic acids. For example some glycoproteins will degrade if exposed to a temperature of 70° C. for thirty minutes. Proteins from bovine extract are also known to degrade at such low temperatures. DNA also begins to denature at this temperature.
>
> "Applicants have discovered, however, that the films of the present invention may be exposed to high temperatures during the drying process without concern for degradation, loss of activity or excessive evaporation due to the inventive process for film preparation and forming. In particular, the films may be exposed to temperatures that would typically lead to degradation, denaturization, or inactivity of the active component, without causing such problems. According to the present invention, the manner of drying may be controlled to prevent deleterious levels of heat from reaching the active component."
>
> '080 Patent. col. 12, ll. 20-36.
>
> "For instance, the films of the present invention desirably are dried for 10 minutes or less. Drying the films at 80° C. for 10 minutes produces a temperature differential of about 5° C. This means that after 10 minutes of drying, the temperature of the inside of the film is 5° C. less than the outside exposure temperature. In many cases, however, drying times of less than 10 minutes are sufficient, such as 4 to 6 minutes. Drying for 4 minutes may be accompanied by a temperature differential of about 30° C., and drying for 6 minutes may be accompanied by a differential of about 25° C. Due to such large temperature differentials, the films may be dried at efficient, high temperatures without causing heat sensitive actives to degrade."
>
> '080 Patent. col. 13, ll. 23-36.
>
> "The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process."

'080 Patent, col. 16, l. 62 through col. 17, l. 3 (emphasis supplied).

"It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and overall appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons."

'080 Patent, col. 28, l. 66 through col. 29, l. 6 (emphasis supplied).

"The cut film then may be sampled by removing small pieces from each of the opposed ends of the portion(s), without disrupting the middle of the portion(s). . . . After the end pieces, or sampling sections, are removed from the film portion(s), they may be tested for uniformity in the content of components between samples."

'080 Patent, col. 29, ll. 20 through 35 (emphasis supplied).

"An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active."

'080 Patent, col. 32, ll. 34-41 (emphasis supplied).

"The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage

units based on films, this virtually mandates that uniformity in the film be present."

'080 Patent, col. 2, ll. 27-46 (emphasis supplied).

"Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight. "

'080 Patent, col. 15, ll. 28-43 (emphasis supplied).

III. Declarations Submitted With This Reply

Along with this Reply, the Patentee is submitting the Declarations of Dr. B. Arlie Bogue (Exhibit A) ("Bogue Declaration") and Dr. David T. Lin (Exhibit B) ("Lin Declaration") under 37 C.F.R. §1.132. The Bogue Declaration provides technical results regarding Patentee's commercial pharmaceutical films manufactured in accordance with the '080 Patent and it should not be counted toward the page limit of 37 C.F.R. §1.943. The Lin Declaration provides Dr. Lin's background information, information relating to FDA uniformity of content dosage requirements, and has six (6) numbered paragraphs of statements (¶¶ 17-22) relating to a prior art disclosure at pages 5-6, which might at most be counted as two (2) pages toward the page limit of 37 C.F.R. §1.943.

IV. Background of the '080 Patent

The '080 Patent is a continuation of U.S. application Ser. No. 10/856,176, filed May 28, 2004 now U.S. Pat. No. 7,666,337 (" '337 Patent"), which claims the benefit of U.S. Provisional Application No. 60/473,902, filed May 28, 2003 and is a continuation-in-part of U.S. application Ser. No. 10/768,809, filed Jan. 30, 2004 now U.S. Pat. No. 7,357,891 (" '891 Patent"), which claims benefit to U.S. Provisional Application No. 60/443,741 filed Jan. 30, 2003 and is a continuation-in-part of:

(a) PCT/US02/32575 filed Oct. 11, 2002, which claims priority to: (1) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002 which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (2) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002;

(b) PCT/US02/32594, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/414,276, filed Sep. 27, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002; and

(c) PCT/US02/32542, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/371,940, filed Apr. 11, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002.

There are pending applications claiming the benefit of the priority of all and/or some of the above.

The '891 Patent is involved in a U.S. litigation wherein Patentee has alleged that the Third Party Requester, BioDelivery Sciences International, Inc. ("BDSI") has infringed its '891 Patent. The litigation is Civil Action No. 10-cv-5695 in the U.S. District Court in the District of New Jersey. In the litigation, Patentee also alleged that the Third Party Requester infringed two other of Patentee's patents, U.S. 7,425,292 (" '292 Patent") and U.S. 7,824,588 (" '588 Patent").

Third Party Requester requested reexamination of the '891 Patent (90/012,098), the '292 Patent (90/012,097) and the '588 Patent (95/001,753) as well. Both the '292 and the '891 Patent successfully exited reexamination. The Examiner on January 23, 2013 issued a Right of Appeal Notice ("RAN") for the '588 Patent reexamination. In response, Patentee filed a Notice of Appeal, a Petition Under 37 C.F.R. § 1.183 Requesting Waiver of the Prohibition of an Extension of Time for Filing an Appeal Brief and for an Extension of Time for Filing an Appeal Brief, and a Petition Under 37 C.F.R. § 1.182 Requesting Continued Reexamination.

Third Party Requester requested reexamination of another of Patentee's related patents namely U.S. Pat. No. 7,666,337 (Control No. 95/002,171), reexamination was ordered, an Office Action issued, Patentee Replied, and Third Party Requester submitted its Comments.

Finally, Third Party Requester requested the reexamination herein of the '080 Patent. .

The '080 Patent has not been and is not currently involved in litigation.

'080 Patent Office Action Statements

In connection with the Order Granting Request for Inter Partes Reexamination of the '080 Patent, Control No. 95/002,170 ("Order Granting IPR Request '080 Patent"), noted above, certain comments were made by the Examiner with respect to Claim 25 of the '337 Patent. The statements were made when the Examiner addressed Third Party Requester's request to find that claim 82 of the '080 Patent should be rejected under 35 U.S.C. § 101 double patenting over claim 25 of the '337 Patent. Patentee supports the Examiner's finding that the Third Party Requester had failed to demonstrate a reasonable likelihood of success of arriving at the subject matter of at least one claim of the '080 Patent. However, Patentee respectfully disagrees with the Examiner's statements interpreting "uniform" and "substantially uniform" therein. In particular, Patentee disagrees that "the active is uniformly distributed (i.e. no variance of active)" in the matrix. Certainly a uniform distribution does not require a state of "no variance". See pages 21 and 22 of the Order Granting IPR Request '080 Patent. "Uniform" and "substantially uniform" are indeed different, but "uniform" from a practical standpoint must of necessity allow for some variance, albeit less than "substantially uniform".

V. The Patented Invention

The present invention is directed to novel and non-obvious processes for manufacturing pharmaceutical and bioactive active containing films, suitable for commercialization and U.S. Food and Drug Administration ("FDA") approval. As noted in the Bogue Declaration, ¶ 4, one manufactured lot of such resulting film can contain 2,000,000 individual dosage units. The claimed processes accomplish this feat while providing the necessary narrow ranges in the amount of active in individual dosage units. As claimed, the '080 Patent, at least, requires a uniformity of content in amount of active (i) in individual dosage units sampled from a resulting film of 10% or less (independent claims 1, 82, 161, and 316-318, see Appendix A, Bogue Declaration), and (ii) in individual dosage units sampled from two or more resulting films of

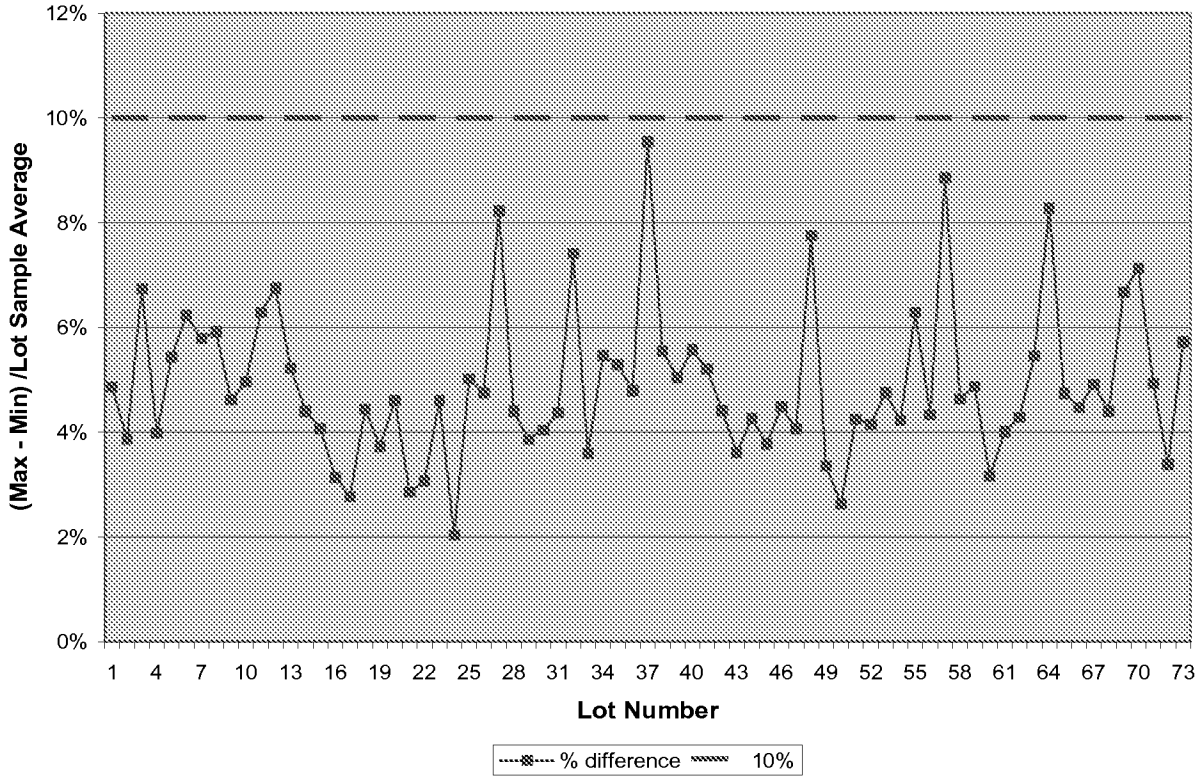
10% or less as a percent difference from a desired amount (independent claim 315, see Appendix B, Bogue Declaration).

One conceptual approach to understanding (i) and (ii) is as follows. A baker has a good recipe or process for making bread. The recipe includes the ingredients and the controlled baking conditions. On Monday the baker bakes a loaf of bread strictly following the recipe. On Friday the baker bakes a loaf of bread again strictly following the recipe. The loaves are cut into individual slices. When tasted, all the slices from Monday's loaf taste almost the same, indeed the tastes differs by only 10% between slices from Monday's loaf. In the same fashion, when tasted, all the slices from Friday's loaf taste almost the same, indeed the tastes differs by only 10% between slices from Friday's loaf. However, when a slice from Monday's loaf is compared to a slice from Friday's loaf, the difference in taste is more pronounced than between individual slices from the same loaf. Since the baker follows the same recipe for all his/her bread the baker expects that all slices from all loaves should taste alike or almost alike. However, the difference in taste between slices from Monday and slices from Friday is greater than the difference between slices in the same loaf. Indeed, the taste difference is now about 10% from what the baker believes all his/her bread should be expected to taste like-- that is, 10% from the high quality standard ("desired amount" and/or "target amount") for all the bread baked.

In a similar fashion, the "recipe" of Patentee's claimed processes keep differences between individual dosage units from one manufactured lot very small-- e.g. smaller than 10% in amount of pharmaceutical active. See, independent claims 1, 82, 161 and 316-318. The "recipe" of Patentee's claimed processes also keeps differences between individual dosage units between different manufactured lots small as well, just not necessarily as small-- e.g. smaller than a 10% difference from the standard, i.e. desired amount. See, independent claim 315.

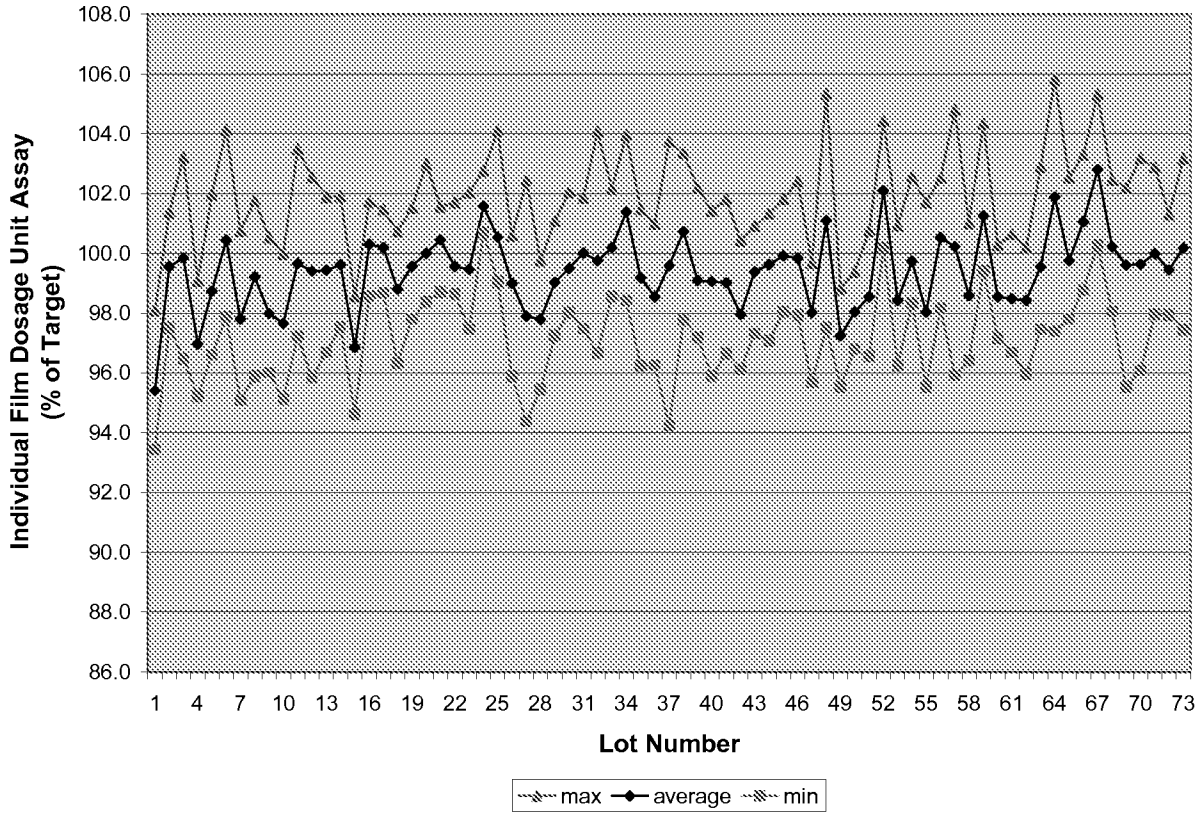
Thus, in the case of a resulting film from one manufacturing lot, the substantially uniform distribution of the active is indicated through analytical chemical tests which indicate that uniformity of content in the amount of the active in substantially equal sized individual dosage units sampled from the resulting film varies by no more than 10%. See Appendix A from Bogue Declaration copied below and Bogue Declaration, ¶ 9, where this is shown to be true for 73 separately manufactured lots of film, all manufactured by Patentee in accordance with the claimed invention.

APPENDIX A (Bogue Declaration)



In the case of resulting films from different manufacturing lots the substantially uniform distribution of the active is indicated through analytical chemical tests which indicate that uniformity of content in the amount of the active varies by no more than 10% from a desired amount. See Appendix B from Bogue Declaration copied below and Bogue Declaration, ¶ 10, where this is shown to be true across 73 separately manufactured lots of film, all manufactured by Patentee in accordance with the claimed invention. 100.0% indicating the desired amount.

APPENDIX B (Bogue Declaration)



Hence, the manufacturing process of the '080 Patent as claimed is a commercially viable processes which yields commercial viable products meeting FDA regulations, including active assaying requirements.

This should be compared to the laboratory produced films described in the prior art relied on by the Examiner. In the cited prior art, terms such as uniformity, substantial uniformity, and homogeneity are all accepted without real support. They cannot be relied upon. What is missing is the support for the statements -- that is, having had the amount of active tested by analytical chemical testing, including assaying. *See* Lin Declaration, ¶¶ 17-22 (statements about insufficient disclosure in cited prior art reference). Patentee uses the '080 Patent invention to manufacture commercially acceptable products for which Patentee must establish uniformity of content in the amount of active in its products by such analytical chemical testing as required by regulatory agencies, such as the FDA. Dr. Bogue's Declaration describes such testing on

Patentee's products produced in accordance with the invention and the results which are consistent with the '080 Patent's claims for uniformity of content in the amount of active (i) in individual dosage units sampled from a resulting film of 10% or less, and (ii) in individual dosage units sampled from two or more resulting films of 10% or less as a percent difference from a desired amount. Bogue Declaration, ¶¶ 4-11.

PATENTEE'S CLAIMS

Patentee's instant claims recite additional details about its processes for manufacturing a resulting pharmaceutical film suitable for commercialization and regulatory approval. Some of the details include: forming a flowable polymer matrix comprising a polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active; casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps; controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less; forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film from one lot, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and, in the case of more than one resulting film lot, repeating the process for forming one film lot such that uniformity of content in the amount of said active across all said resulting film lots varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

Additional claim limitations can be found in some of Patentee's narrower independent claims, for example claims 317-318. These claims generally add to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising continuing evaporation to a water content of said resulting film of 10% or less.

As defined in the '080 Patent, a visco-elastic film is one that has been controllably dried to lock its components into a substantially uniform distribution throughout the film while avoiding problems associated with conventional drying methods. By providing a visco-elastic film product having this compositional uniformity or uniformity of content, the user can be assured that the product includes the proper amount of components, such as an active contained therein. Further, the process can be used to make commercially viable large-scale film products, such as large rolls of film from which smaller individual dosage units are cut, the user can feel confident that no matter where the large roll of film is cut, the resulting pieces (e.g., individual unit dosages) will have a substantially uniform composition. As noted above, Patentee successfully manufactures pharmaceutical films containing 2,000,000 individual dosage units meeting FDA requirements using the claimed processes. Bogie Declaration, ¶ 4. As claimed, the uniformity of content as a percent difference will be no more than 10% and in some cases less. The need for providing a process for obtaining the desired uniformity of content of the desired amount of active in the resulting products is critically important, particularly for regulated products, such as the claimed pharmaceuticals.

Prior to the present invention, it was known to prepare films. However, in many cases the end product was merely assumed to be homogeneous, either because the initial components were blended together or because after the blending step the physically observable properties of the resulting film product, for example, its appearance or weight, were satisfactory. However,

these physical properties do not indicate or establish that the uniformity of content of the components is such that, for example, the amount of the active in individual dosage units varies by no more than 10% for a particular film. By contrast, for example, in one instance, "the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix." '080 Patent, col. 18, ll. 37-40.

Nor do physical properties indicate or establish that that the uniformity of content of the components is such that, for example, the amount of the active in individual dosage units from one film to another film varies by no more than 10% from a desired amount. This range of uniformity is disclosed in connection with, for example, the uniformity of content disclosed in the '080 Patent when referencing the FDA and other regulatory requirements. "Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present." '080 Patent, col 2, ll. 43-45. In these cases, the FDA and/or other regulatory agency sets the amount of active that must be present in an individual dosage unit (or dosage form), *i.e.,* the desired amount, and provides for the necessary uniformity of content, in this case the active may vary by 10% from the desired amount. A "desired amount" is an essential concept, as the FDA indicates the required dosage for each drug, and each drug has its own specified dosage amount. Essential to any pharmaceutical and related product is a viable means of actually testing for the amount of the active present in individual dosage unit samples, and that is to use analytical chemical testing and actually test for the presence of the desired amount of active and thereby determine whether the prescribed uniformity of content of active is present. *See* Lin Declaration, ¶¶ 9-16.

Importantly, the process of forming a proper film product with the claimed levels of uniformity of content in, for example, the amount of active does not end at the mixing stage. Patentee has discovered that the various steps post-mixing play a very important role in ensuring that the resulting product complies with the stringent requirements for uniformity of content. For example, one key step in the formation of a film product is the drying step, particularly when heat and/or radiation is used to dry the film. Patentee has discovered that controlled drying methods is essential in meeting these claimed requirements. Controlled drying includes methods that avoid, for example, the formation of bubbles, or uncontrolled air currents that may cause

movement of particles within the visco-elastic film forming matrix. Controlled drying, as required by the invention as claimed, may be effectuated through evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less.

It is important to understand that compositional uniformity or uniformity of content is not the same as having a surface that appears free of defects. Importantly, having a glossy surface does not equate to a uniform film, because the bottom side of a film product formed on a substrate will take the surface features of the substrate. If the substrate is smooth, the resulting bottom surface will also be smooth and possibly glossy. A product that has a surface that appears free of defects may have experienced significant non-uniformity below the surface, for example due to aggregation and agglomeration of components. It is important to note that just because the surface of a resulting product looks glossy or free of defects does not inherently mean that the actives within the film product exhibit the level of uniformity of content necessary to satisfy regulatory requirements and/or deliver the desired amount to the patient.

The '080 Patent discloses in a section entitled "Testing Films for Uniformity" (col. 28, l. 65 through col. 29, l. 53) that "[i]t may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process". '080 Patent, col. 28, l. 66 through col. 29, l. 1. In particular:

> "It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and over all appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons."
>
> '080 Patent, col. 28, l. 66 through col. 29, l. 6 (emphasis supplied).

Thus disclosed are two general types of testing, one for physical uniformity, and one for chemical uniformity. The disclosure goes on to provide different ways to test for each.

> "After the end pieces, or sampling sections, are removed from the film portion(s), they may be tested for uniformity in the content of components between samples. Any conventional means for examining and testing the film pieces may be employed, such as, for example, visual inspection, use of analytical equipment, and any other suitable means known to those skilled in the art. If the testing results show non-uniformity between film samples, the manufacturing process may be altered. This can save time and expense because the process may be altered prior to completing an entire manufacturing run. For example, the drying conditions, mixing conditions, compositional components and/or film viscosity may be changed. Altering the drying conditions may involve changing the temperature, drying time, moisture level, and dryer positioning, among others."
>
> '080 Patent, col. 29, ll. 33-38 (emphasis supplied).

In this way the '080 Patent provides multiple tests for non-uniformity, which are extremely useful in guiding the commercial manufacture of films. For example, manufacturing runs of films which appear to exhibit "non-uniformity" may be adjusted early in the run with less waste of materials, thus saving time and expense associated with the possibility of a non-uniform film. Physical tests, such as observational tests, are insufficient to determine the level of uniformity of content disclosed and claimed by the '080 Patent-- they do not determine the actual amount of active in samples.

The '080 Patent discloses testing to determine the appropriate degree of uniformity of content of the resulting film involving sampling substantially equal sized individual dosage units of the resulting film, dissolving the active in the sampled resulting film, and testing for the amount of active present in the sampled resulting film. Thus, the '080 Patent discloses that uniformity of the active is demonstrated through testing.

> "An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active."
>
> '080 Patent, col. 32, ll. 36-41 (emphasis supplied).

In this respect the Examiner, in his Scope of Claims section has mistakenly included physical uniformity type tests, used to quickly and/or easily suggest non-uniformity, with chemical uniformity type tests involving analytic equipment, that is, the actual testing of the uniformity of content for the amount of active. In the Scope of Claims section of the Office Action (pp. 3-7), the Examiner refers to two different portions of the '080 Patent's "EXAMPLES" section as follows:

> "An alternative means for evaluating uniformity is to cut the films into individual doses and measure the weight of the doses (col. 31, line 46 through col. 32, line 45). The '080 patent notes that "films of substantially similar size cut from different locations of the same film contain substantially the same amount of active." (col. 32, lines 37-39)."
>
> Office Action, p. 7.

Significantly, the two sentences are not related to each other, other than that both deal with examples and with cutting the film into dosage forms. The first is from a physical test, the second, relating to actives, is from an analytical chemical test for uniformity of content of active.

First is the physical test which refers to uniformity in mass.

> "Uniformity was also measured by first cutting the film into individual dosage forms. Twenty-five dosage forms of substantially identical size were cut from the film of inventive composition (E) above from random locations throughout the film. Then eight of these dosage forms were randomly selected and additively weighed. The additive weights of eight randomly selected dosage forms, are as shown in Table 2 below:
>
> [Table omitted.]
>
> "The individual dosages were consistently 0.04 gm, which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. **Therefore,** when the components of different densities are combined in a uniform manner in a film, as in the present invention, **individual dosages forms from the same film of substantially equal dimensions, will contain the same mass**."
>
> '080 Patent, col. 31, l. 46 through col. 32, l. 34 (emphasis supplied).

In accordance with this test, if the masses are unequal that would be an indication of mass non-uniformity.

Immediately after the above quoted disclosure, the '080 Patent discloses essentially that to demonstrate uniformity of content for active, the amount of active in each substantially similarly sized sample must be determined.

> "An alternative method of determining the uniformity of the active is to cut the film into individual doses. **The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active**."
>
> '080 Patent, col. 32, ll. 35-40 (emphasis supplied).

The Examiner also relies on the paragraph at '080 Patent, col. 31, ll. 38-45 for support that physical type tests, in this case observational tests, are sufficient to establish uniformity of content of active.

> "The uniform distribution of the components within the film was apparent by examination by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another. Therefore, there was substantially no disparity among the amount of active found in any portion of the film."
>
> '080 Patent, col. 31, ll. 38-45

However, it is one thing to have films which appear to be substantially free of aggregation and rely on that to say there is substantially no disparity among the amount of active in any portion of the film, and it is a totally different thing to demonstrate the presence of the required level of uniformity of content in the amount of active by analytical chemical testing and determining the actual amount of active in samples.

This paragraph, again, from the '080 Patent's section on "EXAMPLES", sets the stage for disclosing both the physical and chemical type tests referred to above at '080 Patent, col. 31, l. 46 through col. 32, l. 40, which follows this paragraph (see citation). Moreover, this paragraph

itself follows the manufacture of the film of Examples A-I and starts with what would be an expected quick and inexpensive procedure of looking at the film right after making it to see if it appears non-uniform or uniform. Such an observational test is at a macro level and does not indicate the degree of uniformity. Even if the film appears uniform, analytical chemical tests must then be conducted to verify uniformity of content at the prescribed level. What followed next were the two other tests discussed above.

Importantly, the first test is obviously a physical type test needed to rely on assumptions to reach its conclusion of substantially no disparity among the amount of active found in any portion of the film. Namely, by "viewing the films it was apparent that they were substantially free of aggregation . . . . Therefore, there was substantially no disparity among the amount of active found in any portion of the film." Based on physical observations a conclusion was drawn. The second, another physical test, concluded "individual dosages forms from the same film of substantially equal dimensions will contain the same mass;" again, referring to mass not uniformity of content of active. Again, no simple declarative statement that the amount of active in each sample was substantially the same or that the actual amount of active was determined.

It was only the third test, the analytical chemical type test that could directly establish that "films of substantially similar size cut from different locations on the same film contain substantially the same amount of active". This is to be expected as only the chemical based tests could provide the necessary assurance for the statement that substantially the same amount of active was present in each dose. Thus, one cannot solely rely on physical tests in prior art disclosures to "establish" that the prior art films actually possessed the levels of uniformity of content as claimed by the '080 Patent. However, analytical chemical testing is used in the '080 Patent to establish the actual amount of active in samples. In one example, in the '080 Patent analytical chemical testing was used to test for the amount of one component, a red dye, and in so doing established that the uniformity of content of the component fell well within the 10% level, particularly, it was 4%. See, '080 Patent, col. 33, l. 10 through col. 34, l. 24 (example M).

VI. Arriving at the Invention

The inventors of the '080 Patent are the first to not only identify the problems associated with manufacturing commercially and pharmaceutically viable active containing film individual

dosage units or forms, but also to solve those problems, especially as same relate to obtaining required levels of uniformity of content. Although many prior publications discussed the use of film as a dosage form for drugs, none of the publications identified nor solved the problems and complications associated with their manufacture. These early publications focused on the compositional and qualitative aspects of the films only and merely treated the manufacturing, if mentioned at all, as being simple, such as exposing the cast wet film to a conventional hot air circulating oven. However, especially in a commercial manufacturing setting, drying an active-containing cast wet film (even if the wet film is homogenous), in a conventional hot air circulating oven does not necessarily produce a film that is commercially viable, or deliver a film with the prescribed degree of uniformity of content in said setting. The '080 Patent does. *See* Bogue Declaration, ¶¶ 4-11.

A. Recognition of the Problem

The inventors discovered that it is not commercially viable to manufacture therapeutic–active-containing films using conventional drying methods. Even when a wet film matrix is properly formed so as to have a substantially uniform distribution of active within it, there are numerous factors which can destroy that uniformity of content during later processing such as casting and drying. The present specification describes many of these problems, which include (i) self-aggregation and agglomeration of active; (ii) skinning of the surface (a barrier through which remaining solvent must penetrate) before the thickness of the film is sufficiently dried, resulting in ripping and re-forming of the surface; (iii) forming of ripples on the surface; (iv) formation of air bubbles, which result in voids or air spaces within the film product; (v) maintaining the active in a substantially stable and uniformly dispersed state; (vi) movement of active particles due to uncontrolled air currents during drying; (vii) using air currents which create forces which overcome the yield value of the polymer matrix, or which would disturb or break the surface of the polymer matrix, or which overcome the inherent viscosity of the polymer matrix. See, for example, col. 3, l. 33 through col. 4, l. 6, and col. 11, ll. 14-25, the '080 Patent.

B. Solving the Problem

The inventors not only were the first to identify all the problems described above, but the first to solve them. Failure to solve one or more of these problems results in a film product that lacks the desired degree of uniformity of content of active per unit dose of film and therefore when equal dosage sizes are cut from the bulk film product, the desired amount of active per dosage lacks the desired and/or required degree of uniformity of content of active. The inventive methods and processes of the '080 Patent maintain the desired uniformity of content of active by, *inter alia*, controlling polymer matrix viscosity and controlling the drying processes so as to avoid the aforementioned problems, thereby forming a visco-elastic film that locks-in the substantially uniform distribution of active(s) during the drying steps. As described in the specification and claims, the present invention maintains the claimed levels of uniformity of content of active from the formation of the initial matrix through the final drying process, such that the pharmaceutical active varies by no more than 10% within a film lot, and by no more than 10% when sampled from different film lots.

The Examiner has cited several references, which will be discussed in further detail below. For ease of understanding, the Patentee will briefly discuss the primary cited references herein. During the discussion, it is important to keep in mind that statements from these sources regarding uniformity of content of components, especially actives, are not based on analytical chemical testing for the amount of active present in equally sized samples, but are at best assumptions, generally based on physically observable properties of the film in its intact state. The below discussion is supported by the Bogue Declaration and the Fuller Declaration.

VIII. The Claim Rejections.

The Examiner's rejection of the claims begins on page 7 of the Office Action.

A. Claims 1-299 were improperly rejected.

Claims 1-299 were rejected as allegedly anticipated under 35 U.S.C. §102(b), or, in the alternative under 35 U.S.C. § 103(a), as obvious over, each of the following references: Chen (WO 00/42992) ("Chen"), Staab (U.S. 5,393,528) ("Staab"), Le Person (*Chemical Engineering and Processing*, Vol. 37, pp. 257-263 (1998)) ("Le Person") and Horstmann (U.S.

5,629,003) ("Horstmann") or some combination thereof as set forth in the Office Action. These rejections relied on the Examiner's findings that material claim elements of the '080 Patent's only independent claims in reexamination, Claims 1, 82 and 161, were inherent in the cited references. Two limitations were of paramount importance, namely the limitations of "substantially uniform distribution of components" and of "locking-in or substantially preventing migration of" active.

Patentee maintains that the foregoing claim limitations are sufficent in themselves to establish patentability. Nevertheless, to advance prosecution, Patentee has explicitly added to all the independent claims herein presented specified levels of uniformity of content in the amount of active. Either a 10% limitation on the amount by which an active can vary between individual dosage units sampled from a particular film, and/or a 10% limitation by which the amount of active can vary from a desired amount among individual dosage units sampled from more than one film, which specificed levels of uniformity of content in the amount of active are not disclosed expressly nor are they inherent in the art of record. Patentee has also explicitly required manufacturing resulting pharmaceutical and/or bioactive active-containing films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units. Additional aspects not present in the art of record include, *inter alia*, viscosity ranges, controlled drying, conveying, applying air currents which have forces below the yield value of the polymer matrix during drying, forming a visco-elastic film in about 4 minutes, keeping the polymer matrix temperature below 100 °C, wherein resulting film has a water content of 10% or less. And the foregoing was just a partial listing of new claim elements. Hence, independent claims 1, 82 and 161, as amended, and all the new independent claims, claims 315-318, are not disclosed and/or made obvious, explictly or inherently, in the cited prior art.

The Examiner relies on the Declaration of Edward D. Cohen, Ph.D. under 37 C.F.R. § 1.132, dated September 6, 2012 ("Cohen Declaration) to support the assumption that it would be difficult for a person of ordinary skill in the thin film art not to obtain a film that has uniform content of active. Office Action, pp. 14 and 43. However, Dr. Cohen's assumption is dead wrong on its face or does not apply to the '080 Patent. Importantly, Dr. Cohen does not discuss

the degree of uniformity of content. He refers generally to "substantial uniformity of content of active" and "uniform content of active" per unit dosage. Cohen Declaration, ¶¶ 8-10. Dr. Cohen's statement about uniform content of active, without providing the degree of uniformity of content cannot be applied to the '080 Patent's invention. Especially now that the claims of the '080 Patent expressly require a degree of uniformity of content, namely, that uniformity of content of the resulting film(s) varies (i) no more than 10% with respect to the amount of active within a film (claims 1, 82, 161, 316-318) and/or (ii) no more than 10% from a desired amount with respect to the amount of active; said active sampled from different films in substantially equally sized individual dosage units sampled from different locations of the relevant film(s) (claim 315).

Moreover, as set forth in the Bogue Declaration, ¶¶ 4-11, 730 samples of individual dosage units, ten each from 73 separately manufactured lots of resulting films produced in accordance with Patentee's invention, were tested for active content. The results were that the active content of each individual dosage unit remained well within the control limits of 90% to 110% of the desired amount.

> "The results shown in the appendices establish that the resulting films produced by the inventive method of the '080 Patent as disclosed and claimed have the required uniformity of content based on analytical chemical testing. First, the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film. See Appendix A. Second, the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active. See Appendix B. Finally, the uniformity of content of the 73 lots of resulting film meets even more stringent standards, for example, the data shows: (i) 46 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 5%; (ii) 15 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 4%; 4 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 3%; and 1 lot of resulting film wherein the uniformity of content of active is shown with the amount of active varying by only 2%. See Appendix C.."
>
> Bogue Declaration, ¶ 11.

As noted, the FDA requires that the amount of active vary from dose to dose by no more than a prescribed percentage from the desired amount of active, essentially prescribing a degree

of uniformity of content in the amount of active which must be met. *See* Lin declaration, ¶¶ 9-16. Dr. Cohen provides no support for any prescribed degree of uniformity, and certainly not for the prescribed degree of uniformity of content in the amount of active explicitly recited by Patentee's claims under examination to meet commercial and/or regulatory requirements, or the degree of uniformity present in resulting films manufactured in accordance with Patentee's invention, as clearly demonstrated by the Bogue Declaration.

As held by the Court of Appeals for the Federal Circuit ("Federal Circuit") inherency requires much more than probabilities, possibilities, or for that matter assumptions. In *Crown Operations Intern., Ltd. V. Solutia Inc.*, 289 F.3d 1367 (Fed.Cir. 2002) ("*Crown*"), the patents at issue related to layered films used to create safety and solar control glass. The multi-layer film added properties to the glass assembly, such as impact resistance. An inner layer had solar control properties to reflect, absorb (and thus convert to heat), or transmit defined percentages of certain wavelengths of light. *Crown*, at 1370. The district court had held the only relevant independent claim of one of the patents, the '511 patent, not invalid on the grounds of anticipation and obviousness. It claimed a composite solar/safety film, comprised of a solar control film "wherein said solar control film contributes no more than about 2% visible reflectance". *Crown*, at 1372.

> "Crown [the declaratory judgment plaintiff] argued that U.S. Patent No. 4,017,661 to Gillery (the "Gillery patent") anticipates the '511 patent. The district court held otherwise, because, while the Gillery patent discloses the first three limitations of claim 1 of the '511 patent, it does not disclose the two percent visible reflectance limitation. The court found that neither the Gillery patent claims nor its description expressly disclose a two percent limit on reflectance contribution from the solar control film layer. Crown argued that the two percent limitation was inherently present in the Gillery patent's teachings because the Gillery patent disclosed an assembly with PVB layers, substrate layer, and substrate metal-coating — arguably of the same composition and thickness of the films disclosed by the '511 patent. Thus, Crown argued, because the structure, thickness and materials of the assembly were the same or within the same range(s), the Gillery patent must inherently disclose a two percent limitation. The district court rejected this argument because it found that none of the embodiments disclosed by the Gillery patent meet the two percent visible light reflectance limit."
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> *Crown*, at 1372.

The Federal Circuit, in upholding the decision of the District Court as well as the validity of the '511 patent, discussed the application of inherency to validity that is most relevant here.

> "Regarding alleged anticipation by the Gillery patent, on its face the Gillery patent does not disclose or discuss a two percent limitation for the reflectance contribution of the solar control film. Crown maintains that the '511 patent merely claims a preexisting property inherent in the structure disclosed in the prior art. Crown urges us to accept the proposition that if a prior art reference discloses the same structure as claimed by a patent, the resulting property, in this case, two percent solar control film reflectance, should be assumed. We decline to adopt this approach because this proposition is not in accordance with our cases on inherency. If the two percent reflectance limitation is inherently disclosed by the Gillery patent, it must be necessarily present and a person of ordinary skill in the art would recognize its presence. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed.Cir.1999); *Continental Can*, 948 F.2d at 1268, 20 USPQ2d at 1749. **Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient**." *Id.* at 1269, 20 USPQ2d at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981)) (emphasis supplied)."

The alleged inherency of the art cited by the Examiner and discussed below has not been established other than by statements of probabilities and/or possibilities and/or just statements that things are uniform without providing any degree of uniformity that must be present. For example, the assumption that by starting with so-called "uniform" mix of materials, stirring them, then casting and drying as alleged to be disclosed in the prior art is insufficient to establish inherency. Again, inherency requires that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. Importantly, the mere possibility that some of the films produced as disclosed by the art cited might result in some type of "uniform" film is not sufficent.

1. Chen's alleged inherency.

> "The claimed "substantially uniform distribution of components" and "locking-in or substantially preventing migration" of the active in independent claims 1, 82 and 161, and the variation of active content of 10% or less in dependent claims 254-255,272-273 and 290-291, are inherent in Chen's exemplified films and process. Inherency is based on the following: As discussed above, Chen uses the

> same materials and method as here claimed. Chen's ingredients are mixed until they are uniformly dispersed or dissolved in the hydrocolloid (p. 17, lines 8-11). Chen uses the same criteria discussed above with respect to the '080 patent in the Scope of Claims section for evaluation of substantial uniform distribution, i.e., weight of dosages and visual inspection."
>
> Office Action, p. 13.

The criteria used by Chen as cited by the Examiner for evaluation of "substantial uniform distribution" are physical observations. Such "observations" cannot be used, either inherently or otherwise, to establish the uniformity of content in the actual amount of active in equally sized samples in Chen's examples. Absent statements or data based on analytical chemical testing, not weighing or visual inspection, for the amount of active present in the film, Chen does not and cannot inherently disclose Patentee's resulting film having the claimed levels of uniformity of content. Moreover, even if Chen disclosed, which it does not, the use of the same materials and methods as the '080 Patent, the mere fact that a certain thing may result from a given set of circumstances is not sufficient to support inherency. *Crown, supra*, at 1378.

Moreover, Third Party Requester has not provided any proof that Chen's process examples when followed exactly, with all the components exactly as listed, and all other conditions of Chen exactly met, will provide a process suitable for commercial manufacture, a process which produces products which are regulatory approvable by the FDA, and which exhibit the levels of uniformity of content in actual amount of active claimed by Patentee's processes. Indeed, FIG. 5 of Chen describes a release profile of almost 120% of active from a film, which certainly exceeds the levels of uniformity of content in the amount of active that Patentee claims. This single active content result voids all claims to Chen's alleged inherency regarding same.

> "Finally, Chen's patent discloses the release profiles of four active agents from films. See Chen, Figure 5. The release profile data presented in Figure 5 show a high degree of variability at each data point. For example, the release profile for nicotine containing film product show that the amount of nicotine released at the 5 minute and 8 minute time point can be as high as approximately 115-120%. This level of active agent is greater than the 110% level (from an expected amount of 100%) that is considered acceptable to FDA for regulatory approval of a product that purports to be manufactured consistently with acceptable content uniformity. These data indicate that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity

between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film."

Lin Declaration, ¶ 22.

The Examiner states that the films made in accordance with the claims as issued are inherent in Chen. This conclusion is based on the belief that Chen uses the "same materials and method" as the Patentee, but even if true, much more is required. Patentee respectfully submits that this conclusion is incorrect, and particularly incorrect in light of the claims as amended. The Examiner erroneously states that Chen "uses the same criteria" as the '080 Patent that issued in evaluating substantial uniform distribution, i.e. weights of dosages and visual inspection." Although, a number of ways to test films in the patent are disclosed, in order to test content uniformity of an FDA regulated film product, it is necessary to assay using analytical chemical tests for drug or therapeutic active content of unit film doses. *See*, Lin declaration, ¶¶ 9-16. This is necessary to ensure the amount of active is within acceptable guidelines. Visual observation and physical measurements such as weight is insufficient to determine the active amount in equally sized dosage units at the level of uniformity of content required.

All of Patentees' claims now require analytical chemical testing and that the films have levels of uniformity in the amount of active which varies by no more than 10% from film to film and/or no more than 10% from a desired amount across several films. The Examiner's assumption that visual inspection and weight measurements establish these levels of uniformity of content in and by themselves is therefore incorrect, in so far at least as is required by the FDA, for example. Moreover, "Chen's disclosure is lacking, both explicitly and inherently, the disclosure necessary to provide for the manufacture of drug-containing films with the uniformity of content in amount of drug (active) in individual dosage units to make FDA approvable film products." Lin Declaration, ¶ 21.

Finally, there is a misplaced reliance on the physical terms "glossy" and "transparent" in the Office Action, which the Examiner use to establish the presence of "uniformity" in Chen's films. However, the term "glossy" is purely a visual characteristic ("surface luster or brightness") and is not interchangeable with nor equivalent to the uniformity of content of components of a film, nor the content uniformity of an active in the film. *See,* www.merriam-

webster.com/dictionary/glossy. It is also not interchangeable with specified levels of uniformity of content in amount of active in individual dosage units sampled from a film or sampled from different films. The term transparent is also a purely visual appearance characteristic ("transmitting light without appreciable scattering …"). *See,* www. merriam-webster.com/ dictionary/transparent. It is not indicative of the uniformity of content of the film. As such, Chen can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

2. Staab's alleged inherency.

> "Staab also discloses that "[t]he device of the invention thus is composed of a biologically-compatible material that has been blended homogeneously" with the drug (see col. 6, lines 5-10). In the Example at cols. 11-12, Staab prepares a four-foot wide film which is then cut into two inch by two inch films each weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (see col. 11, line 52 through col. 12, line 3). Accordingly, Staab's films inherently have the instantly claimed substantially uniform distribution of components and active. Also, in view of the fact that each film contains 19 mg of benzalkonium chloride and in view of said homogeneous blending, the variation of active in the dosage units is 0% (*sic* 10%), as per claims 254, 255, 272, 273, 290 and 291."
>
> Office Action, p. 29.
>
> "In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Staab uses the same hydrocolloid as in the '080 patent, i.e. said HPMC. Accordingly, Staab's film in the Example at cols. 11-12 is inherently viscoelastic before drying. Accordingly, after drying for about 10 minutes, a viscoelastic film having less water that before drying is formed."
>
> Office Action, p. 30.
>
> "While Staab does not discuss viscoelasticity or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the active, Staab, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process."
>
> Office Action, p. 31.

Again, as with Chen, absent statements based on testing to determine the actual uniformity of content in the amount of active present in the film, so as to meet FDA approval, Staab does not and cannot inherently disclose Patentee's resulting film having the claimed levels of uniformity of content, with respect to the amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film and/or of different resulting films. Staab does not and cannot inherently form a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content within the recited levels of uniformity of content.

Moreover, even if Staab disclosed, which it does not, the use of the same materials and methods as the '080 Patent, the mere fact that a certain thing may result from a given set of circumstances is not sufficient to support inherency. *Crown, supra*, at 1378. Moreover, Staab just states that there is 19 mg of benzalkonium chloride present in each sample weighing 190 mg. However, Staab does not disclose testing to determine the amount of benzalkonium chloride present in the final film product or even how each and every sample turned out to be 19 mg. Staab, col. 11, l. 35 - col. 12, l. 3. Staab's resulting structure is a foam rather than the recited visco-elastic film formed within 4 minutes and Staab also would not inherently have the recited degree of uniformity of amount of active in substantially equal sized dosage units. Moreover, Staab starts with a composition having 10% by weight of benzalkonium chloride (50% aqueous) yet allegedly obtains a resulting film with 19 mg benzalkonium chloride in a 190 mg film, to once again obtain a 10% benzalkonium chloride resulting composition. A perfect yield must must always be considered suspect. Inherency should never be based on a suspect disclosure. As such, Staab can neither anticipate, explicitly nor inherently, nor make obvious the '080 Patent claims, see discussion below.

3. Le Person's alleged inherency.

> "Le Person discloses that after 5 min of the drying, 'the polymeric network is not turgescent and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [i.e., pharmaceutical or drug] when the system reequilibrates.' (See p. 262, col. 2, third full paragraph.) Le Person also teaches that '[b]etween the 5th and 10th min of drying the heavy solvent migrates... active substance, slowed down in its migration, stays in the bottom of the layer.' (See the

> last four lines at page 262, col. 2). It is noted that the heavy solvent only accounts for 2% of the wet composition of the coating (see page 258, Table 1). As such, within 5-10 minutes, the solvent has been sufficiently evaporated such that, inherently, a substantial uniform distribution of the active is locked-in and migration is substantially prevented within the film, as here claimed. The active material homogenizes and a quasi-equilibrium is obtained for the components of the Page 38 active phase, taking into account evaporation of the heavy solvent (p. 263, col. 1, lines 8-13), and thus, there is a variation of active content of less than 10%, as per claims 272, 273, 290 and 291.
>
> Office Action, pp. 37-38.
>
> "While Le Person does not discuss viscoelasticity or that the films in its process have a 'substantially uniform distribution of components' or disclose 'locking-in or substantially preventing migration' of the active, Le Person, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 82, 89-91,161,171-173, 272-274 and 290-292, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a)."
>
> Office Action, p. 38.

Le Person is entirely devoid of any details with respect to its process and materials. For example, nowhere does Le Person discuss what type of acrylic polymer he uses nor the molecular weight of the polymer. Thus, Le Person allows for materials which may have such a low molecular weight that forming a visco-elastic film may not be possible. Moreover, Le Person lacks sufficient enabling disclosure to be an effective reference as applied in view of the amended claims. Such deficiencies cannot be used in support of an inherency argument. Again, absent statements and data based on testing for the amount of active present in the film with results establishing a substantial uniformity of content at the claimed levels and suitable for FDA approval, Le Person does not and cannot inherently disclose Patentee's resulting film. Moreover, Le Person does not and cannot inherently form a viscoelastic film in about 4 minutes which locks-in the claimed uniformity of content in the amount of active.

Le Person discloses very little about the acrylic polymer, such as the molecular weight. If the molecular weight was low enough it may not become a viscoelastic material. Patentee asks, how could Le Person anticipate and/or make obvious the '080 Patent which is directed to the commercial manufacture of a regulatory approvable resulting film meeting required specified

levels of uniformity of content in the amount of the active, where Le Person's goal, as noted in its abstract, was devoted to determining "cases of maldistribution of the active substance," in connection with different drying methods, and not to providing a process for manufacturing films with uniformity of content of the desired amount of an active. Importantly, Patentee has added several additional process steps not in the prior art. These new process steps present in the amended independent claim, as well as the new independent claims, further distance Patentee's patent from the prior art. As such, Le Person can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

4. Horstmann's alleged inherency.

> "The claimed substantially uniform distribution of components and active, and locking-in or substantially preventing migration of active, and the variance of active content of 10% or less in dependent claims 254, 272 and 290 are also inherent in Horstmann's Examples 1, 3 and 4. In particular, Horstmann's films before drying are described as being uniform and homogeneous (see col. .3, line 11-19, 29-34 and 37-41; col. 5, lines 1 and 50), and as noted above, Horstmann uses the same components and process steps as here claimed. The '080 patent notes that Horstmann addressed the problem of self-aggregation and nonuniformity by increasing the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film (see col. 2, line 60 through col. 3, line 1).
>
> Office Action, p. 43.
>
> "While Horstmann does not discuss viscoelasticity, water content of its dried films or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the, active, Horstmann, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 1, 5,7-10,12-1423,63,64,82,84,86-89,91-93,102,142,143,161, 166, 168-171, 173-175, 184,224,225,249,254,267,272,285 and 290, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a)."
>
> Office Action, pp. 43-44.

Horstmann forms a gel, rather than a solid film as in the present invention. Thus the gel rheological properties of Horstmann are very different than a solid visco-elastic film having a

water content of 10% or less. Moreover, Horstmann specifically teaches protecting the gels from drying up by placing the cut out gel shapes in a water vapor impermeable sealing material. See Horstmann, col. 5, ll. 11-13. This is a direct teaching away from drying to a water content of 10% or less. Horstmann at col. 2, ll. 25-29, suggests drying may not be necessary.

Again, absent statements based on testing for the amount of active present in the film with results establishing a the claimed levels of uniformity of content in the amount of active, suitable for FDA approval, Horstmann does not and cannot inherently disclose Patentee's resulting film claiming the specified levels of uniformity of content in the amount of active.

Additionally, as the Examiner admits, Horstmann discloses only that its film is alleged to be uniform at a point prior to drying. Horstmann, col. 3, ll. 37-41. Horstmann says nothing about the uniformity of the product during or after drying. Again, *Crown* holds that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* A disclosure of some unspecified degree of uniformity of a film prior to drying in Horstmann does not establish that the product after drying is uniform, let alone the degree of uniformity as claimed by the '080 Patent. As noted throughout the '080 Patent, controlled drying is required for ensuring the claimed levels of uniformity of content. As such, Horstmann can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

Importantly, Patentee has added several additional process steps also not in the prior art. See above. These new process steps present in the amended independent claims, as well as the new independent claims, further distance Patentee's patent from the prior art, by negating any anticipation and obviousness assertions. Even without the additional process steps, even if it were possible that a resulting film with the proper levels of uniformity of content in the amount of active might possibly result from some manipulations of the disclosures given in any of Chen, Staab, Le Person and/or Horstmann, it is incorrect to rely on these references in an attempt to show they inherently disclosed Patentee's resulting film. See *Crown*, at 1377-1378, *supra*.

As the absence of inherency in and of itself removes Chen, Staab, Le Person and Horstmann as viable prior art for rejecting Patentee's claims under 35 U.S.C. § 102, the Examiner should withdraw his rejections of Patentee's claims 1, 82 and 161 based on same. For the same reasons new independent claims 315-318 are allowable. Moreover, these references for

the same reasons discussed above, as well as the reason discussed below, do not support any finding of obviousness, and thus the rejections of claims 1, 82, and 161 based on 35 U.S.C. § 103 should be withdrawn as well. For the same reasons new independent claims 315-318 are not obvious in light of the prior art. Finally, Patentee's claims 2 through 81, 83 through 160, 162 through 299 and 300 through 314 as they depend from independent claims 1, 82, 161 should all be allowed as well, with any rejections withdrawn.

B. Third Party Requester's Wherein Argument is Wrong

Patentee finds it necessary to address Third Party Requester's attempt to vitiate the '080 Patent's claim language beginning with "wherein". Third Party Requester cites to the Federal Circuit for the premise that "a whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." *Minton v. Nat'l Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed.Cir.2003). Third Party Requester's Request for Inter Partes Reexamination ("The Request"), p. 16.

However, the Federal Circuit has also strongly held that "when the 'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." *Hoffer v. Microsoft Corp.*, 405 F. 3d 1326, 1329 (Fed. Cir. 2005). Essentially, Requester proposes that with elimination of the "whereby" clauses, the claims 1, 82 and 161 (before the amendments herein) would not require "wherein said resulting film has a water content of 10% or less and said uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained." The Request, p. 20.

As noted above, "when the whereby clause states a condition that is material to patentability, it cannot be ignored to change the substance of the invention." *Hoffer v. Microsoft Corp.*, 405 F.3d 1326 (Fed. Cir. 2005); *see also Fantasy Sports Properties, Inc. v. Sportsline.com, Inc.*, 287 F.3d 1108, 1111-16 (Fed. Cir. 2002); *Griffin v. Bertina*, 285 F.3d 1029, 1034 (Fed. Cir. 2002). In *Griffin*, for example, the court found that "wherein" clauses were claim limitations "because they relate back to and clarify what is required by the count. Each 'wherein' clause ... expresses the inventive discovery [and] ... elaborates the meaning of the preamble." *Griffin*, 285 F. 3d at 1033-34. Further, "the allegedly inherent properties of the 'wherein clauses' provide the necessary purpose to the steps." *Id.* See also, MPEP, § 2111.04.

The '080 Patent independent claims' wherein clause limitations cannot be disregarded. The '080 Patent claims processes for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films. The ability to make such films with the required level of uniformity in content of active is the essence of Patentee's invention. Thus, such wherein clauses which express the inventive discovery and elaborates the meaning of the preamble cannot be ignored for purposes of patentability.

Finally, Third Party Requester has made many allegations about the '080 Patent and its specifications and claims, and the prior art in The Request. Patent owner believes that the amendments to claims 1, 82 and 161 herein clarifying the scope of same and thereby advancing the prosecution of same, obviate the need to address Third Party Requester's allegations or the Examiner's statements made without the benefit of the amendments. Nevertheless, to the extent that any are not explicitly addressed herein, Patentee hereby asserts they are wrong and unsupported in either fact or law.

C. Claims 1, 4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84,87-97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-262, 264, 265, 267-280, 282, 283 and 285-299 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chen.
Claims 2, 3, 6, 7, 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 85, 86, 98, 112, 114, 120-122, 127-129, 131, 134-137, 139, 140, 167, 168, 180, 194, 196, 202-204, 209-211, 213, 216-219, 221, 222, 245, 248, 263, 266, 281 and 284 were rejected under 35 U.S.C. 103(a) as being unpatentable over Chen.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Chen, WO 00/42992 ("Chen") or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Chen. Patentee incorporates its previous discussions in sections A. and B. above. Chen is a primary reference relied upon by the Examiner in the Office Action. Patentee

respectfully traverses the above rejections on the basis, among others, that Chen does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of a lot of the resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Chen also fails to disclose, explicitly or inherently, the additional elements found in Claim 317. Claim 317 generally adds, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Chen discloses two methods of forming a film product, a solvent casting method and an extrusion method. The extrusion method does not rely upon putting a hydrocolloid in a solvent, nor does the extrusion method use a drying oven and is apparently preferred by Chen over the solvent method. Chen, page 15, lines 9-21. In the solvent casting method, Chen states that a hydrocolloid is dissolved or dispersed in water, and mixed to form a homogeneous solution. The active agent and other ingredients may be added and dispersed or dissolved uniformly in the hydrocolloid solution. The coating solution with a solid content of 5-50% and a viscosity of 500-15000cps is degassed and coated onto a polyester film and "dried under aeration" at a temperature between 40-100°C to avoid destabilizing the agents. Chen, p. 15, ll. 19- 29. The dry

film formed by this process is described to be a "glossy, stand alone, self supporting, non-tacky and flexible film". Chen, p. 15, ll. 30-31. These very general statements are all that are given by Chen as to the formation and drying of Chen's film product. These statements cannot support either anticipation or obviousness rejections.

Chen's drying process is so general and devoid of detail so as to provide no guidance other than that to dry, one places a film in a conventional hot air circulating oven at temperatures of from 40-100°C and leaves it for a period of time. Chen does not disclose any other drying methods beyond drying "under aeration", nor does Chen disclose any controlled drying processes whatsoever. Chen showed no recognition of the complexities involved in the commercial manufacturing of films, as Chen's focus relates solely to the ingredients and mechanical properties, not the process. Without any recognition of the problems, and without any appreciation of the difficulties in preventing the settling, migration and/or aggregation or agglomeration of active(s) in the cast flowable mass, Chen neither sought nor found the solution to creating commercial scale films having uniformity of content of pharmaceutical and bioactive actives per individual dosage unit and meet FDA requirements regarding same. Chen lacks substantial disclosure in view of the '080 Patent. Among its deficiencies, Chen lacks any disclosure as to specific processing means (beyond generally drying in a generic oven) or the formation of a visco-elastic film state. Chen only discloses the apparent homogeneity of a blended matrix, and this is prior to the addition of actives. There is no disclosure or suggestion as to how to create a substantially uniform distribution of the pharmaceutical or biological active in the blended matrix and then cast that matrix to maintain uniformity, and then control drying through among other processes conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to rapidly form a visco-elastic film having said pharmaceutical active uniformly distributed throughout by rapidly increasing the viscosity of said polymer matrix upon initiation of drying within about the first 4 to maintain said uniform distribution of said pharmaceutical or biological active by locking-in or substantially preventing migration of said pharmaceutical active within said visco-elastic film and then test it to establish the substantially uniform distribution of pharmaceutical or biological active content, in compliance with FDA regulations.

Among other things, the '080 Patent claims are directed to locking-in an active such as a pharmaceutical or biological active, by controlling drying to form a viscoelastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes. The Examiner has stated in the Reexamination, Reasons for Patentability/ Confirmation ("RFP/C"), in connection with both the '292 Patent and the '891 Patent reexaminations that "Chen does not discuss what happens within the first 4 minutes of drying." Moreover, in the '891 Patent RFP/C the Examiner goes on to state that: "Chen does not discuss uniformity of pharmaceutical or biological active components in its doses. Table 4 of Chen gives the grams per unit dosage film and density for Example 1 with standard deviation based on three or four measurements, but does not give compositional uniformity." Additionally, Chen's Example 1 contains only food flavorings and a sweetener.

Chen does not disclose that the resulting products are compositionally uniform, but only that they are "glossy". As stated above, glossy does not imply or establish compositionally uniformity. In fact, Chen's Figure 5 (Examples 5-8) clearly shows a lack of compositional uniformity of active. Although statistics are not defined in the text, the error bars represent either high or low values, standard deviation or some measure of variation. Given that the compositions of Examples 5-8 are the same, except for the amount of active, it is reasonable to conclude that the active is not uniformly present in the individual films due to the wide variation of release of active from the same film compositions. For example, with regard to the release of nicotine in the same film compositions, the release reaches in excess of 118%. Certainly there is neither disclosure of, nor inherency in, the that the level uniformity of content in the amount of active as sampled in individual dosage units of the same film be 10% or less. "The release profile data presented in Figure 5 show a high degree of variability at each data point. This indicates that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film." Lin Declaration, ¶ 22.

As defined in the specification for the '080 Patent as filed, a visco-elastic solid is one that has been sufficiently dried to lock its active components into a substantially uniform distribution throughout the film. The '080 Patent claims require that this be done within about the first 4

minutes or less. The Examiner has previously acknowledged that Chen does not disclose that the resulting film product has any compositional uniformity of pharmaceutical or biological active at that point in time. See '891 Patent RFP/C. Neither Chen nor the other references teach this step.

As explained throughout the '080 Patent and as summarized above, the present invention is based upon the discovery that certain process parameters, such as, viscosity and controlled drying methods to avoid non-uniformity of content in the amount of active must be employed to provide a commercially and FDA viable film product. Chen does not disclose or suggest such a resulting product. *See* Lin Declaration, ¶¶ 17-22. Chen discloses that various components (absent the active) are combined and that the mixture is blended to form a "uniform" solution. (Chen, p. 20, ll. 19-20). although even the formation of a uniform solution in a blender is beneficial, it is not the end of the process by any means. Further, as explained above, conventional drying methods do not inherently provide uniform films and, in fact, would not be expected to provide resulting films having the claimed uniformity of content in the amount of active.

Patentee's claimed processes are not present in Chen, either expressly or inherently, and Chen cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited Chen reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Chen does not render obvious the pending claims .

D. Claims 2, 3, 16, 32, 55, 72-81, 95, 111, 134, 151-160, 177, 193, 216 and 233-242 were rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teaching of Chen and Staab.

The Office Action rejected the above claims under 35 U.S.C. § 103(a), as being unpatentable over the combined teaching of Chen and Staab, U.S. 5,393,528 ("Staab"). Patentee incorporates its previous discussions in sections A., B. and C., above, and E., below and traverses all said rejections thereon. As all the above claims depend from one of the independent claims, claims 1, 82 and 161, they are allowable for all the reasons provided in the sections dealing with Chen, above, and Staab, below and even combined Chen and Staab do not render obvious the pending claims of this rejection.

E. Claims 1-5, 10, 12-16, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78- 84, 89, 91-95, 100, 103, 104,111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171,173-177,182,185,186,193,205-207,215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Staab.
Claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 were rejected under 35 U.S.C. 103(a) as being unpatentable over Staab.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Staab, or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Staab. Patentee incorporates its previous discussions in sections A., B., C. and D., above, Patentee respectfully traverses the rejection on the basis, among others, that Staab does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the pharmaceutical and/or bioactive active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of one lot of the resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Staab certainly does not disclose, explicitly or inherently, the additional claim elements of Claim 317. Claim 317 generally adds to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising

drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Moreover, Staab teaches the benefits of using a "gas foamed film" or films. Staab, col. 5, ll.33-35; col. 8, ll. 33. Staab thus teaches away from the '080 Patent by teaching that air bubbles are necessary, which are contraindicated in Patentee's invention requiring a substantially uniform distribution of active. Staab instead teaches that gas bubbles must be added to the polymer/drug mixture prior to casting.

> "It should be noted that heretofore, the significance of the addition of gases in the formation of the film to alter the texture and solubility of the film has not been recognized."
> Staab, col. 3, ll. 15-20.

> "**The fine tuning of dissolution rates and delivery of agent material, by the addition of gases and by altering the grades or mixtures of polymer materials or layers, is an important aspect of the present invention.**
>
> * * * *
>
> **"The gases, for example, air or nitrogen are introduced near the point of application of the liquid polymer material to the stainless steel casting sheet. The gases are added in a closed system by mixing with whipping blades or a motor driven homogenizer to homogenize the mixture of polymer, active material and gas to form a frothy foam. The final mixture then sets up or gels as a foam.** It is also possible to pour the frothy foam mixture into a mold. The mold is then deformed and the formed device such as a diaphragm, is removed."
> Staab, col. 8, ll. 29-64 (emphasis supplied).

In direct conflict with Staab's teaching, the '080 Patent teaches the use of anti-foaming agents to **prevent** gas bubble formation and thereby promote uniformity. Importantly, Patentee's processes, in many cases, avoid the formation of bubbles, without the need to use anti-foaming agents.

> **" Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product."**
>
> '080 Patent, col. 4, ll. 5-21 (emphasis supplied).

> "A number of techniques may be employed in the mixing stage to **prevent bubble inclusions in the final film. To provide a composition mixture with**

substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed.."

'080 Patent, col. 9, ll. 56-65 (emphasis supplied).

See also section of '080 Patent entitled "Anti-foaming and De-foaming Compositions" ('080 Patent, col. 22, l. 47 through col. 23, l. 53).

Staab addresses the fine tuning of dissolution rates and delivery of active agent, by teaching the addition of gases as an important aspect of his invention (Staab, col. 8, ll. 30-34). Staab is silent with respect to the recited levels of uniformity of content. The '080 Patent in connection with achieving uniformity of content in the amount of active teaches avoiding bubble formation and the removal of such gases and bubbles ('080 Patent, col. 9, ll. 56-65). Moreover, Staab uses conventional drying (Staab, col. 11, ll. 64-65) rather than the particular drying methods used to ensure the uniformity of content claimed by the '080 Patent.

The presently claimed process is not disclosed in Staab, either expressly or inherently, and Staab does not anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Staab does not render obvious the pending claims of the above rejections.

F. Claims 82, 89-91, 161, 171-173, 272-274 and 290-292 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Le Person.
Claims 92 and 174 were rejected under 35 U.S.C. 103(a) as being unpatentable over Le Person.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Le Person, Chemical Engineering and Processing, Vol. 37, pp. 257-263 (1998) ("Le Person") or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Le Person. Patentee incorporates its previous discussions in sections A., B., C., D. and E., above, Patentee respectfully traverses the rejection on the basis, among others, that Le Person does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by

locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of one lot of resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Le Person certainly does not disclose, either explicitly or inherently, the additional claim elements found in Claim 317. Claim 317 generally adds to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Le Person does disclose that the drying step used plays a role in the final product, but fails to disclose or suggest how to achieve a uniform final product. In fact, Le Person discloses methods that result in a non-uniform product prior to and at 10 minutes. According to Le Person, the resulting product dried in 9 minutes would not have claimed uniformity of content of active.

Le Person's goal was to determine "cases of maldistribution of the active substance," in connection with different drying methods, said maldistribution having consequences on storage and delivery of a drug and proposes the use of Laser Scanning Confocal Microscopy on the active substance and the heavy solvent to determine same. (Le Person, Abstract). Le Person acknowledges that in the formation of a film product, "drying is the essential unit operation necessary to form the final product." (Le Person, p. 257). Le Person's experimental set-up was composed of two parts, "the drying cell and the wind tunnel. . . . [wherein] the wind tunnel is a conventional drying rig. . . ." Le Person, p. 258, col. 2 & Fig. 1. Le Person's disclosure of the

use of a wind tunnel further negates any argument that Le Place inherently anticipates or makes obvious Patentee's invention.

It is important to note that Le Person simply recognized the overall, general difficulty in obtaining films with a substantially uniform distribution of active. Le Person did not try to solve this problem, only to determine means to identify it. Thus, Le Person did not recognize the specific reasons therefor, nor did Le Person recognize the solutions needed to overcome this difficulty. Le Person's goal was to find ways to best determine whether or not there was homogeneity of film product.

However, the point of Le Person is that, in the time period (i.e., less than 10 minutes), there is non-uniformity of the product. Le Person even states that "intense moisture removal through the exposed surface of the layer to the radiation, during the first 3 min of drying (Le Person, Fig. 7) produces a stress on the polymer skeleton … and as a result the acrylic polymer becomes more and more dense in the upper part of the layer (exposed surface)." (Le Person, p. 261). As a result, this "intense" shrinkage results in displacement of the active phase. As such, Le Person's disclosure is not directed towards achievement of a film having a substantially uniform distribution of an active through drying, and in fact, if anything, teaches away from achieving uniformity of content in the amount of an active.

The presently claimed processes are not present in Le Person, either expressly or inherently, and Le Person does not anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Le Person does not render obvious the pending claims.

G. Claims 1, 5, 7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166, 168-171, 173-175, 184, 224, 225, 249, 254, 267, 272, 285 and 290 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hortsmann.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Horstman, et al. U.S. 5,629,003 ("Horstmann") or, in the alternative under 35 U.S.C. § 103(a), as obvious over Horstmann. Patentee incorporates its previous discussions in sections A., B., C., D., E. and F., above, Patentee respectfully traverses the rejection on the basis, among

others, that Horstmann does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film, by no more than 10% from the desired amount across different resulting films, and is in compliance with FDA regulations governing same.

Horstmann certainly does not disclose, either explicitly or inherently, the additional claime elements of Claim 317. Claim 317 generally adds to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Moreover, the '080 Patent's description of the differences between Horstmann and Patentee's invention claimed in the '080 Patent is relevant to the Examiner's current rejections as well. For example:

> "In one attempt to overcome non-uniformity, U.S. Pat. No. 5,629,003 to Horstmann . . . incorporated additional ingredients, i.e. gel formers and polyhydric alcohols respectively, to increase the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film. These methods have the disadvantage of requiring additional components, which translates to additional cost and manufacturing steps. Furthermore, both methods employ the use the conventional time-consuming drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other

such drying equipment. The long length of drying time aids in promoting the aggregation of the active and other adjuvant, notwithstanding the use of viscosity modifiers. " '080 Patent, col. 2, l. 63 to col. 3, l. 9.

Horstmann's use of conventional drying methods and need for gel formers teaches away from obtaining a resulting film with the desired levels of uniformity of content in the amount of active. Horstmann does not disclose the degree of uniformity of content, merely, for example, in Example 2, referring to film sections containing "approximately" 3 mg of active and a weight of "approximately" 80 mg. Horstmann, col. 5, ll. 15-36. Horstmann does not disclose that these amounts are based on any testing, or for that matter what they are based upon, or that they comply with FDA requirements relating to drug products.

The presently claimed process is not present in Horstmann, either expressly or inherently, and Horstmann cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Horstmann does not render obvious the pending claims.

IX. Conclusion

No reference, either alone or in combination with other references, teaches the processes claimed by the '080 Patent. Entry of the amendments herein is respectfully requested. Patentee traverses all rejections of its claims. For at least the reasons set forth above, independent claims 1, 82, 161, and 315-318 are allowable. Claims 2 - 81, 83 - 160, 162 - 314 are allowable at least based on their dependencies, whether direct or indirect, from independent Claims 1, 82, 161 . Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejections to same. Should the Examiner have any questions regarding this response, the undersigned would be pleased to address them.

Respectfully submitted,

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CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **REPLY BY PATENTEE TO A NON-FINAL OFFICE ACTION PURSUANT TO 37 C.F.R. §1.111** has been served, by first class mail, on March 13, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

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EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	March 13, 2013	M&E Docket:	117744-00023

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Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on
March 13, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, B. Arlie Bogue, Ph.D., do hereby make the following declaration:

I. Technical Background

1. I have worked in the field of pharmaceutical development, and particularly oral dosage form development, for 22 years. I am employed by MonoSol Rx, LLC. ("Patentee" and/or "MonoSol"), the assignee of issued patent U.S. 7,897,080 ("the '080 Patent"), as Senior Director for Manufacturing Strategy and Innovation.

2. I have a BS in Physical Chemistry from Colorado State University and a Ph.D. in Chemical and BioEngineering from Arizona State University. I have participated in postdoctoral studies in Biochemical Engineering at the University of Virginia. During my career, I have been named as an inventor on over 23 U.S. patents and numerous foreign patents directed to the formulation,

processing and/or packaging of pharmaceutical oral disintegrating unit doses (tablets and film strips). I have direct experience with the commercial scale processing of pharmaceutical film systems as well as an understanding of the uniformity of content of active and methods for testing the same.

3. I have read the '080 Patent and the Office Action issued on November 29, 2012 in the reexamination of the '080 Patent ("Office Action") and the references cited therein, and I have also reviewed the amendment as to the independent claims set forth in Patentee's Reply to the Office Action concurrently filed herewith.

II. Producing resulting films in accordance with the '080 Patent

4. Each of the 73 lots of resulting films (Lots 1-73) containing approximately 2,000,000 individual dosage units per lot discussed herein were manufactured: (i) for commercial use and regulatory approval; (ii) in compliance with U.S Food and Drug Administration ("FDA") standards and regulations, including those relating to analytical chemical testing for variation in active in individual dosage units; and (iii) in accordance with the invention disclosed in the '080 Patent, and as claimed by the '080 Patent both as issued and as amended in the Patentee's Reply to the Office Action; by:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a pharmaceutical active, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less;

(d) forming the resulting pharmaceutical film from said visco-elastic film, wherein said resulting pharmaceutical film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting pharmaceutical film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting pharmaceutical film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10%, [see Appendix A] said resulting pharmaceutical film suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

5. Additionally, the uniformity of content in the amount of active as sampled from the 73 lots of resulting film varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests from 4(e) above. [See Appendix B]

III. Analytical Chemical Testing for Uniformity of Content of Patentee's Resulting Films

6. To demonstrate the uniformity of individual dosage unit films, I compiled individual dosage unit assay data for individual Lots 1- 73, all of which were disclosed in MonoSol's 2012 Annual Product Review to the FDA.

7. Ten (10) individual dosage units all having the same dimensions were cut out from different locations of each of the 73 lots of resulting films using a commercial packaging machine, thus providing 730 randomly sampled individual dosage units, ten each from the 73 separate lots. All samples were analyzed by a validated method, in compliance with FDA guidelines and regulations regarding same, using analytical chemical testing, in which the pharmaceutical active

was extracted and analyzed by High Performance Liquid Chromatography (HPLC) against an external standard to quantify the amount of active present in each individual dosage unit.

8. According to the inventive process set forth and claimed in the '080 Patent, and in accordance with FDA nomenclature, I have prepared tables shown as Appendices A, B and C, reflecting the uniformity of content of active of individual dosage units within particular lots and across different lots.

9. First, the uniformity of content of active in a lot is determined through establishing the amount of active ($A_{N(i)}$) actually present in each sampled individual dosage unit from the same lot (N) as determined by taking the difference between the amount of active in the sample with the most active ($Max_{LOT(N)}$) minus the amount of active in the sample with the least amount of active ($Min_{LOT(N)}$) and dividing the difference by the average amount of active in the lot samples ($Lot_{(N)}$ Sample Average). That is: $(Max_{LOT(N} - Min_{LOT(N)}) / ((A_{N(1)} + A_{N(2)} + + + A_{N(10)})/10)$. The results are shown in Appendix A.

10. Second, the uniformity of content across different lots is determined through establishing the amount of active actually present in each sampled individual dosage unit from all 73 lots and comparing that amount of active with a "target" or "desired" amount of active contained therein. The target amount of active, when it is a pharmaceutical, is referred to as the "Label Claim", thus identifying the amount of pharmaceutical active in the film to a user. The desired amount is 100% of the target amount. Each individual dosage unit film cut from any individual lot must have the desired content of pharmaceutical active, varying no more that 10% from the target or desired amount. See Appendix B.

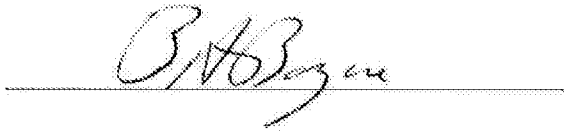
IV. '080 Patent Process Produces Films With Required Uniformity of Content of Active

11. The results shown in the appendices establish that the resulting films produced by the inventive method of the '080 Patent as disclosed and claimed have the required uniformity of content based on analytical chemical testing. First, the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film. See Appendix A.

Second, the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active. See Appendix B. Finally, the uniformity of content of the 73 lots of resulting film meets even more stringent standards, for example, the data shows: (i) 46 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 5%; (ii) 15 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 4%; 4 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 3%; and 1 lot of resulting film wherein the uniformity of content of active is shown with the amount of active varying by only 2%. See Appendix C.

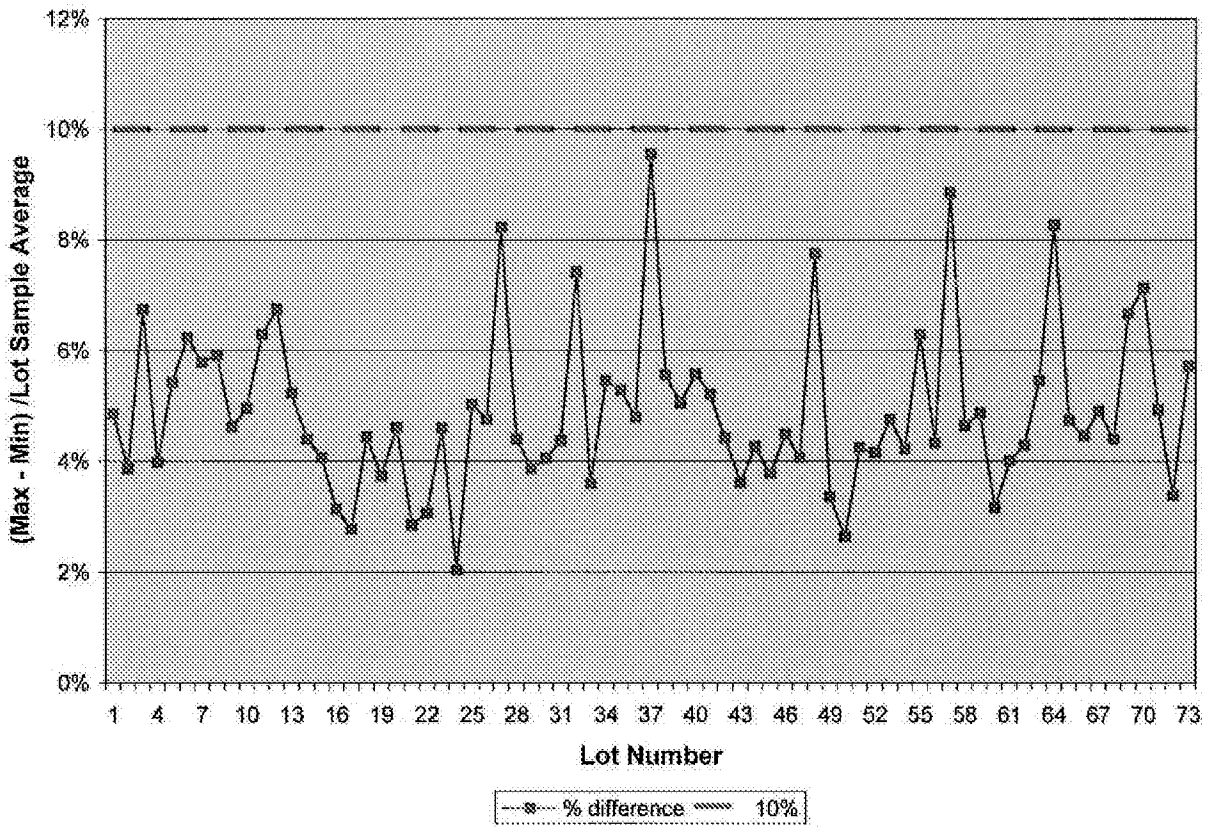
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and. that such statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 13th day of March, 2013

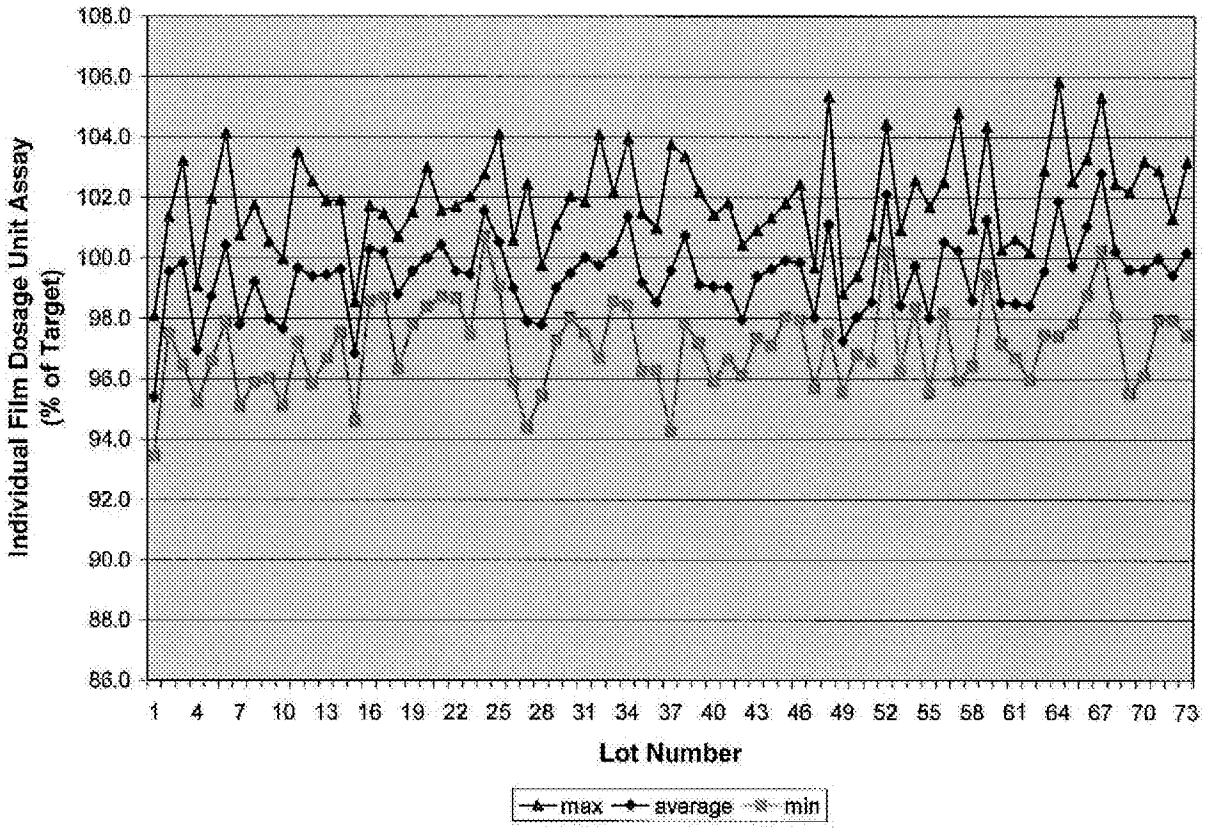


B. Arlie Bogue

APPENDIX A



APPENDIX B



APPENDIX C

Lots less than 5%			lots 5% to 10%	
Lot #	% Difference		Lot #	% Difference
24	2.0%		10	5.0%
45	2.6%		25	5.0%
17	2.8%		39	5.0%
21	2.8%		41	5.2%
22	3.1%		13	5.2%
16	3.1%		35	5.3%
60	3.2%		5	5.4%
50	3.4%		63	5.5%
72	3.4%		34	5.5%
33	3.6%		38	5.6%
43	3.6%		40	5.6%
19	3.7%		73	5.7%
46	3.8%		7	5.8%
29	3.9%		8	5.9%
2	3.9%		6	6.2%
4	4.0%		11	6.3%
61	4.0%		55	6.3%
30	4.0%		69	6.7%
48	4.1%		3	6.7%
15	4.1%		12	6.7%
52	4.2%		70	7.1%
54	4.2%		32	7.4%
51	4.2%		49	7.8%
44	4.3%		27	8.2%
62	4.3%		64	8.3%
56	4.3%		57	8.9%
31	4.4%		37	9.5%
28	4.4%			
14	4.4%			
68	4.4%			
42	4.4%			
18	4.4%			
66	4.5%			
47	4.5%			
23	4.6%			
20	4.6%			
9	4.6%			
58	4.6%			
65	4.7%			
26	4.8%			
53	4.8%			
36	4.8%			
1	4.9%			
59	4.9%			
67	4.9%			
71	4.9%			
total	46		total	27

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132** has been served, by first class mail, on March 13, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

EXHIBIT B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
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U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
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March 13, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF DAVID T. LIN, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, David T. Lin, Ph.D. do hereby make the following declaration:

I. SUMMARY OF CREDENTIALS AND EXPERIENCE

1. Since January 2005, I have served as a Senior Consultant to Biologics Consulting Group, Inc. ("BCG"), a team of consultants who provide national and international regulatory and product development advice on the development and commercial production of small molecular weight synthetic drug, biotechnological and biological products.

2. While BCG is being paid for my time, I am not an employee of, nor do I have any financial interest in, MonoSol Rx, LLC ("Patentee" and/or "MonoSol").

3. Before joining BCG, I held various positions with the United States Food and Drug Administration ("FDA"). From 1997-2001, I was a Chemistry Reviewer in the Division of Reproductive and Urologic Drug Products, Center for Drug Evaluation and Research ("CDER"). In 2001, I became the Team Leader in the same Division and served in that role until 2003 when I was promoted to the position of acting Deputy Division Director in the Division of New Drug Chemistry III, Office of New Drug Chemistry (currently referred to as Office of New Drug Quality Assessment). In 2004, I was promoted to the position of acting Division Director.

4. As a Chemistry Reviewer at CDER, I was responsible for the comprehensive review of Chemistry, Manufacturing and Controls ("CMC") data for drugs being investigated during Phase 1, 2, and 3 clinical studies. I was also responsible for the review of CMC data in New Drug Applications and provided regulatory input to CMC reviewers responsible for review of Abbreviated New Drug Applications. This included providing scientific and regulatory guidance during development of small molecular weight drugs and biotechnological/biological drugs across a wide variety of dosage forms. I have reviewed CMC data submitted with respect to over 100 Investigational New Drug Applications and New Drug Applications (original and supplemental) as a chemistry reviewer, contributed to decisions regarding the approval of drugs, made presentations before scientific and regulatory conferences and participated in a variety of special FDA projects and committees, including serving as the co-Chair of the CMC Good Review Practices Committee.

5. As Team Leader, acting Deputy Division Director and acting Division Director in the Office of New Drug Chemistry, I was actively involved in directing the content of FDA guidances that pertained to CMC topics. As acting Deputy Division Director and Division Director, I was directly involved in discussions, regarding the content of the 2003 FDA draft guidance on Drug Product-Chemistry, Manufacturing, and Controls Information, with the committee responsible for writing this guidance. I had signatory authority for this draft guidance prior to public issuance by FDA. As acting Deputy Division Director and Division Director, I was involved in regular meetings with the supervisory staff in the Office of Generic Drugs to discuss regulatory and review policy issues that are common to both New Drug Applications and Abbreviated New Drug Applications.

6. I consider myself an expert in the fields of FDA practice and procedure as applicable to the testing requirements for drugs and review of Investigational New Drug Applications (INDs) and New Drug Applications (NDAs).

7. I received my B.A. in Biochemistry from the University of Pennsylvania in 1984, my Ph.D. in Organic Chemistry from the University of Maryland in 1989 and my M.B.A. from the University of Maryland's RH Smith School of Business in 2002. Attached hereto as Exhibit A is my curriculum vitae, including a list of my publications for the past ten years.

8. I have carefully reviewed Chen (WO 00/42992) ("Chen").

II. U.S. STATUTORY AND REGULATORY BACKGROUND FOR TESTING DRUGS FOR POTENCY AND DOSAGE UNITS FOR UNIFORMITY

9. From a US regulatory perspective, for a drug to be approved for commercial marketing and distribution, specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product must be provided in a New Drug Application.[1] In addition, reference to the current U.S. Pharmacopeia (USP) may satisfy these requirements.

10. Section 501(b) of the Food, Drug, and Cosmetic Act (the Act) deems an official drug (i.e., a drug represented as a drug which is recognized in the U.S. Pharmacopeia) to be adulterated if it fails to conform to compendial standards of quality, strength or purity. Compendial tests or assay methods are used when determining such conformance under 501(b); the standards are stated in individual monographs as well as portions of the General Notices section of the USP/NF. Standards and test methods have been established for such characteristics as potency and content uniformity.

11. Section 501(c) of the Act deems a drug that is not recognized in the USP to be adulterated if it fails to meet the strength, purity or quality which it is represented to possess.

[1] 21 CFR 314.50(d)(1)(ii)(a)

The applicable quality standards for a drug not recognized in the USP can be determined from such sources as the labeling of the drug (or drug product), the manufacturer's written specifications, and new drug applications.

12. The current good manufacturing practice (cGMP) regulations include the minimum requirements for the preparation of drug product for administration to humans. One of the requirements is that the strength[2] of the drug (active ingredient) in the drug product must be determined for each batch of drug product manufactured for commercial distribution.[3] Strength is taken to mean content or assay of the drug.

13. Batch uniformity of the drug products is ensured with procedures that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch.[4] FDA also describes in guidance that it is expected the sampling plan for drug product is representative of the batch.[5]

14. Controls include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that the drug product conform to appropriate standards of identity, strength, quality, and purity.[6]

15. Regulatory specifications must be established to ensure that the dosage form will meet acceptable therapeutic and physicochemical standards throughout the shelf-life of the marketed product.[5] These specifications include tests for strength (content or assay) and uniformity of dosage units.

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[2] 21 CFR 210.3(b)(16)

[3] 21 CFR 211.165(a)

[4] 21 CFR 211.110(a)

[5] FDA Guideline for Submitting Documentation for the Manufacture and Controls for Drug Products, February 1987

[6] 21 CFR 211.160(b)

16. Testing to establish uniformity of dosage units is defined in the USP under the USP general chapter <905>.[7]

III. CHEN'S DISCLOSURE IS INSUFFICIENT

17. I have been asked to review Chen and render an opinion as to whether there is sufficient information contained within to allow regulatory FDA approval and commercialization of a drug product that is manufactured as described. After review of the patent in light of FDA practice and procedure, it is my opinion that there is insufficient disclosure to allow FDA to determine that a drug product as described can be manufactured for commercial distribution, manufactured in a consistent manner and meet specifications that will ensure the identity, strength, quality, purity, and potency of the drug product. In particular, Chen lacks any disclosure which would necessarily lead to the manufacture of films with uniformity of content (strength) of drug active required for FDA approval.

18. As would be required for FDA approval Chen does not disclose sufficient information that films containing drug can be produced consistently with respect to uniformity of content of the drug. No information was disclosed that demonstrated uniformity of content in the amounts of drug in individual dosage units. Chen discloses no specific test methods, and hence no test results, that could allow for the determination of the actual amount of drug (active) in individual dosage units.

19. As required for FDA approval, Chen's patent did not disclose sufficient information regarding the manufacturing process and process controls. The information disclosed by Chen would not ensure that films containing drug could be manufactured to meet specifications that ensure consistent strength.

20. Even if the information disclosed in Chen could be utilized to develop a manufacturing process for films containing drug, there is no information regarding the test methods that are necessary to determine the amount of drug in individual dosage units.

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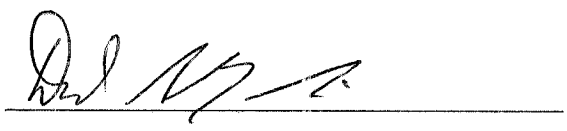
[7] USP General Chapter <905> Uniformity of Dosage Units

21. Therefore, Chen's disclosure is lacking, both explicitly and inherently, the disclosure necessary to provide for the manufacture of drug-containing films with the uniformity of content in amount of drug (active) in individual dosage units to make FDA approvable film products. It is my understanding that an inherent disclosure may not be established by probabilities or possibilities and that the mere fact that a certain thing may result from a given set of circumstances is not sufficient and that to be inherent requires that the missing disclosure is necessarily present.

22. Finally, Chen's patent discloses the release profiles of four active agents from films. See Chen, Figure 5. The release profile data presented in Figure 5 show a high degree of variability at each data point. For example, the release profile for nicotine containing film product show that the amount of nicotine released at the 5 minute and 8 minute time point can be as high as approximately 115-120%. This level of active agent is greater than the 110% level (from an expected amount of 100%) that is considered acceptable to FDA for regulatory approval of a product that purports to be manufactured consistently with acceptable content uniformity. These data indicate that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film.

23. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and. that such statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 13th day of March, 2013



David T. Lin

CERTIFICATE OF FIRST CLASS SERVICE

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DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

EXHIBIT A

DAVID TSOCHUNG LIN

9121 Fall River Lane, Potomac, MD 20854 (301) 299-2853 dlin@bcg-usa.com

EXPERTISE

- 18+ years pharmaceutical regulatory experience.
  - 7+ years regulatory chemistry, manufacturing and controls (CMC) experience at CDER/FDA on small molecular-weight drugs, botanical drugs, peptide drugs, and protein drugs formulated in a broad range of sterile and non-sterile dosage forms.
  - 3+ years research experience at CBER/FDA.
  - 8+ years experience as regulatory CMC consultant.
- Unique combination of biologic/biotechnological and small molecular-weight drug regulatory experience, including device/drug and device/biologics combination products.
- Understanding of FDA regulatory requirements and expectations for drug development and marketing approval.
- Performed primary CMC review and assessment of drug products for treatment of reproductive and urologic disorders and diseases.
- Supervised CMC review activities in 7 CDER medical reviewing divisions including Reproductive/Urologic, Anti-viral, Dermatologic/Dental, Anti-inflammatory/ Analgesic/Ophthalmologic, Anti-infective, Special Pathogen/Immunologic, and Over-the-Counter drug products.
- Understanding of drug substance and drug product analytical method development and validation.
- Understanding of drug substance and drug product stability protocol development and stability data analysis.
- Understanding of current Good Manufacturing Practices (cGMPs)
- Experienced in chemical synthesis, small-scale and pilot-scale fermentation, biologics/ biotechnology, and protein chemistry.
- Experienced working in cross-functional teams (i.e., Pharmacology/toxicology, Clinical, Biostatistics, Biopharmaceutics, and Analytical).
- Ph.D. in Organic Chemistry; M.B.A. degree and training for managers.

EXPERIENCE

BIOLOGICS CONSULTING GROUP, INC. Alexandria, VA
January 2005 – Present
Senior Consultant

- Evaluate and provide advice on client CMC scientific and regulatory strategies for a wide range of therapeutic drug products (biologic and non-biologic) in dosage forms that include tablets, topicals, injectables, transdermals, implants, sprays, and inhalation, at all stages of product development, from pre-IND through post-NDA/BLA approval.
- Review and provide advice on IND and NDA/BLA submissions for suitability relative to FDA expectations for CMC data.
- Perform gap analysis audits for deficiencies relative to FDA expectations.
- Conduct regulatory and scientific due diligence audits for business acquisitions and licensing partnerships. Provide assessment of strengths and deficiencies.
- Represent clients in interactions with FDA.
- Prepare and write submissions to FDA, with focus on CMC sections.
- Represent client as FDA regulatory expert in legal proceedings.
- Advise clients on manufacturing contractor and vendor evaluation and selection.
- Provide management and technical oversight of contract manufacturing organizations (CMOs).
- Involved in business development to increase client base.
- Provide scientific and regulatory training and presentations at pharmaceutical/biopharmaceutical conferences.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, OFFICE OF NEW DRUG CHEMISTRY, DIVISION OF NEW DRUG CHEMISTRY III. Rockville, MD
July 2003 – December 2004
Division Director (acting) *March 2004 – December 2004*
Deputy Division Director (acting) *July 2003 – March 2004*

- Supervised 34 employees in 9 therapeutic product classes, includes 6 Team Leaders, review chemists and administrative staff. Responsible for employee work performance review and career development.
- Planned and set long-range plans and schedules for Division work. Directed and coordinated workload, and assured implementation of Division policies, goals and objectives.
- Evaluated budget and fiscal controls to manage Division functions.
- Made critical decisions and provided expert advice concerning regulatory, scientific and compliance approaches and options consistent with Office policies and objectives.
- Represented FDA in dealing and negotiating with the regulated industry, and professional and industry organizations.
- Participated as invited speaker at regulatory and scientific conferences on behalf of FDA.
- Served as the Chair of the Stability Guidance Technical Committee, Co-chair of the Conjugated Estrogens Working Group and Co-chair of the Good Review Practices Working Group.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS. Rockville, MD
October 2001-July 2003
Lead Chemist (Team Leader)

- Managed a team of 4 review chemists in 2 therapeutic product classes.
- Responsible for secondary review, consistency of CMC reviews and adherence to FDA/ONDC policies and guidances.
- Coordinated reviewers' workload of IND and NDA submissions to ensure that reviews were conducted in timely manner.
- Interacted extensively with the regulated industry to provide regulatory direction during IND drug development and NDA post-approval activities.
- Active in the development of FDA guidances for industry and internal good review practices. Served as the Chair of the Stability Guidance Technical Committee, Co-chair of the Conjugated Estrogens Working Group and Co-chair of the Good Review Practices Working Group.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS. Rockville, MD
April 1997-October 2001
Chemistry Reviewer

- Evaluated the quality of new drug products submitted to the FDA for approval.
- Integral part of a cross-functional review team responsible for evaluating the quality and effectiveness of reproductive and urologic drug products being investigated in clinical studies.
- Major contributor to committees responsible for establishing drug product quality standards and publishing guidances for pharmaceutical companies.
- Provided regulatory guidance to pharmaceutical company representatives during drug development.
- Mentored new reviewers.
- Served as computer focal point to facilitate and troubleshoot computer issues.

FOOD & DRUG ADMINISTRATION, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, LABORATORY OF PARASITIC BIOLOGY AND BIOCHEMISTRY. Bethesda, MD
February 1994-April 1997
National Research Council Fellow

- Investigated the biological role of specific proteins in the sexual differentiation of the malaria parasite. Published three research papers in peer-reviewed journals.
- Presented research data at three separate scientific conferences.
- Supervised the research projects of college students.
- Responsible for the coordination of instrument repairs and the ordering of laboratory supplies.

GENERAL ELECTRIC CO., CORPORATE RESEARCH & DEVELOPMENT, BIOLOGICAL SCIENCES LABORATORY. Schenectady, NY
July 1989-January 1994
Staff Scientist

- Developed recombinant biphenyl-metabolizing microorganisms capable of degrading environmental contaminants. Marketed this technology to the GE business units and government agencies responsible for environmental clean-up.
- Investigated the factors affecting aerobic biodegradation of indigenous PCBs in Hudson River sediment by various bacterial strains.
- Isolated and conducted mechanistic studies of the dioxygenase enzymes involved in biodegradation.
- Investigated the scientific and economic feasibility of biologically synthesizing aromatic monomers for use as a feedstock to produce biodegradable polymers.
- Supervised research projects of summer interns.
- Published research in peer-reviewed journals.
- Recruited at major East Coast universities. Interviewed and screened graduating science Ph.D. students for second round interviews at the Research Center.

UNIVERSITY OF MARYLAND, Dept. of Chemistry/Biochemistry. College Park, MD
May 1985-May 1989
Research Assistant

- Investigated mechanism of action of two bacterial enzymes, mandelate racemase and D-amino acid oxidase.
- Synthesized and tested novel halogenated aromatic hydroxy- and amino- acid analogs as potential irreversible inhibitors.
- Published research in peer-reviewed journals and co-authored one chapter in a biotechnology book. In addition, the research data was presented at two national scientific conferences.
- Served as the computer expert for the laboratory group.

EDUCATION

ROBERT H. SMITH SCHOOL OF BUSINESS. College Park, MD
University of Maryland
Master of Business Administration (MBA), *2002*
Concentration: Finance

UNIVERSITY OF MARYLAND. College Park, MD
Department of Chemistry and Biochemistry
Ph. D. -- Organic Chemistry, *1989*
Research Advisor -- Dr. John W. Kozarich

UNIVERSITY OF PENNSYLVANIA. Philadelphia, PA
Bachelor of Arts with Honors – Biochemistry, *1984*
Dean's List, Phi Lambda Upsilon Chemical Honor Society

TRAINING

- Facilitation Skills, CDER/FDA (Fall 2002)
- Six Sigma Strategy and Methods, Univ. of MD (Summer 2002)
- Group Decision-Making Techniques, CDER/FDA (Feb. 2002)
- Managing Written Communications for Team Leaders, CDER/FDA (Spring 2002)
- Organizational Behavior and Human Resources, Univ. of MD (Fall 1999)
- Management of Human Resources, Univ. of MD (Fall 1999)
- Introduction to Drug Law and Regulation, CDER/FDA (Nov. 1998)
- Basic Statistical Methods, CDER/FDA (Fall 1998)

HONORS/AWARDS

- CDER's Team Excellence Award (Nov 2004)
- FDA's Group Recognition Award (May 2004)
- CDER's Special Recognition Award (Nov 2002)
- CDER's Team Excellence Award (Nov 2002)
- OPS/ONDC Special Recognition Award (Dec 2001)
- CDER's Team Excellence Award (Nov 2000)
- OPS/ONDC Special Recognition Award (Jun 2000)
- CDER's Excellence in Mentoring Award (Nov 1999)

PRESENTATIONS

- Conducting Effective & Compliant Stability Programs for Pharmaceuticals & Biologics, "Stability Studies During Development", "Stability of Biopharmaceuticals", "Development of Specifications for Biopharmaceuticals", and "Extractables, Leachables, and Particulates – Safety Concern for Biotechnology Products", Dubai, UAE (Sep 2012).
- 4th DIA China Annual Meeting, "ICH Guidelines Q1D, Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products", and "Q1E, Evaluation of Stability Data", Shanghai, China (May 2012).
- IPA's Current Trends and Practices in Stability Testing, "Stability Testing Requirements for Biopharmaceutical Products", Montreal, Canada (Oct 2011)
- IPA's Current Trends and Practices in Stability Testing, "Stability Program for Combination Products", Montreal, Canada (Oct 2011)
- 3rd DIA China Annual Meeting, "Thinking About Comparability for Biosimilar Proteins", Beijing, China (May 2011).
- IPA's Current Trends and Practices in Stability Testing, "Stability Challenges for Combination Products", Boston, MA (May 2011).
- IPA's Current Trends and Practices in Stability Testing, "Country Specific Stability Requirements", Boston, MA (May 2011).
- Stability Programs Forum, "Stability Testing for Biotechnology/Biologic Products", Philadelphia, PA (Dec 2010).
- 11th Annual EuroTIDES/EuroPEPTIDES Conference, "Stability Considerations and Testing for Peptide-and Oligo-Based Therapeutics", Barcelona, Spain (Nov 2010).
- International Summit of China Pharmaceutical Industry, "FDA Requirements for Peptide Product Development: Considerations from Small Molecule and Biological Products", Hangzhou, China (Oct 2010).

- 7th Annual Method Validation Conference, "Ensure Method Validation Compliance through a Review of FDA Warning Letters", San Francisco, CA (Jul 2010).
- 6th Annual BioProcess International European Conference, "Extractables, Leachables and Particulates – Safety Concern for Biotechnology Products," Vienna, Austria (May 2010)
- ISPE-CSAC Meeting, "Biotechnological Drug Development and Interactions with CDER," Raleigh, NC (Oct 2009).
- Seminar on China International Bio-medicine Outsourcing Service, "Product Quality Issues with GLPs and GCPs," Hangzhou, China (Sep 2009).
- Informa Stability Testing for Biologics Conference, "Understanding Product Expiry and Shelf-Life," Prague, Czech Republic (Sep 2009).
- Informa Stability Testing for Biologics Conference Workshop, "Stability Testing Performed Over a Product Lifecycle," Prague, Czech Republic (Sep 2009).
- IVT Lab Compliance Conference, "Implement a Comprehensive and Compliant Stability Program," Philadelphia, PA (Aug 2009).
- OKBio ACCELERATE Workshop, "Product Development – Regulatory CMC Considerations," Oklahoma City, OK (Jun 2009).
- IVT Method Validation Conference, "Challenges in Understanding Impurities and Degradants for Biological/Biotechnological Products," San Francisco, CA (Oct 2008).
- IVT Method Validation Conference, "Strategies for Setting Biological Product Specifications," San Francisco, CA (Oct 2008).
- CBI 3rd Annual Stability Programs Conference, "Complex Stability Programs for Biologics," Philadelphia, PA (Jun 2008).
- IVT Lab Compliance Conference, "Stability Testing Fundamentals and Considerations in the Current Regulatory Environment," Baltimore, MD (Apr 2008).
- R&D Direction's 5th Annual Drug Development Summit, "Looking Forward in 2008: Regulatory Priorities and Considerations," Amelia Island, FL (Feb 2008).
- 2007 AAPS Annual Meeting, "Critical Stability Evaluation of Biopharmaceuticals During Clinical Development Stages," San Diego, CA (Nov 2007).
- 2007 DIA Annual Meeting, "The Impact of FDA's Quality by Design Initiative on Biologics Development," Atlanta, GA (Jun 2007).
- Institute for International Research: Formulation and Forced Degradation Strategies for Biomolecules, "Regulatory Requirements for Successful Product Development," San Diego, CA (Mar 2007).
- International Pharmaceutical Academy: Effective Management of Stability Programs, "Stability Design Considerations for Global Regulatory Filings," Toronto, Canada (Feb 2007).
- Cambridge Healthtech Institute's PepTalk: Optimizing Protein and Antibody Therapeutics, "Regulatory Considerations for the Development of Protein Therapeutic Products," San Diego, CA (Jan 2007).
- 2006 AAPS Annual Meeting, "The Impact of FDA Initiatives on the Development of Biological Products," San Antonio, TX (Nov 2006).
- SWE Enterprises: Stability Testing for the FDA Regulated Industry, "In-Use Testing of Biotechnological and Biologic Products," Boston, MA (Oct 2006).
- SWE Enterprises: Stability Testing for the FDA Regulated Industry, "Cost Efficient Design of Stability Studies," Boston, MA (Oct 2006).
- Institute for International Research: Chemistry Manufacturing & Controls, "Clarifying and Understanding ICH Guidance to Help Meet International Requirements for Submissions," Philadelphia, PA (July 2006).
- IVT Stability Testing: Implementing Effective Processes for Stability Program Development, "Cost Efficient Design of Stability Studies," San Diego, CA (June 2006).
- IVT Stability Testing: Implementing Effective Processes for Stability Program Development, "Stability Requirements for Global Regulatory Filings," San Diego, CA (June 2006).

- CBI Stability Programs: New Approaches to Test, Analyze and Document Data for Improved Program Design and Global Compliance, "In Use Testing of Biotechnological and Biological Products," Princeton, NJ (June 2006).
- IBC/TIDES: Oligonucleotide and Peptide Technology and Product Development, "Stability Considerations and Testing for Oligo- and Peptide-Based Therapeutics," Carlsbad, CA (May 2006).
- IBC Biopharm Manufacturing and Distribution Summit: Logistics for Biopharmaceutics, "Stability Studies to Support the Chain of Custody of Biotechnology Products," Reston, VA (Dec 2005).
- 2005 AAPS Annual Meeting: AAPS Short Course on Degradation and Stability in Small Molecule Active Pharmaceutical Ingredients/Stability Testing for Global Filings, "Stability Requirements for Global Regulatory Filings," Nashville, TN (Nov 2005).
- Therapeutic Strategies Against Neurodegenerative Conditions, "The Regulatory Product Development Process," Burlington, MA (Oct 2005).
- International Pharmaceutical Federation (FIP) Workshop: Harmonizing Clinical Trial GMP and Quality Requirements Across the EU and Beyond, "The US Investigational New Drug (IND) System," Noordwijk Zee, The Netherlands (Mar 2005).
- 2004 AAPS Annual Meeting, "Phase 2 and 3 IND CMC Guidance: FDA Perspective," Baltimore, MD (Nov 2004).
- 64th Annual World FIP Congress, "Clinical Trial Application Process – CMC: US FDA Perspective," New Orleans, LA (Sep 2004).
- AAPS Pharmaceutical Technologies 3rd Summer Conference: Optimizing the Global Clinical Trial Process, "IND Applications – FDA Perspective," Cherry Hill, NJ (Aug 2004).
- 2004 DIA Annual Meeting, "FDA Stability Guidance Update," Washington, DC (Jun 2004).
- DIA Meeting on CM&C/Regulatory and Technical Strategies, "Challenges and Opportunities in CMC Requirements for Phase 2-3," Bethesda, MD (Mar 2004).
- 2003 PDA Annual Meeting, "Draft FDA Stability Guidance," Atlanta, GA (Nov 2003).
- 2003 DIA Annual Meeting, "Product Quality of Non-clinical and Clinical Trial Materials," San Antonio, TX (Jun 2003).
- PARCS Meeting, "Managing CMC Requirements during IND," Irvine, CA (Apr 2003).
- PARCS Meeting, "Use of SUPAC Guidances during IND Development," Irvine, CA (Apr 2003).
- DIA Meeting on Global Chemistry, Manufacturing and Controls: Pre IND/CTX and IND/CTX Development Challenges, "FDA Perspective on Stability Testing during IND Development," Philadelphia, PA (Feb 2003).

PUBLICATIONS

- C. Syin, D. Parzy, F. Traincard, I. Boccaccio, M.G. Joshi, D.T. Lin, X.-M. Yang, K. Assemat, C. Doerig, and G. Langeley, "The H89 cAMP-dependent protein kinase inhibitor blocks *Plasmodium falciparum* development in infected erythrocytes," *Eur. J. Biochem. 268*, 4842 (2001).
- J.P. McDaniel, C. Syin, D.T. Lin, M.B. Joshi, S. Li, and N.D. Goldman, "Expression and characterization of a *Plasmodium falciparum* protein containing domains homologous to sarcalumenin and a tyrosine kinase substrate, eps15," *Int. J. Parasitol. 29*, 723 (1999).
- D.T. Lin, N.D. Goldman, and C. Syin, "Stage specific expression of a *Plasmodium falciparum* protein related to the eukaryotic mitogen-activated protein kinase," *Mol. Biochem. Parasitol. 78*, 67 (1995).
- M.R. Harkness, J.B. McDermott, D.A. Abramowicz, J.J. Salvo, W.P. Flanagan, M.L. Stephens, F.J. Mondello, R.J. May, J.H. Lobos, K.M. Carroll, M.J.Brennan, A.A. Bracco, K.M. Fish, G.L. Warner, P.R. Wilson, D.K. Dietrich, D.T. Lin, C.B. Morgan, and W.L. Gately, "*In situ* stimulation of aerobic PCB biodegradation in Hudson River sediments," *Science 259*, 503 (1993).
- D.T. Lin, V.M. Powers, L.J. Reynolds, C.P. Whitman, G.L. Kenyon and J.W. Kozarich, "Evidence for the generation of α-carboxy-α-hydroxy-*p*-xylylene from *p*-(bromomethyl)mandelate by mandelate racemase," *J. Am. Chem. Soc. 110*, 323 (1988).

- M.S. Lakshmikumaran, E. D'Ambrosio, L.A. Laimins, D.T. Lin and A.V. Furano, "Long interspersed repeat DNA(LINE) causes polymorphism at the rat insulin 1 locus," *Mol. Cell. Biol. 5*, 2197 (1985).

BOOK CHAPTER

- N.R. Schmuff and D.T. Lin, "Contents of Module 3 for an Electronic Common Technical Document Investigational New Drug Application," in Preparation and Maintenance of the IND Application in eCTD Format, W.K. Sietsema (ed.), FDAnews, Falls Church, VA, 117-134 (2008).
- N.R. Schmuff and D.T. Lin, "Chemistry, Manufacturing and Controls (CMC)," in Wiley Encyclopedia of Clinical Trials, (2008).
- J.A. Gerlt, G.L. Kenyon, J.W. Kozarich, D.T. Lin, D.C. Neidhart, G.A. Petsko, V.M. Powers, S.C. Ransom and A.Y. Tsou, "Structure-function relationships in mandelate racemase and muconate lactonizing enzyme," in Chemical Aspects of Enzyme Biotechnology, T.O. Baldwin, F.M. Raushel and A.I. Scott (eds.), Plenum, New York, NY, 9-21 (1990).

PROCEEDINGS OF MEETINGS

- D.T. Lin, N.D. Goldman, and C. Syin, "*Plasmodium falciparum* mitogen-activated protein kinase homologue contains an unusually large carboxyl terminal domain which is highly charged and homologous to merozoite surface antigens," Molecular Parasitology Meeting, Woods Hole, MA (1995).
- C. Syin, D. Lin, B. Krzyzanowska, and N.D. Goldman, "*Plasmodium* cGMP-dependent protein kinase," FDA Science Forum on Regulatory Sciences, Washington, D.C. (1994).
- J. H. Lobos, M. J. Brennan, J. T. Jackman and D. T. Lin, "*In situ* stimulation of PCB biodegradation in Hudson River sediment: III. enumeration and characterization of aerobic bacteria," ASM Meeting, New Orleans (1992).
- G.L. Kenyon, D.T. Lin, V.M. Powers, L.J. Reynolds, C.P. Whitman and J.W. Kozarich, "Generation of α-carboxy-α-hydroxy-*p*-xylylene from *p*-bromomethyl-mandelate by mandelate racemase-- further evidence for a carbanion mechanism," *FASEB J. 2*, 1329 (1988).
- D.T. Lin, V.M. Powers, L.J. Reynolds, C.P. Whitman, G.L. Kenyon and J.W. Kozarich, "Formation of *p*-xylylene species in the mandelate racemase catalyzed reaction of *p*-(bromomethyl)mandelate," *Fed. Proc. 46*, 2042 (1987)

Electronic Patent Application Fee Transmittal

Application Number:	95002170
Filing Date:	10-Sep-2012
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Filer:	Stephen J. Brown
Attorney Docket Number:	117744-00023

Filed as Large Entity

inter partes reexam Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Request for Inter Reexamination	1813	1	0	0
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**0**

Electronic Acknowledgement Receipt

EFS ID:	15215642
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Stephen J. Brown
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	13-MAR-2013
Filing Date:	10-SEP-2012
Time Stamp:	23:15:29
Application Type:	inter partes reexam

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Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response after non-final action-owner timely	FINAL080REPLYTOOA.pdf	653223 8fc8f0e3f49f5bcf46d57581b8d7765071574da1	no	86

Warnings:	
Information:	

2	Response after non-final action-owner timely	Declarations.pdf	9066001 fa617de5bca4c8f01850c9912482145029fb095c	no	26
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30246 0f8873435e13b90bd937cd3b03eb008e2ed9e7c7	no	2
Warnings:					
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			Total Files Size (in bytes):	9749470	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

EXHIBIT C

EXHIBIT C
Comparison of Supplemental Response filed March 13, 2013
with Reply filed January 29, 2013

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.:	6418
Filed:	September 10, 2012	H&B Docket:	119-26 RCE/CON/REX
Dated:	~~January 29~~March 13, 2013	M&E Docket:	117744-00023

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
U.S. Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on ~~January 29~~March 13, 2013
Signed: Michael J. Chakansky /Michael J. Chakansky/

REPLY BY PATENTEE TO A NON-FINAL OFFICE ACTION PURSUANT TO 37 C.F.R. §1.111

Madame:

In compliance with the Notice Re Defective Paper in *Inter Partes* Reexamination, mail date February 26,2013, Patent owner MonoSol Rx, LLC ("Patentee" and/or "MonoSol") hereby presents its re-drafted response to ~~an~~the Office Action in the above-identified *Inter Partes* Reexamination, dated November 29, 2012 ("Office Action"), a reply to which is due ~~January 29~~March 13, 2013~~, please~~. Please amend U.S. Patent No. 7,897,080 ("the '080 Patent") in reexamination as set forth hereinbelow. The present amendments are being made in accordance with 37 C.F.R. §1.530(d~~) (j). If~~)G). Patentee has previously paid fees for the addition of 4 new independent claims and 324 new dependent in connection with this reexamination. Accordingly, no claim fees are believed to be due with this submission. If, however, there are any fees due in connection with this submission, authorization to charge such fees, including any claim fees, and authorization to credit any overpayments, to Deposit Account No. 08-2461 ~~is~~are hereby provided.

Amendment to the Claims begins on page 2 of this paper.

Remarks-begin on page ~~79~~42 of this paper.

EXHIBIT C
Comparison of Supplemental Response filed March 13, 2013
with Reply filed January 29, 2013

Claim Amendments[1]

1. (Amended) A process for manufacturing a resulting ~~pharmaceutical~~ film suitable for commercialization and regulatory approval**, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units,** said [making a]film having a substantially uniform distribution of **components ~~a pharmaceutical active~~** [of components] **comprising a substantially uniform distribution of said active in individual dosage units of said resulting film**, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding [an]**said ~~a pharmaceutical~~** active**, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof,** to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) **controlling drying through a process comprising** conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent **from said flowable polymer matrix** [from said flowable polymer matrix] to **~~rapidly~~** form a visco-elastic film, having said **~~pharmaceutical~~** active **substantially** uniformly distributed throughout **~~by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying,~~** within

[1] The claim amendments show the original amendments filed in the January 2013 Reply in underlining and brackets, and the NEW amendments filed in the March 13, 2013 reply in bold, underlining and strikethrough.

about the first [10]4 minutes [or fewer]**by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying** to maintain said substantially uniform distribution of said ~~**pharmaceutical**~~ active by locking-in or substantially preventing migration of said ~~**pharmaceutical**~~ active within said visco-elastic film**,** wherein **during said drying said flowable** ~~**the**~~ polymer matrix temperature is 100°C or less; [and]

(e) forming [a]**said** ~~**the**~~ resulting ~~**pharmaceutical**~~ film from said visco-elastic film, wherein said resulting ~~**pharmaceutical**~~ film has a water content of 10% or less and said substantially uniform distribution of ~~**pharmaceutical**~~ active by said locking-in or substantially preventing migration of said ~~**pharmaceutical**~~ active is maintained; and

(f) ~~**forming a plurality of individual dosage unit samples of substantially the same size from said resulting pharmaceutical film; and**~~

~~(g)~~ performing analytical chemical tests for ~~**content**~~ uniformity ~~**on said plurality**~~ of **content of said active in substantially equal sized** individual dosage units **sampled** ~~**samples**~~ from **different locations of** said resulting ~~**pharmaceutical**~~ film, said tests indicating ~~**said substantially uniform distribution of the pharmaceutical active, in that the amount of the pharmaceutical active in the individual dosage unit samples**~~ **that uniformity of content in the amount of the active** varies by no more than 10% **and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration**.

2. (Original) The process of claim 1, wherein said pre-determined amount ofmaster batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.

3. (Original) The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.

4. (Original) The process of claim 1, wherein said water-soluble polymer comprises polyethylene oxide.

5. (Original) The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

6. (Original) The process of claim 5, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

7. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

8. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and

combinations thereof.

9. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

10. (Original) The process of claim 1, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

11. (Original) The process of claim 10, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

12. (~~Original~~ Cancelled) ~~The process of claim 1, wherein said active is selected from the group consisting ofbioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.~~

13. (Amended) The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti -convulsants, anti -depressants, anti -diabetic agents, anti -diarrhea preparations, antidotes, anti -histamines, anti -hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-

thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and nonsystemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, antithrombotic drugs, hypnotics, anti -emetics, anti -nauseants, [anti -convulsants,]neuromuscular drugs, hyper-and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, antispasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

14. (Amended) The process of claim 1, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

15 (Original) The process of claim 1, wherein said active is a bioactive active.

16. (Cancelled)

17. (Original) The process of claim 1, wherein said active is an opiate or opiate-derivative.

18. (Original) The process of claim 1, wherein said active is an anti-emetic.

19. (Original) The process of claim 1, wherein said active is an amino acid preparation.

20. (Original) The process of claim 1, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

21. (Original) The process of claim 1, wherein said active is a protein.

22. (Original) The process of claim 1, wherein said active is insulin.

23. (Original) The process of claim 1, wherein said active is an anti-diabetic.

24. (Original) The process of claim 1, wherein said active is an antihistamine.

25. (Original) The process of claim 1, wherein said active is an anti-tussive.

26. (Original) The process of claim 1, wherein said active is a non-steroidal anti-inflammatory.

27. (Original) The process of claim 1, wherein said active is an anti-asthmatics.

28. (~~Original~~ **Amended**) The process of claim 1, wherein said active is an anti-diarrhea **preparation**.

29. (Original) The process of claim 1, wherein said active is an alkaloid.

30. (Original) The process of claim 1, wherein said active is an anti-psychotic.

31. (Original) The process of claim 1, wherein said active is an anti-spasmodic.

32. (Original) The process of claim 1, wherein said active is a biological response modifier.

33. (Original) The process of claim 1, wherein said active is an anti-obesity drug.

34. (Original) The process of claim 1, wherein said active is an H2-antagonist.

35. (Original) The process of claim 34, wherein said H2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

36. (Original) The process of claim 1, wherein said active is a smoking cessation aid.

37. (Original) The process of claim 1, wherein said active is an anti-parkinsonian agent.

38. (Original) The process of claim 1, wherein said active is an anti-depressant.

39. (Original) The process of claim 1, wherein said active is an anti-migraine.

40. (Original) The process of claim 1, wherein said active is an anti-Alzheimer's agents.

41. (Original) The process of claim 1, wherein said active is a dopamine receptor agonist.

42. (Original) The process of claim 1, wherein said active is a cerebral dilator.

43. (Original) The process of claim 1, wherein said active is a psychotherapeutic agent.

44. (Original) The process of claim 1, wherein said active is an antibiotic.

45. (Original) The process of claim 1, wherein said active is an anesthetic.

46. (Original) The process of claim 1, wherein said active is a contraceptive.

47. (Original) The process of claim 1, wherein said active is an anti-thrombotic drug.

48. (Original) The process of claim 1, wherein said active is diphenhydramine.

49. (Original) The process of claim 1, wherein said active is nabilone.

50. (Original) The process of claim 1, wherein said active is albuterol sulfate.

51. (Original) The process of claim 1, wherein said active is an anti-tumor drug.

52. (Original) The process of claim 1, wherein said active is a glycoprotein.

53. (Original) The process of claim 1, wherein said active is an analgesic.

54. (Original) The process of claim 1, wherein said active is a hormone.

55. (Original) The process of claim 1, wherein said active is a decongestant.

56. (Original) The process of claim 1, wherein said active is a loratadine.

57. (Original) The process of claim 1, wherein said active is dextromethorphan.

58. (Original) The process of claim 1, wherein said active is chlorpheniramine maleate.

59. (Original) The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

60. (Original) The process of claim 1, wherein said active is an appetite stimulant.

61. (Original) The process of claim 1, wherein said active is a gastrointestinal agent.

62. (Original) The process of claim 1, wherein said active is a hypnotic.

63. (Original) The process of claim 1, wherein said active is taste-masked.

64. (Original) The process of claim 1, wherein said active is taste-masked using a flavor.

65. (Original) The process of claim 1, wherein said active is coated with a controlled release composition.

66. (Original) The process of claim 65, wherein said controlled release composition provides an immediate release.

67. (Original) The process of claim 65, wherein said controlled release composition provides a delayed release.

68. (Original) The process of claim 65, wherein said controlled release composition provides

a sustained release.

69. (Original) The process of claim 65, wherein said controlled release composition provides a sequential release.

70. (Original) The process of claim 1, wherein said active is a particulate.

71. (Original) The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.

72. (Original) The process of claim 1, further comprising a step of providing a second film layer.

73. (~~Amended~~ **Original**) The process of claim 72, wherein said second film layer is coated onto said resulting ~~pharmaceutical~~ film.

74. (~~Amended~~ **Original**) The process of claim 72, wherein said second film layer is spread onto said resulting ~~pharmaceutical~~ film.

75. (~~Amended~~ **Original**) The process of claim 72, wherein said second film layer is cast onto said resulting ~~pharmaceutical~~ film.

76. (~~Amended~~ **Original**) The process of claim 72, wherein said second film layer is extruded onto said resulting ~~pharmaceutical~~ film.

77. (~~Amended~~ **Original**) The process of claim 72, wherein said second film layer is sprayed onto said resulting ~~pharmaceutical~~ film.

78. (~~Amended~~ **Original**) The process of claim 72, wherein said second film is laminated

onto said resulting **~~pharmaceutical~~** film.

79. (**~~Amended~~** **Original**) The process of claim 72, further comprising laminating said resulting film to another **~~pharmaceutical~~** film.

80. (**~~Amended~~** **Original**) The process of claim 72, wherein said second film layer comprises an active.

81. (Amended) The process of claim **~~72~~80**, wherein said active in said second film **~~layer~~** is different than said active in said resulting **~~pharmaceutical~~** film.

82. (Amended) A process for manufacturing resulting films suitable for commercialization and regulatory approval**,** said **regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said** [making a]film**s** having a substantially uniform distribution of **components** **~~an active~~** [of components], **comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films,** comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and **~~an~~** **said** active**, said active** selected from the group consisting of bioactive actives, pharmaceutical actives**~~, drugs, medicaments~~** and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) **controlling drying through a process comprising** conveying said flowable polymer matrix

through a drying apparatus and evaporating at least a portion of said solvent from **said flowable polymer matrix** [said flowable polymer matrix] to ~~**rapidly**~~ form a visco-elastic film**,** having said active **substantially** uniformly distributed throughout ~~**by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying,**~~ within about the first [10]4 minutes [or fewer]**by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying** to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein **during said drying said flowable** ~~**the**~~ polymer matrix temperature is 100°C or less, and wherein ~~**content**~~ uniformity **of content** of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%; [and]

(d) forming [a] ~~**the**~~ **said** resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(e) ~~**forming a plurality of individual dosage unit samples of substantially the same size form said resulting film: and**~~

~~**(f)**~~ performing analytical chemical tests for ~~**content**~~ uniformity ~~**on said plurality**~~ **of content of said active in substantially equal sized** individual dosage units ~~**samples**~~ **sampled** from **different locations of** said resulting film, said tests indicating ~~**said substantially uniform distribution of the active, in that the amount of the active in the individual dosage unit samples**~~ **that uniformity of content in the amount of said active** varies by no more than 10% **and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and**

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said

analytical chemical tests.

83. (Original) The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.

84. (Original) The process of claim 82, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

85. (Original) The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

86. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting ofmethylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

87. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum,

acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

88. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

89. (Original) The process of claim 82, wherein said solvent is selected from the group consisting ofwater, polar organic solvent, and combinations thereof.

90. (Original) The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

91. (Cancelled)

92. (Amended) The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti -convulsants, anti -depressants, anti -diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid

preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and nonsystemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, antithrombotic drugs, hypnotics, anti -emetics, anti -nauseants, [anti -convulsants,]neuromuscular drugs, hyper-and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, antispasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

93. (Amended) The process of claim 82, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

94. (Original) The process of claim 82, wherein said active is a bioactive active.

95. (Cancelled)

96. (Original) The process of claim 82, wherein said active is an opiate or opiate-derivative.

97. (Original) The process of claim 82, wherein said active is an anti-emetic.

98. (Original) The process of claim 82, wherein said active is an amino acid preparation.

99. (Original) The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

100. (Original) The process of claim 82, wherein said active is a protein.

101. (Original) The process of claim 82, wherein said active is insulin.

102. (Original) The process of claim 82, wherein said active is an anti-diabetic.

103. (Original) The process of claim 82, wherein said active is an antihistamine.

104. (Original) The process of claim 82, wherein said active is an anti-tussive.

105. (Original) The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.

106. (Original) The process of claim 82, wherein said active is an anti-asthmatics.

107. (~~**Original**~~ **Amended**) The process of claim 82, wherein said active is an anti-diarrhea **preparation**.

108. (Original) The process of claim 82, wherein said active is an alkaloid.

109. (Original) The process of claim 82, wherein said active is an anti-psychotic.

110. (Original) The process of claim 82, wherein said active is an anti-spasmodic.

111. (Original) The process of claim 82, wherein said active is a biological response modifier.

112. (Original) The process of claim 82, wherein said active is an anti-obesity drug.

113. (Original) The process of claim 82, wherein said active is an H_2-antagonist.

114. (~~Original~~ **Amended**) The process of claim ~~82~~ **113**, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

115. (Original) The process of claim 82, wherein said active is a smoking cessation aid.

116. (Original) The process of claim 82, wherein said active is an anti-parkinsonian agent.

117. (Original) The process of claim 82, wherein said active is an anti-depressant.

118. (Original) The process of claim 82, wherein said active is an anti-migraine.

119. (Original) The process of claim 82, wherein said active is an anti-Alzheimer's agents.

120. (Original) The process of claim 82, wherein said active is a dopamine receptor agonist.

121. (Original) The process of claim 82, wherein said active is a cerebral dilator.

122. (Original) The process of claim 82, wherein said active is a psychotherapeutic agent.

123. (Original) The process of claim 82, wherein said active is an antibiotic.

124. (Original) The process of claim 82, wherein said active is an anesthetic.

125. (Original) The process of claim 82, wherein said active is a contraceptive.

126. (Original) The process of claim 82, wherein said active is an anti-thrombotic drug.

127. (Original) The process of claim 82, wherein said active is diphenhydramine.

128. (Original) The process of claim 82, wherein said active is nabilone.

129. (Original) The process of claim 82, wherein said active is albuterol sulfate.

130. (Original) The process of claim 82, wherein said active is an anti-tumor drug.

131. (Original) The process of claim 82, wherein said active is a glycoprotein.

132. (Original) The process of claim 82, wherein said active is an analgesic.

133. (Original) The process of claim 82, wherein said active is a hormone.

134. (Original) The process of claim 82, wherein said active is a decongestant.

135. (Original) The process of claim 82, wherein said active is a loratadine.

136. (Original) The process of claim 82, wherein said active is dextromethorphan.

137. (Original) The process of claim 82, wherein said active is chlorpheniramine maleate.

138. (Original) The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

139. (Original) The process of claim 82, wherein said active is an appetite stimulant.

140. (Original) The process of claim 82, wherein said active is a gastrointestinal agent.

141. (Original) The process of claim 82, wherein said active is a hypnotic.

142. (Original) The process of claim 82, wherein said active is taste-masked.

143. (Original) The process of claim 82, wherein said active is taste-masked using a flavor.

144. (Original) The process of claim 82, wherein said active is coated with a controlled release composition.

145. (Original) The process of claim 144, wherein said controlled release composition provides an immediate release.

146. (Original) The process of claim 144, wherein said controlled release composition provides a delayed release.

147. (Original) The process of claim 144, wherein said controlled release composition provides a sustained release.

148. (Original) The process of claim 144, wherein said controlled release composition provides a sequential release.

149. (Original) The process of claim 82, wherein said active is a particulate.

150. (Original) The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.

151. (Original) The process of claim 82, further comprising a step ofproviding a second film layer.

152. (Original) The process of claim 151, wherein said second film layer is coated onto said resulting film.

153. (Original) The process of claim 151, wherein said second film layer is spread onto said resulting film.

154. (Original) The process of claim 151, wherein said second film layer is cast onto said resulting film.

155. (Original) The process of claim 151, wherein said second film layer is extruded onto said resulting film.

156. (Original) The process of claim 151, wherein said second film layer is sprayed onto said resulting film.

157. (Original) The process of claim 151, wherein said second film layer is laminated onto said resulting film.

158. (Original) The process of claim 151, further comprising laminating said resulting film to another film.

159. (~~Amended~~ **Original**) The process of claim 151, wherein said second film ~~layer~~ comprises an active.

160. (Amended) The process of claim ~~151~~**159**, wherein said active in said second film ~~layer~~ is different than said active in said resulting film.

161. (Amended) A process for manufacturing a resulting ~~pharmaceutical~~ film suitable for commercialization and regulatory approval**, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units,** said[making a] film capable of being administered to a body surface and having a substantially uniform distribution of **a** ~~pharmaceutical active~~[components] **components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film**, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and **a**[n] ~~pharmaceutical~~ **said** active, **said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof,** said matrix having a substantially uniform distribution of said ~~pharmaceutical~~ active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) **controlling drying through a process comprising** conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent **from said flowable**

polymer matrix [from said flowable polymer matrix] to ~~rapidly~~ form a visco-elastic film**,** having said ~~pharmaceutical~~ active **substantially** uniformly distributed throughout ~~by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying,~~ within about the first [10]4 minutes [or fewer]**by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying** to maintain said substantially uniform distribution of said ~~pharmaceutical~~ active by locking-in or substantially preventing migration of said ~~pharmaceutical~~ active within said visco-elastic film**,** wherein **during said drying said flowable** ~~the~~ polymer matrix temperature is 100°C or less**, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%**;

(d) forming [a] ~~the~~ **said** resulting ~~pharmaceutical~~ film from said visco-elastic film, wherein said resulting ~~pharmaceutical~~ film has a water content of 10% or less and said substantially uniform distribution of ~~pharmaceutical~~ active by said locking-in or substantially preventing migration of said ~~pharmaceutical~~ active is maintained; [and]

(e) [administering said resulting film to a body surface] ~~forming a plurality of individual dosage unit samples of substantially the same size from said resulting pharmaceutical film;~~ **performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration, and**

(f) ~~performing analytical chemical tests for content uniformityon said plurality of individual dosage unit samples from said resulting pharmaceutical film, said tests indicating said substantially uniform distribution of the pharmaceutical active, in that the amount of the pharmaceutical active in the individual dosage unit samples varies by no~~

~~more than 10%; and~~ **administering said resulting film to a body surface~~, and~~**

~~(g) administering said resulting pharmaceutical film to a body surface~~ .

162. (Original) The process of claim 161, wherein said body surface is a mucous membrane.

163. (Original) The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.

164. (Original) The process of claim 161, wherein said body surface is the surface of a wound.

165. (Original) The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.

166. (Original) The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

167. (Original) The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

168. (Original) The process of claim 166, wherein said polymer further comprises a polymer

selected from the group consisting ofmethylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

169. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

170. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

171. (Original) The process of claim 161, wherein said solvent is selected from the group consisting ofwater, polar organic solvent, and combinations thereof.

172. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

173. (~~Original~~ Cancelled) ~~The process of claim 161, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.~~

174. (Amended) The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti -convulsants, anti -depressants, anti -diabetic agents, anti -diarrhea preparations, antidotes, anti -histamines, anti -hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and nonsystemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, antithrombotic drugs, hypnotics, anti -emetics, anti -nauseants, [anti -convulsants,]neuromuscular drugs, hyper-and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, antispasmodics, uterine relaxants, anti-obesity drugs, erythropoietic

drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

175. (Amended) The process of claim 161, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,

176. (Original) The process of claim 161, wherein said active is a bioactive active.

177. (Cancelled)

178. (Original) The process of claim 161, wherein said active is an opiate or opiate-derivative.

179. (Original) The process of claim 161, wherein said active is an anti-emetic.

180. (Original) The process of claim 161 wherein said active is an amino acid preparation.

181. (Original) The process of claim 161, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

182. (Original) The process of claim 161, wherein said active is a protein.

183. (Original) The process of claim 161, wherein said active is insulin.

184. (Original) The process of claim 161, wherein said active is an anti-diabetic.

185. (Original) The process of claim 161, wherein said active is an antihistamine.

186. (Original) The process of claim 161, wherein said active is an anti-tussive.

187. (Original) The process of claim 161, wherein said active is a non-steroidal anti-inflammatory.

188. (Original) The process of claim 161, wherein said active is an anti-asthmatics.

189. (~~Original~~ **Amended**) The process of claim 161, wherein said active is an anti-diarrhea **preparation**.

190. (Original) The process of claim 161, wherein said active is an alkaloid.

191. (Original) The process of claim 161, wherein said active is an anti-psychotic.

192. (Original) The process of claim 161, wherein said active is an anti-spasmodic.

193. (Original) The process of claim 161, wherein said active is a biological response modifier.

194. (Original) The process of claim 161, wherein said active is an anti-obesity drug.

195. (Original) The process of claim 161, wherein said active is an H2-antagonist.

196. (Original) The process of claim 195, wherein said H2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

197. (Original) The process of claim 161, wherein said active is a smoking cessation aid.

198. (Original) The process of claim 161, wherein said active is an anti-parkinsonian agent.

199. (Original) The process of claim 161, wherein said active is an anti-depressant.

200. (Original) The process of claim 161, wherein said active is an anti-migraine.

201. (Original) The process of claim 161, wherein said active is an anti-Alzheimer's agents.

202. (Original) The process of claim 161, wherein said active is a dopamine receptor agonist.

203. (Original) The process of claim 161, wherein said active is a cerebral dilator.

204. (Original) The process of claim 161, wherein said active is a psychotherapeutic agent.

205. (Original) The process of claim 161, wherein said active is an antibiotic.

206. (Original) The process of claim 161, wherein said active is an anesthetic.

207. (Original) The process of claim 161, wherein said active is a contraceptive.

208. (Original) The process of claim 161, wherein said active is an anti-thrombotic drug.

209. (Original) The process of claim 161, wherein said active is diphenhydramine.

210. (Original) The process of claim 161, wherein said active is nabilone.

211. (Original) The process of claim 161, wherein said active is albuterol sulfate.

212. (Original) The process of claim 161, wherein said active is an anti-tumor drug.

213. (Original) The process of claim 161, wherein said active is a glycoprotein.

214. (Original) The process of claim 161, wherein said active is an analgesic.

215. (Original) The process of claim 161, wherein said active is a hormone.

216. (Original) The process of claim 161, wherein said active is a decongestant.

217. (Original) The process of claim 161, wherein said active is a loratadine.

218. (Original) The process of claim 161, wherein said active is dextromethorphan.

219. (Original) The process of claim 161, wherein said active is chlorpheniramine maleate.

220. (Original) The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

221. (Original) The process of claim 161, wherein said active is an appetite stimulant.

222. (Original) The process of claim 161, wherein said active is a gastrointestinal agent.

223. (Original) The process of claim 161, wherein said active is a hypnotic.

224. (Original) The process of claim 161, wherein said active is taste-masked.

225. (Original) The process of claim 161, wherein said active is taste-masked using a flavor.

226. (Original) The process of claim 161, wherein said active is coated with a controlled release composition.

227. (Original) The process of claim 226, wherein said controlled release composition provides an immediate release.

228. (Original) The process of 226, wherein said controlled release composition provides a delayed release.

229. (Original) The process of claim 226, wherein said controlled release composition

230. (Original) The process of claim 226, wherein said controlled release composition provides a sequential release.

231. (Original) The process of claim 161, wherein said active is a particulate.

232. (Original) The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.

233. (Original) The process of claim 161, further comprising a step ofproviding a second film layer.

234. (~~Amended~~ **Original**) The process of claim 233, wherein said second film layer is coated onto said resulting ~~pharmaceutical~~ film.

235. (~~Amended~~ **Original**) The process of claim 233, wherein said second film layer is spread onto said resulting ~~pharmaceutical~~ film.

236. (~~Amended~~ **Original**) The process of claim 233, wherein said second film layer is cast

onto said resulting ~~**pharmaceutical**~~ film.

237. (~~**Amended**~~ **Original**) The process of claim 233, wherein said second film layer is extruded onto said resulting ~~**pharmaceutical**~~ film.

238. (~~**Amended**~~ **Original**) The process of claim 233, wherein said second film layer is sprayed onto said resulting ~~**pharmaceutical**~~ film.

239. (~~**Amended**~~ **Original**) The process of claim 233, wherein said second film layer is laminated onto said resulting ~~**pharmaceutical**~~ film.

240. (~~**Amended**~~ **Original**) The process of claim 233, further comprising laminating said resulting film to another ~~**pharmaceutical**~~ film.

241. (Original) The process of claim 233, wherein said second film comprises an active.

242. (Amended) The process of claim ~~**233**~~**241**, wherein said active in said second film is different than said active in said resulting ~~**pharmaceutical**~~ film.

243. (~~**Amended**~~ **Original**) The process of claim 1, ~~**wherein**~~ said active is an anti-nauseant.

244. (Amended) The process of claim 1, ~~**wherein**~~ said active is an erectile dysfunction **drug** ~~**therapy**~~.

245. (~~**Amended**~~ **Original**) The process of claim 1, ~~**wherein**~~ said active is a vasoconstrictor.

246. (~~**Amended**~~ **Original**) The process of claim 1, ~~**wherein**~~ said active is a stimulant.

247. (~~**Amended**~~ **Original**) The process of claim 1, ~~**wherein**~~ said active is a migraine

treatment.

248. (~~Amended~~ **Original**) The process of claim 1, ~~wherein~~ said active is granisetron hydrochloride.

249. (~~Amended~~ **Original**) The process of claim 1, wherein said resulting ~~pharmaceutical~~ film provides administration of said active to an individual through the buccal cavity of said individual.

250. (~~Amended~~ **Original**) The process of claim 1, wherein said resulting ~~pharmaceutical~~ film provides administration of said active through gingival application ~~to an~~ [of said] **of said** individual.

251. (~~Amended~~ **Original**) The process of claim 1, wherein said resulting ~~pharmaceutical~~ film provides administration of said active through sublingual application ~~to an~~ [of said] **of said** individual.

252. (~~Amended~~ **Original**) The process of claim 1, wherein said resulting ~~pharmaceutical~~ film provides administration of said active to an individual through a mucosal membrane of said individual.

253. (~~Amended~~ **Original**) The process of claim 1, wherein said resulting ~~pharmaceutical~~ film provides administration of said active to an individual by administration within the body ofthe individual during surgery.

254. (~~Amended~~ **Cancelled**) ~~The process of claim 1, wherein said resulting pharmaceutical film has a variation of the amount of the pharmaceutical active~~ [content]~~of less than~~ [10%]~~5%~~ ~~per~~ [film unit]~~individual dosage unit.~~

255. (Cancelled)

256. (~~Amended~~ **Original**) The method of claim 1, wherein said resulting ~~**pharmaceutical**~~ film contains less than about 6% by weight solvent.

257. (~~Original~~ **Cancelled**) ~~**The method of claim 1, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.**~~

258. (~~Amended~~ **Original**) The method of claim 1, wherein said resulting ~~**pharmaceutical**~~ film is orally administrable.

259. (Original) The method of claim 1, wherein said active is in the form of a particle.

260. (Original) The method of claim 1, wherein said matrix comprises a dispersion.

261. (~~Amended~~ **Original**) The process of claim 82, ~~**wherein**~~ said active is an anti-nauseant.

262. (Amended) The process of claim 82, ~~**wherein**~~ said active is an erectile dysfunction **drug** ~~**therapy**~~.

263. (~~Amended~~ **Original**) The process of claim 82, ~~**wherein**~~ said active is a vasoconstrictor.

264. (~~Amended~~ **Original**) The process of claim 82, ~~**wherein**~~ said active is a stimulant.

265. (~~Amended~~ **Original**) The process of claim 82, ~~**wherein**~~ said active is a migraine treatment.

266. (~~Amended~~ **Original**) The process of claim 82, ~~**wherein**~~ said active is granisetron hydrochloride.

267. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

268. (~~Amended~~ **Original**) The process of claim 82, wherein said resulting film provides administration of said active through gingival application ~~to an~~ [of said] **of said** individual.

269. (~~Amended~~ **Original**) The process of claim 82, wherein said resulting film provides administration of said active through sublingual application ~~to an~~ [of said] **of said** individual.

270. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

271. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

272. (~~Amended~~ Cancelled) ~~The process of claim 82, wherein in step (e) the active varies less than 5% and in step (f) said resulting film has a variation of the amount of active~~ [content]~~of less than 5%~~[10%] ~~per~~ [film unit]~~individual dosage unit.~~

273. (Cancelled)

274. (Original) The method of claim 82, wherein said resulting film contains less than about 6% by weight solvent.

275. (~~Original~~ Cancelled) ~~The method of claim 82, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.~~

276. (Original) The method of claim 82, wherein said resulting film is orally administrable.

277. (Original) The method of claim 82, wherein said active is in the form of a particle.

278. (Original) The method of claim 82, wherein said matrix comprises a dispersion.

279. (~~Amended~~ **Original**) The process of claim 161, ~~wherein~~ said active is an anti-nauseant.

280. (Amended) The process of claim 161, ~~wherein~~ said active is an erectile dysfunction **drug** ~~therapy~~.

281. (~~Amended~~ **Original**) The process of claim 161, ~~wherein~~ said active is a vasoconstrictor.

282. (~~Amended~~ **Original**) The process of claim 161, ~~wherein~~ said active is a stimulant.

283. (~~Amended~~ **Original**) The process of claim 161, ~~wherein~~ said active is a migraine treatment.

284. (~~Amended~~ **Original**) The process of claim 161, ~~wherein~~ said active is granisetron hydrochloride.

285. (~~Amended~~ **Original**) The process of claim 161, wherein said resulting ~~pharmaceutical~~ film provides administration of said active to an individual through the buccal cavity of said individual.

286. (~~Amended~~ **Original**) The process of claim 161, wherein said resulting ~~pharmaceutical~~ film provides administration of said active through gingival application ~~to an~~ [of said] **of said** individual.

287. (~~Amended~~ **Original**) The process of claim 161, wherein said resulting ~~pharmaceutical~~

film provides administration of said active through sublingual application ~~to an~~ [of said] **of said** individual.

288. (~~Amended~~ **Original**) The process of claim 161, wherein said resulting ~~pharmaceutical~~ film provides administration of said active to an individual through a mucosal membrane of said individual.

289. (~~Amended~~ **Original**) The process of claim 161, wherein said resulting ~~pharmaceutical~~ film provides administration of said active to an individual by administration within the body of the individual during surgery.

290. (~~Amended~~ **Cancelled**) ~~The process of claim 161, wherein said resulting pharmaceutical film has a variation of in the amount of pharmaceutical active~~ [content]~~of less than~~ [10%]~~5% per~~ [film unit] ~~individual dosage unit.~~

291. (Cancelled)

292. (~~Amended~~ **Original**) The method of claim 161, wherein said resulting ~~pharmaceutical~~ film contains less than about 6% by weight solvent.

293. (~~Original~~ **Cancelled**) ~~The method ofclaim 161, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.~~

294. (~~Amended~~ **Original**) The method of claim 161, wherein said resulting ~~pharmaceutical~~ film is orally administrable.

295. (Original) The method of claim 161, wherein said active is in the form of a particle.

296. (Original) The method of claim 161, wherein said matrix comprises a dispersion.

297. (Original) The method of claim 1, wherein said matrix comprises an emulsion, a colloid or a suspension.

298. (Original) The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.

299. (Original) The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.

300. (New) ~~The process of claim 1, wherein the forming of a plurality of individual dosage unit samples and performing analytical chemical tests comprises:~~

~~(a) cutting the substantially equally sized individual dosage unit samples from the different locations of the resulting film;~~

~~(b) dissolving at least a portion of said dosage unit samples: and~~

~~(c) testing for the amount of the pharmaceutical active present in each dosage unit sample.~~

301. (New) ~~The process of claim 1, wherein regulatory approval is provided by the U.S. Food and Drug Administration.~~

300 ~~302~~. (New) The process of claim 1, wherein **said tests further indicate that** the amount of **~~pharmaceutical~~** active in **~~of~~ said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 5%.

301 ~~303~~. (New) The process of claim 1, wherein **said tests further indicate that** the amount of **~~pharmaceutical~~** active in **~~of~~ said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 2%.

302 ~~304~~. (New) The process of claim 1, wherein **said tests further indicate that** the amount of ~~**pharmaceutical**~~ active in ~~**of**~~ **said** individual dosage units **sampled from said resulting film** ~~**has a variance of**~~ **varies by** less than 1 %.

303 ~~305~~. (New) The process of claim 1, wherein **said tests further indicate that** the amount of ~~**pharmaceutical**~~ active in ~~**of**~~ **said** individual dosage units **sampled from said resulting film** ~~**has a variance of**~~ **varies by** less than 0.5%.

~~**306. (New) The process of claim 82, wherein the forming of a plurality of individual dosage unit samples and performing analytical chemical tests comprises:**~~

~~**(a) cutting the substantially equally sized individual dosage unit samples from the different locations ofthe resulting film;**~~

~~**(b) dissolving at least a portion of said dosage unit samples; and**~~

~~**(c) testing for the amount of the active present in each dosage unit sample.**~~

~~**307. (New) The process of claim 82, wherein regulatory approval is provided by the U.S. Food and Drug Administration.**~~

304 ~~308~~. (New) The process of claim 82, wherein **said tests further indicate that** the amount of ~~**pharmaceutical**~~ active in ~~**of**~~ **said** individual dosage units **sampled from said resulting film** ~~**has a variance of**~~ **varies by** less than 5%.

305 ~~309~~. (New) The process of claim 82, wherein **said tests further indicate that** the amount of ~~**pharmaceutical**~~ active in ~~**of**~~ **said** individual dosage units **sampled from said resulting film** ~~**has a variance of**~~ **varies by** less than 2%.

306 ~~310~~. (New) The process of claim 82, wherein **said tests further indicate that** the amount of ~~**pharmaceutical**~~ active in ~~**of**~~ **said** individual dosage units **sampled from said resulting film** ~~**has a variance of**~~ **varies by** less than 1 %.

307 ~~311~~. (New) The process of claim 82, wherein **said tests further indicate that** the amount of ~~**pharmaceutical**~~ active in ~~**of**~~ **said** individual dosage units **sampled from said resulting film** ~~**has a variance of**~~ **varies by** less than 0.5%.

~~**312. (New) The process of claim 161. wherein the forming of a plurality of individual dosage unit samples and performing analytical chemical tests comprises:**~~

~~**(a) cutting the substantially equally sized individual dosage unit samples from the different locations of the resulting film;**~~

~~**(b) dissolving at least a portion of said dosage unit samples; and**~~

~~**(c) testing for the amount of the pharmaceutical active present in each dosage unit sample.**~~

~~**313 (New) The process of claim 161. wherein regulatory approval is provided by the U.S. Food and Drug Administration.**~~

308 ~~314~~. (New) The process of claim 161, wherein **said tests further indicate that** the amount of ~~**pharmaceutical**~~ active in ~~**of**~~ **said** individual dosage units **sampled from said resulting film** ~~**has a variance of**~~ **varies by** less than 5%.

309 ~~315~~. (New) The process of claim 161, wherein **said tests further indicate that** the amount of ~~**pharmaceutical**~~ active in ~~**of**~~ **said** individual dosage units **sampled from said resulting film** ~~**has a variance of**~~ **varies by** less than 2%.

310 ~~316~~. (New) The process of claim 161, wherein **said tests further indicate that** the amount of ~~**pharmaceutical**~~ active in ~~**of**~~ **said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 1 %.

311 ~~317~~. (New) The process of claim 161, wherein **said tests further indicate that** the amount of ~~**pharmaceutical**~~ active in ~~**of**~~ **said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 0.5%.

312 ~~318~~. (New) The process of claim 1, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

313 ~~319~~. (New) The process of claim 82, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

314 ~~320~~. (New) The process of claim 161, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

315 ~~321~~. (New) A process for manufacturing resulting ~~**pharmaceutical**~~ films suitable for commercialization and regulatory approval**, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units,** said films having a substantially uniform distribution of **components comprising a substantially uniform distribution of a desired amount of said ~~an~~** active **in individual dosage units of said resulting films**, comprising the steps of:

(a) forming a **flowable polymer matrix** ~~**masterbach pre-mix**~~ comprising a ~~**polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof**~~ **water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active**;

(b) ~~**adding an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;**~~

~~(c)~~ casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

~~(d)~~ **(c) controlling drying through a process comprising** conveying said ~~**flowable**~~ polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to ~~**rapidly**~~ form a visco-elastic film**,** having said active **substantially** uniformly distributed throughout ~~**by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying,**~~ within about the first 4 minutes **by rapidly increasing the viscosity of said polymer matrix upon initiation of drying** to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film**,** wherein **during said drying said flowable** ~~**the**~~ polymer matrix temperature is 100°C or less;

~~(e)~~ **(d)** forming **said** ~~**the**~~ resulting ~~**pharmaceutical**~~ film from said visco-elastic film, wherein said resulting ~~**pharmaceutical**~~ film has a water content of 10% or less and said substantially uniform distribution of **said** active by said locking-in or substantially preventing migration of said active is maintained**, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%**;

~~(f) forming a plurality of individual dosage units of substantially the same size from said resulting pharmaceutical film; and~~

~~(g)~~ (e) performing analytical chemical tests for ~~content~~ uniformity ~~on said plurality~~ of **content of said active in said substantially equal sized** individual dosage units ~~from~~ **of** said **sampled** resulting ~~pharmaceutical~~ film, said tests indicating ~~said substantially uniform distribution of the active, in~~ that **uniformity of content in** the amount of the active ~~in individual dosage units~~ varies by no more than 10% **and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and**

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of said active as indicated by said analytical chemical tests.

316 ~~(322)~~. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval**, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units,** said film ~~capable of being administered to a body surface~~ having a substantially uniform distribution of ~~an active~~ **components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film**, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and ~~an~~ **said** active**, said active** selected from the group consisting of bioactive actives, pharmaceutical actives~~, drugs, medicaments~~ and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) **controlling drying through a process comprising** conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to ~~**rapidly**~~ form a visco-elastic film**,** having said active substantially uniformly distributed throughout ~~**by rapidly increasing the viscosity of said flowable polymer matric upon initiation of drying**~~, within about the first 4 minutes **by rapidly increasing the viscosity of said polymer matrix upon initiation of drying** to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film**,** wherein **during said drying said flowable** ~~**the**~~ polymer matrix temperature is 100°C or less;

(d) forming **said** ~~**the**~~ resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained**, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and**
~~**(e) forming a plurality of individual dosage units of substantially the same size from said resulting film;**~~

~~(f)~~ **(e)** performing analytical chemical tests for ~~**content**~~ uniformity ~~**on said plurality**~~ of **content of said active in said substantially equal sized** individual dosage units ~~**from**~~ **of** said **sampled** resulting film, said tests indicating ~~**said substantially uniform distribution**~~ **that uniformity of content in the amount** of ~~**the**~~ **said** active ~~**in individual dosage units**~~ varies by no more than 10% **and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration**~~**; and**~~

~~(g) administering said resulting film to a body surface~~.

317 ~~323~~. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval**, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units,** said film having a substantially uniform distribution of **components comprising a substantially uniform distribution of said** ~~a desired amount of an~~ active in individual ~~doses~~ **dosage units** of **said** ~~the~~ resulting ~~pharmaceutical~~ film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and **said** ~~a pharmaceutical~~ active**, said active** selected from the group consisting of bioactive actives, pharmaceutical actives~~, drugs, medicaments~~ and combinations thereof**, said matrix having a substantially uniform distribution of said active**;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) **controlling drying through a process comprising** conveying said **flowable** polymer matrix through a drying apparatus **using air currents, which have forces below a yield value of said flowable polymer matrix during drying, to evaporate** ~~evaporating~~ at least a portion of said solvent to ~~rapidly~~ form a visco-elastic film, having said ~~pharmaceutical~~ active **substantially** uniformly distributed throughout ~~by rapidly increasing the viscosity of said polymer matrix upon initiation of drying~~, within about the first 4 minutes **by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying** to maintain said **substantially** uniform distribution of said ~~pharmaceutical~~ active by lockingin or substantially preventing migration of said ~~pharmaceutical~~ active within said visco-elastic film**, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by no more than 10%, and**

wherein **during said drying said flowable ~~the~~** polymer matrix temperature is 100°C or less;

(d) forming **said ~~the~~** resulting **~~pharmaceutical~~** film from said visco-elastic film**~~, wherein said resulting pharmaceutical film has~~ by further controlling drying by continuing evaporation to** a water content **of said resulting film** of 10% or less and **wherein** said **substantially** uniform distribution of **~~pharmaceutical~~** active by said locking-in or substantially preventing migration of said **~~pharmaceutical~~** active is maintained, such that uniformity of content in the amount of **said ~~the~~** active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies **by** no more than 10% **~~from the desired amount of the active~~**; and

(e) performing analytical chemical tests for **~~content~~** uniformity **of content** of said **~~pharmaceutical~~** active in substantially equal sized individual dosage units of said sampled resulting **~~pharmaceutical~~** film, said tests indicating that uniformity of content in the amount of **said ~~the~~** active varies by no more than 10% **~~from the desired amount of the active~~ and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration**.

318 ~~324~~. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval**, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units,** said film having a substantially uniform distribution of **~~an active~~ components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film**, comprising the steps of:

(a) forming a flowable polymer matrix comprising **~~a polymer selected from the group consisting of~~** a water-soluble polymer, **~~a water swellable polymer and combinations thereof,~~** a solvent and said active**, said active** selected from the group consisting of bioactive actives, pharmaceutical actives**~~, drugs, medicaments~~** and combinations thereof, said matrix having a

substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) **controlling drying through a process comprising** conveying said flowable polymer matrix through a drying apparatus **at a temperature of about 60°C and using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate ~~and evaporating~~** at least a portion of said solvent to **~~rapidly~~** form a visco-elastic film, having said active **substantially** uniformly distributed throughout **~~by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying,~~** within about the first 4 minutes **by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying** to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said viscoelastic film**, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and** wherein **during said drying said flowable ~~the~~** polymer matrix temperature is 100°C or less**~~, wherein content uniformity of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%~~**;

(d) forming **said ~~the~~** resulting film from said visco-elastic film**~~, wherein said resulting film has~~ by further controlling by continuing evaporation to** a water content of **said resulting film of** 10% or less and **wherein** said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained**, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by less than 5%**; and

(e) **~~forming a plurality of individual dosage unit samples of substantially the same size from~~**

~~said resulting film, wherein the amount of the active in the individual dosage unit samples varies by no more than 10%~~ performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by less than 5% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

~~325. (New) The process of claim 321, wherein said water-soluble polymer comprises polyethylene oxide.~~

~~326. (New) The process of claim 321, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.~~

~~327. (New) The process of claim 326, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, polyClactic acid)/polyCglycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.~~

~~328. (New) The process of claim 326, wherein said polymer further comprises a polymer selected from the group consisting of methyl methacrylate copolymer, polyacrylic acid polymer, polyCglycolic acid) CPGA), poly(lactic acid) (PLA)' polyClactic~~

acid)/poly(glycolic acidVpolyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

329. (New) The process of claim 326, wherein said polymer further comprises a polymer selected from the grOUP consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

330 . (New) The process of claim 326, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyyinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acidVpoly(glycolic acidVpolyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLAt poly(lactic acidVpoly(glycolic acidVpolyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageen an, locust bean gum, dextran, gellan gum and combinations thereof.

331. (New) The process of claim 321. wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

332. (New) The process of claim 331, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

333. (New) The process of claim 321, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti¬lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti¬uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, neuromuscular drugs, hyper-and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

334. (New) The process of claim 321, wherein said active is selected from the group consisting of antigens, allergens, spores, microorganisms, seeds, enzymes, vitamins and combinations thereof.

335. (New) The process of claim 321, wherein said active is a bioactive active.

336. (New) The process of claim 321, wherein said active is an opiate or opiate-derivative.

337. (New) The process of claim 321, wherein said active is an anti-emetic.

338. (New) The process of claim 321, wherein said active is an amino acid preparation.

339. (New) The process of claim 321, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

340. (New) The process of claim 321, wherein said active is a protein.

341. (New) The process of claim 321, wherein said active is insulin.

342. (New) The process of claim 321, wherein said active is an anti-diabetic.

343. (New) The process of claim 321, wherein said active is an antihistamine.

344. (New) The process of claim 321, wherein said active is an anti-tussive.

345. (New) The process of claim 321, wherein said active is a non-steroidal anti-inflammatory.

~~346. (New) The process of claim 321, wherein said active is an anti-asthmatics.~~

~~347. (New) The process of claim 321, wherein said active is an anti-diarrhea.~~

~~348. (New) The process of claim 321, wherein said active is an alkaloid.~~

~~349. (New) The process of claim 321, wherein said active is an anti-psychotic.~~

~~350. (New) The process of claim 321, wherein said active is an anti-spasmodic.~~

~~351. (New) The process of claim 321, wherein said active is a biological response modifier.~~

~~352. (New) The process of claim 321, wherein said active is an anti-obesity drug.~~

~~353. (New) The process of claim 321, wherein said active is an H_2-antagonist.~~

~~354. (New) The process of claim 321, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.~~

~~355. (New) The process of claim 321, wherein said active is a smoking cessation aid.~~

~~356. (New) The process of claim 321, wherein said active is an anti-parkinsonian agent.~~

~~357. (New) The process of claim 321, wherein said active is an anti-depressant.~~

~~358. (New) The process of claim 321, wherein said active is an anti-migraine.~~

~~359. (New) The process of claim 321, wherein said active is an anti-Alzheimer's agents.~~

~~360. (New) The process of claim 321, wherein said active is a dopamine receptor agonist.~~

~~361. (New) The process of claim 321, wherein said active is a cerebral dilator.~~

~~362. (New) The process of claim 321, wherein said active is a psychotherapeutic agent.~~

~~363. (New) The process of claim 321, wherein said active is an antibiotic.~~

~~364. (New) The process of claim 321, wherein said active is an anesthetic.~~

~~365. (New) The process of claim 321, wherein said active is a contraceptive.~~

~~366. (New) The process of claim 321, wherein said active is an anti-thrombotic drug.~~

~~367. (New) The process of claim 324, wherein said active is an analgesic.~~

~~368. (New) The process of claim 324, wherein said active is a hormone.~~

~~369. (New) The process of claim 324, wherein said active is a decongestant.~~

~~370. (New) The process of claim 324, wherein said active is a loratadine.~~

~~371. (New) The process of claim 324, wherein said active is dextromethorphan.~~

~~372. (New) The process of claim 324, wherein said active is chlorpheniramine maleate.~~

373. (New) The process of claim 324, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamIne, a decongestant, a cough suppressant and combinations thereof.

374. (New) The process of claim 324, wherein said active is an appetite stimulant.

375. (New) The process of claim 324, wherein said active is a gastrointestinal agent.

376. (New) The process of claim 324, wherein said active is a hypnotic.

377. (New) The process of claim 321, wherein said active is diphenhydramine.

378. (New) The process of claim 321, wherein said active is nabilone.

379. (New) The process of claim 321, wherein said active is albuterol sulfate.

380. (New) The process of claim 321, wherein said active is an anti-tumor drug.

381. (New) The process of claim 321, wherein said active is a glycoprotein.

382. (New) The process of claim 321, wherein said active is an analgesic.

383. (New) The process of claim 321, wherein said active is a hormone.

384. (New) The process of claim 321, wherein said active is a decongestant.

385. (New) The process of claim 321, wherein said active is a loratadine.

386. (New) The process of claim 321, wherein said active is dextromethomhan.

387. (New) The process of claim 321, wherein said active is chlorpheniramine maleate.

388. (New) The process of claim 321, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

389. (New) The process of claim 321, wherein said active is an appetite stimulant.

390. (New) The process of claim 321, wherein said active is a gastrointestinal agent.

391. (New) The process of claim 321, wherein said active is a hypnotic.

392. (New) The process of claim 321, wherein said active is taste-masked.

393. (New) The process of claim 321, wherein said active is taste-masked using a flavor.

394. (New) The process of claim 321, wherein said active is coated with a controlled release composition.

395. (New) The process of claim 394, wherein said controlled release composition provides an immediate release.

396. (New) The process of claim 394, wherein said controlled release composition provides a delayed release.

397. (New) The process of claim 394, wherein said controlled release composition provides a sustained release.

398. (New) The process of claim 394, wherein said controlled release composition provides a sequential release.

399. (New) The process of claim 321, wherein said active is a particulate.

400. (New) The process of claim 321, further comprising adding a degassing agent to said flowable polymer matrix.

401. (New) The process of claim 321, further comprising a step of providing a second film layer.

402. (New) The process of claim 401, wherein said second film layer is coated onto said resulting pharmaceutical film.

403. (New) The process of claim 401, wherein said second film layer is spread onto said resulting pharmaceutical film.

404. (New) The process of claim 401, wherein said second film layer is cast onto said resulting pharmaceutical film.

405. (New) The process of claim 401, wherein said second film layer is extruded onto said resulting pharmaceutical film.

406. (New) The process of claim 401, wherein said second film layer is sprayed onto said resulting pharmaceutical film.

407. (New) The process of claim 401, wherein said second film layer is laminated onto said resulting pharmaceutical film.

~~408. (New) The process of claim 401, further comprising laminating said resulting pharmaceutical film to another film.~~

~~409. (New) The process of claim 401, wherein said second film layer comprises an active.~~

~~410. (New) The process of claim 401, wherein said active in said second film layer is different than said active in said resulting pharmaceutical film.~~

~~411. (New) The process of claim 322, wherein said water-soluble polymer comprises polyethylene oxide.~~

~~412. (New) The process of claim 322, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullu1an, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyviny1 copolymers, hydroxypropy1methy1 cellulose, hydroxyethy1 cellulose, hydroxypropy1 cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, po1yacrylic acid, methy1methacry1ate copolymer, carboxyviny1 copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.~~

~~413. (New) The process of claim 412, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellu10se, hydroxypropy1 ethyl cellulose, cellulose acetate phthalate, hydroxypropy1 methyl cellulose phthalate, po1yviny1acetatephtha1ates, phtha1ated gelatin, crosslinked gelatin, po1y(1actic acid)/po1y(glyco1ic acid)/po1ythy1eneg1yco1 copolymers, po1ycapro1actone and combinations thereof.~~

~~414. (New) The process of claim 412, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid~~

~~polymer, polyCglycolic acid) CPGA), poly(lactic acid) CPLAt poly(lactic acid)/polyCglycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, polyCorthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.~~

~~415. (New) The process of claim 412, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.~~

~~416. (New) The process of claim 412, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, polyClactic acid)/polyCglycolic acid)/polyethyleneglycol~~

~~copolymers, p~lycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, polyCglycolic acid) (PGA), polyClactic acid) CPLA), polY(lactic acid)/polyCglycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, polyCa-esters), polyanhydrides, polyacetates, polycaprolactones, polyCorthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.~~

~~417. (New) The process of claim 322, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.~~

418. (New) The process of claim 417, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

419. (New) The process of claim 322, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti¬lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti¬uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, synipatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, neuromuscular drugs, hyper-and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity

drugs, erythropoietic drugs, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

420. (New) The process of claim 322, wherein said active is selected from the group consisting of antigens, allergens, spores, microorganisms, seeds, enzymes, vitamins and combinations thereof.

421. (New) The process of claim 322, wherein said active is a bioactive active.

422. (New) The process of claim 322, wherein said active is an opiate or opiate-derivative.

423. (New) The process of claim 322, wherein said active is an anti-emetic.

424. (New) The process of claim 322, wherein said active is an amino acid preparation.

425. (New) The process of claim 322, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

426. (New) The process of claim 322, wherein said active is a protein.

427. (New) The process of claim 322, wherein said active is insulin.

428. (New) The process of claim 322, wherein said active is an anti-diabetic.

429. (New) The process of claim 322, wherein said active is an antihistamine.

430. (New) The process of claim 322, wherein said active is an anti-tussive.

~~431. (New) The process of claim 322, wherein said active is a non-steroidal anti-inflammatory.~~

~~432. (New) The process of claim 322, wherein said active is an anti-asthmatics.~~

~~433. (New) The process of claim 322, wherein said active is an anti-diarrhea.~~

~~434. (New) The process of claim 322, wherein said active is an alkaloid.~~

~~435. (New) The process of claim 322, wherein said active is an anti-psychotic.~~

~~436. (New) The process of claim 322, wherein said active is an anti-spasmodic.~~

~~437. (New) The process of claim 322, wherein said active is a biological response modifier.~~

~~438. (New) The process of claim 322, wherein said active is an anti-obesity drug.~~

~~439. (New) The process of claim 322, wherein said active is an Hrantagonist.~~

~~440. (New) The process of claim 322, wherein said Hk-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.~~
~~441. (New) The process of claim 322, wherein said active is a smoking cessation aid.~~

~~442. (New) The process of claim 322, wherein said active is an anti-parkinsonian agent.~~

~~443. (New) The process of claim 322, wherein said active is an anti-depressant.~~

~~444. (New) The process of claim 322, wherein said active is an anti-migraine.~~

~~445. (New) The process of claim 322, wherein said active is an anti-Alzheimer's agents.~~

~~446. (New) The process of claim 322, wherein said active is a dopamine receptor agonist.~~

~~447. (New) The process of claim 322, wherein said active is a cerebral dilator.~~

~~448. (New) The process of claim 322, wherein said active is a psychotherapeutic agent.~~

~~449. (New) The process of claim 322, wherein said active is an antibiotic.~~

~~450. (New) The process of claim 322, wherein said active is an anesthetic.~~

~~451. (New) The process of claim 322, wherein said active is a contraceptive.~~

~~452. (New) The process of claim 322, wherein said active is an anti-thrombotic drug.~~

~~453. (New) The process of claim 322, wherein said active is diphenhydramine.~~

~~454. (New) The process of claim 322, wherein said active is nabilone.~~

~~455. (New) The process of claim 322, wherein said active is albuterol sulfate.~~

~~456. (New) The process of claim 322, wherein said active is an anti-tumor drug.~~

~~457. (New) The process of claim 322, wherein said active is a glycoprotein.~~

~~458. (New) The process of claim 322, wherein said active is an analgesic.~~

~~459. (New) The process of claim 322, wherein said active is a hormone.~~

~~460. (New) The process of claim 322, wherein said active is a decongestant.~~

~~461. (New) The process of claim 322, wherein said active is a loratadine.~~

~~462. (New) The process of claim 322, wherein said active is dextromethorphan.~~

~~463. (New) The process of claim 322, wherein said active is chlorpheniramine maleate.~~

~~464. (New) The process of claim 322, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.~~

~~465. (New) The process of claim 322, wherein said active is an appetite stimulant.~~

~~466. (New) The process of claim 322, wherein said active is a gastrointestinal agent.~~

~~467. (New) The process of claim 322, wherein said active is a hypnotic.~~

~~468. (New) The process of claim 322, wherein said active is taste-masked.~~

~~469. (New) The process of claim 322, wherein said active is taste-masked using a flavor.~~

~~470. (New) The process of claim 322, wherein said active is coated with a controlled release composition.~~

471. (New) The process of claim 470, wherein said controlled release composition provides an immediate release.

472. (New) The process of claim 470, wherein said controlled release composition provides a delayed release.

473. (New) The process of claim 470, wherein said controlled release composition provides a sustained release.

474. (New) The process of claim 470, wherein said controlled release composition provides a sequential release.

475. (New) The process of claim 322, wherein said active is a particulate.

476. (New) The process of claim 322, further comprising adding a degassing agent to said flowable polymer matrix.

477. (New) The process of claim 322, further comprising a step of providing a second film layer.

478. (New) The process of claim 477, wherein said second film layer is coated onto said resulting film.

479. (New) The process of claim 477, wherein said second film layer is spread onto said resulting film.

480. (New) The process of claim 477, wherein said second film layer is cast onto said resulting film.

481. (New) The process of claim 477, wherein said second film layer is extruded onto said resulting film.

482. (New) The process of claim 477, wherein said second film layer is sprayed onto said resulting film.

483. (New) The process of claim 477, wherein said second film layer is laminated onto said resulting film.

484. (New) The process of claim 477, further comprising laminating said resulting film to another film.

485. (New) The process of claim 477, wherein said second film layer comprises an active.

486. (New) The process of claim 477, wherein said active in said second film layer is different than said active in said resulting film.

487. (New) The process of claim 323, wherein said water-soluble polymer comprises polyethylene oxide.

488. (New) The process of claim 323, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

~~489. (New) The process of claim 488, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, polyClactic acid)/polyCglycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.~~

~~490. (New) The process of claim 488, wherein said polymer further comprises a polymer selected from the group consisting of methyl methacrylate copolymer, polyacrylic acid polymer, polyCglycolic acid) CPGA), poly(lactic acid) CPLA)' polyClactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.~~

~~491. (New) The process of claim 488, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, caragccnan, locust bean gum, dextran, gellan gum and combinations thereof.~~

~~492. (New) The process of claim 488, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, polyClactic acid)/polyCglycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), polyClactic acid) (PLA). polyClactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamin~ acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides,~~

poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

493. (New) The process of claim 323, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

494. (New) The process of claim 493, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

495. (New) The process of claim 323, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti¬lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti¬uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite

~~suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, neuromuscular drugs, hyper-and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.~~

~~496. (New) The process of claim 323, wherein said active is selected from the group consisting of antigens, allergens, spores, microorganisms, seeds, enzymes, vitamins and combinations thereof.~~

~~497. (New) The process of claim 323, wherein said active is a bioactive active.~~

~~498. (New) The process of claim 323, wherein said active is an opiate or opiate-derivative.~~

~~499. (New) The process of claim 323, wherein said active is an anti-emetic.~~

~~500. (New) The process of claim 323, wherein said active is an amino acid preparation.~~

~~501. (New) The process of claim 323, wherein said active is selected from the grOUP consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.~~

~~502. (New) The process of claim 323, wherein said active is a protein.~~

~~503. (New) The process of claim 323, wherein said active is insulin.~~

504. (New) The process of claim 323. wherein said active is an anti-diabetic.

505. (New) The process of claim 323. wherein said active is an antihistamine.

506. (New) The process of claim 323. wherein said active is an anti-tussive.

507. (New) The process of claim 323. wherein said active is a non-steroidal anti-inflammatory.

508. (New) The process of claim 323. wherein said active is an anti-asthmatics.

509. (New) The process of claim 323. wherein said active is an anti-diarrhea.

510. (New) The process of claim 323. wherein said active is an alkaloid.

511. (New) The process of claim 323. wherein said active is an anti-psychotic.

512. (New) The process of claim 323. wherein said active is an anti-spasmodic.

513. (New) The process of claim 323. wherein said active is a biological response modifier.

514. (New) The process of claim 323. wherein said active is an anti-obesity drug.

515. (New) The process of claim 323. wherein said active is an H:6-antagonist.

516. (New) The process of claim 323. wherein said Hz.-antagonist is selected from the group consisting of cimetidine. ranitidine hydrochloride. famotidine. nizatidine. ebrotidine. mifentidine. roxatidine. pisatidine. aceroxatidine and combinations thereof.

~~517. (New) The process of claim 323. wherein said active is a smoking cessation aid.~~

~~518. (New) The process of claim 323. wherein said active is an anti-parkinsonian agent.~~

~~519. (New) The process of claim 323. wherein said active is an anti-depressant.~~

~~520. (New) The process of claim 323. wherein said active is an anti-migraine.~~

~~521. (New) The process of claim 323. wherein said active is an anti-Alzheimer's agents.~~

~~522. (New) The process of claim 323. wherein said active is a dopamine receptor agonist.~~

~~523. (New) The process of claim 323. wherein said active is a cerebral dilator.~~

~~524. (New) The process of claim 323. wherein said active is a psychotherapeutic agent.~~

~~525. (New) The process of claim 323. wherein said active is an antibiotic.~~

~~526. (New) The process of claim 323. wherein said active is an anesthetic.~~

~~527. (New) The process of claim 323. wherein said active is a contraceptive.~~

~~528. (New) The process of claim 323. wherein said active is an anti-thrombotic drug.~~

~~529. (New) The process of claim 323. wherein said active is diphenhydramine.~~

~~530. (New) The process of claim 323. wherein said active is nabilone.~~

531. (New) The process of claim 323, wherein said active is albuterol sulfate.

532. (New) The process of claim 323, wherein said active is an anti-tumor drug.

533. (New) The process of claim 323, wherein said active is a glycoprotein.

534. (New) The process of claim 323, wherein said active is an analgesic.

535. (New) The process of claim 323, wherein said active is a hormone.

536. (New) The process of claim 323, wherein said active is a decongestant.

537. (New) The process of claim 323, wherein said active is a loratadine.

538. (New) The process of claim 323, wherein said active is dextromethorphan.

539. (New) The process of claim 323, wherein said active is chlorpheniramine maleate.

540. (New) The process of claim 323, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

541. (New) The process of claim 323, wherein said active is an appetite stimulant.

542. (New) The process of claim 323, wherein said active is a gastrointestinal agent.

543. (New) The process of claim 323, wherein said active is a hypnotic.

544. (New) The process of claim 323. wherein said active is taste-masked.

545. (New) The process of claim 323. wherein said active is taste-masked using a flavor.

546. (New) The process of claim 323. wherein said active is coated with a controlled release composition.

547. (New) The process of claim 546. wherein said controlled release composition provides an immediate release.

548. (New) The process of claim 546. wherein said controlled release composition provides a delayed release.

549. (New) The process of claim 546. wherein said controlled release composition provides a sustained release.

550. (New) The process of claim 546. wherein said controlled release composition provides a sequential release.

551. (New) The process of claim 323. wherein said active is a particulate.

552. (New) The process of claim 323. further comprising adding a degassing agent to said flowable polymer matrix.

553. (New) The process of claim 323. further comprising a step of providing a second film layer.

554. (New) The process of claim 553, wherein said second film layer is coated onto said resulting pharmaceutical film.

555. (New) The process of claim 553, wherein said second film layer is spread onto said resulting pharmaceutical film.

556. (New) The process of claim 553, wherein said second film layer is cast onto said resulting pharmaceutical film.

557. (New) The process of claim 553, wherein said second film layer is extruded onto said resulting pharmaceutical film.

558. (New) The process of claim 553, wherein said second film layer is sprayed onto said resulting pharmaceutical film.

559. (New) The process of claim 553, wherein said second film layer is laminated onto said resulting pharmaceutical film.

560. (New) The process of claim 553, further comprising laminating said resulting pharmaceutical film to another film.

561. (New) The process of claim 553, wherein said second film layer comprises an active.

562. (New) The process of claim 553, wherein said active in said second film layer is different than said active in said resulting pharmaceutical film.

563. (New) The process of claim 324, wherein said water-soluble polymer comprises polyethylene oxide.

564. (New) The process of claim 324, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers,

~~hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.~~

~~565. (New) The process of claim 564, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(1actic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.~~

~~566. (New) The process of claim 564, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (POA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers,polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.~~

~~567. (New) The process of claim 564, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.~~

~~568. (New) The process of claim 564, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates,~~

~~phthalated gelatin, crosslinked gelatin, poly(1actic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(1actic acid) (PLA)' poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.~~

~~569. (New) The process of claim 324, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.~~

~~570. (New) The process of claim 569, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.~~

~~571. (New) The process of claim 324, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti¬lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti¬uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones,~~

hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, neuromuscular drugs, hyper-and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

572. (New) The process of claim 324, wherein said active is selected from the group consisting of antigens, allergens, spores, microorganisms, seeds, enzymes, vitamins and combinations thereof.

573. (New) The process of claim 324, wherein said active is a bioactive active.

574. (New) The process of claim 324, wherein said active is an opiate or opiate-derivative.

575. (New) The process of claim 324, wherein said active is an anti-emetic.

576. (New) The process of claim 324, wherein said active is an amino acid preparation.

577. (New) The process of claim 324, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

578. (New) The process of claim 324, wherein said active is a protein.

579. (New) The process of claim 324, wherein said active is insulin.

580. (New) The process of claim 324, wherein said active is an anti-diabetic.

581. (New) The process of claim 324, wherein said active is an antihistamine.

582. (New) The process of claim 324, wherein said active is an anti-tussive.

583. (New) The process of claim 324, wherein said active is a non-steroidal anti-inflammatory.

584. (New) The process of claim 324, wherein said active is an anti-asthmatics.

585. (New) The process of claim 324, wherein said active is an anti-diarrhea.

586. (New) The process of claim 324, wherein said active is an alkaloid.

587. (New) The process of claim 324, wherein said active is an anti-psychotic.

588. (New) The process of claim 324, wherein said active is an anti-spasmodic.

589. (New) The process of claim 324, wherein said active is a biological response modifier.

590. (New) The process of claim 324. wherein said active is an anti-obesity drug.

591. (New) The process of claim 324. wherein said active is an H6-antagonist.

592. (New) The process of claim 324, wherein said H_2-antagonist is selected from the group consisting of cimetidine. ranitidine hydrochloride. famotidine. nizatidine. ebrotidine. mifentidine, roxatidine, pisatidine. aceroxatidine and combinations thereof.

593. (New) The process of claim 324, wherein said active is a smoking cessation aid.

594. (New) The process of claim 324. wherein said active is an anti-parkinsonian agent.

595. (New) The process of claim 324. wherein said active is an anti-depressant.

596. (New) The process of claim 324, wherein said active is an anti-migraine.

597. (New) The process of claim 324. wherein said active is an anti-Alzheimer's agents.

598. (New) The process of claim 324. wherein said active is a dopamine receptor agonist.

599. (New) The process of claim 324. wherein said active is a cerebral dilator.

600. (New) The process of claim 324, wherein said active is a psychotherapeutic agent.

601. (New) The process of claim 324. wherein said active is an antibiotic.

602. (New) The process of claim 324. wherein said active is an anesthetic.

603. (New) The process of claim 324, wherein said active is a contraceptive.

604. (New) The process of claim 324, wherein said active is an anti-thrombotic drug.

605. (New) The process of claim 324. wherein said active is diphenhydramine.

606. (New) The process of claim 324. wherein said active is nabilone.

607. (New) The process of claim 324. wherein said active is albuterol sulfate.

608. (New) The process of claim 324. wherein said active is an anti-tumor drug.

609. (New) The process of claim 324, wherein said active is a glycoprotein.

610. (New) The process of claim 324, wherein said active is taste-masked.

611. (New) The process of claim 324. wherein said active is taste-masked using a flavor.

612. (New) The process of claim 324. wherein said active is coated with a controlled release composition.

613. (New) The process of claim 612. wherein said controlled release composition provides an immediate release.

614. (New) The process of claim 612. wherein said controlled release composition provides a delayed release.

615. (New) The process of claim 612, wherein said controlled release composition provides a sustained release.

~~616. (New) The process of claim 612, wherein said controlled release composition provides a sequential release.~~

~~617. (New) The process of claim 324, wherein said active is a particulate.~~

~~618. (New) The process of claim 324, further comprising adding a degassing agent to said flowable polymer matrix.~~

~~619. (New) The process of claim 324, further comprising a step of providing a second film layer.~~

~~620. (New) The process of claim 619, wherein said second film layer is coated onto said resulting film.~~

~~621. (New) The process of claim 619, wherein said second film layer is spread onto said resulting film.~~

~~622. (New) The process of claim 619, wherein said second film layer is cast onto said resulting film.~~

~~623. (New) The process of claim 619, wherein said second film layer is extruded onto said resulting film.~~

~~624. (New) The process of claim 619. wherein said second film layer is sprayed onto said resulting film.~~

~~625. (New) The process of claim 619, wherein said second film layer is laminated onto said resulting film.~~

~~626. (New) The process of claim 619, further comprising laminating said resulting film to another film.~~

~~627. (New) The process of claim 619, wherein said second film layer comprises an active.~~

~~628. (New) The process of claim 619, wherein said active in said second film layer is different than said active in said resulting film.~~

Remarks[2]

I. Description of the Patent and the Applicant's Reply

The above-identified U.S. Patent No. 7,897,080 (" '080 Patent") is presently under reexamination. Claims 1-299 were issued in the '080 Patent. Claims 1-299, subject to reexamination, were rejected in the Office Action. Claims 16, 95 and 177, have been canceled herein as they are identical to claims 32, 111 and 193, respectively. See Office Action, p. 7. Claims ~~91, 255, 273 and 291~~12, 91, 173, 254, 255, 257, 272, 273, 275, 290, 291, and 293 have also been canceled purely for clarity. Claims 300 through ~~628~~318 are new.

While the Examiner's rejection of all the claims is respectfully traversed in all respects, claims 1,82 and 161 of the '080 Patent have been amended in an effort to ~~expedite~~advance the prosecution of the present reexamination. Claims 1,82 and 161 are hereby amended in accordance with 37 C.F.R. §1.530(d) (2) and (f). In accordance with 35 U.S.C. § 314(a), the amendments to claims 1,82 and 161, new independent claims ~~321~~315-~~324~~318, and new dependent claims 300-~~320 and claims 325628,~~ 314 do not enlarge the scope of the claims of the '080 Patent. Explanation of the support for these claims appears below. Entry of this amendment and reconsideration is respectfully

[2] This exhibit shows the differences between the NEW remarks filed in the March 13, 2013 Supplemental Reply and the original remarks filed in the January 29, 2013 Reply, with deletions struck through and additions underlined.

requested.

II. Status of Claims and Support for Claim Changes Pursuant to 37 C.F.R. §1.530(e)

The status of the claims as of the date of this amendment is as follows: Claims 1-299 were issued in the '080 Patent and are subject to reexamination. Claims 1-299, subject to reexamination, were rejected in the Office Action. Claims 300 through ~~628~~318 are new and are subject to examination. Please cancel claims 16, 95 and 177, as they are identical to claims 32, 111 and 193, respectively. See Office Action, p. 7. Please cancel ~~claims 91, 255, 273 and 291~~Claims 12, 91, 173, 254, 255, 257, 272, 273, 275, 290, 291, and 293, for clarity, including some limitations which now appear in the independent claims from which some depend.

In compliance with 37 C.F.R. § 1.530(j), the amendments to claims 1,82 and 161 do not enlarge their scope or the scope of the original claims or introduce new matter, nor do the amendments adding new claims 300 through ~~628~~318 enlarge the scope of the original claims or introduce new matter.

Support for the amendments to claims 1, 82 and 161 and new claims 300 through ~~628~~318 may be found throughout the '080 Patent, including, the Abstract, Specification, Figures and Claims, for example, at col. 13, ll. 23-36, col. 16, l. 62 through col. 17, l. 3, col. 28, l. 66 through col. 29, 1. 6; col. 29, ll. 20-35 and 38; col. 32, ll. 34-~~39~~41; col. 2, ll. 27-46; col. ~~28-40~~15,11. 28-43, and the Abstract; quoted in detail below; ~~and col. 2, 1. 57,~~ col. 3, ll. 58-60 ("the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval"); col. 19, 1. 30 through col. 21, l. ~~30~~31 (actives including pharmaceutical actives, bioactive actives, and combinations thereof); col. 6, ~~11.49~~ll. 49-52 ("These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process."); Figures 6, 7, 8, 35 and 36 and col. 14, ll. 20-25 ("drying" and "drying apparatus"); col. ~~13, 11.~~11, ll. 17-19 ("Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition"); col. 11,ll.

21-23 ("yield values ... force"); col. 12,11. 20-36, col. 13,11. 37-38 ("After mechanical mixing, the film may be placed on a conveyor"); col. 29, 11. 11-13 ("As the film is conveyed through the manufacturing process, for example on a conveyor belt apparatus"); col. ~~10,11.47-48 ("The film ... is finally formed on the substrate"); col. 26~~33, 1. ~~33~~10 through col. ~~27~~34, 1. ~~10 ("the coating is then deposited onto the substrate"~~24 (example M); col. 44, 11. 9-13 ("the controlled drying process of the present invention allows for uniform drying to occur, whereby evaporative cooling and thermal mixing contribute to the rapid formation of viscoelastic film and the 'locking-in' of uniformity of content throughout the film"); col. ~~58, claim 28 ("wherein the visco-elastic film is formed within about 4 minutes"); col.~~ 4, 1. 8; col. ~~6,11.46~~6, 11. 46-52; col. ~~13,11.36~~13,11. 36-43; col. 26, ~~11.9~~11. 9-27; col. 28, 11. 24-58; col. 29, ~~11.8~~11. 8-10; col. ~~18,11.53-58; col. 29, 1. 63 through col. 30, 1.2; support~~20, 11. 65-66 ("Erectile dysfunction ... drugs"); col. 19, 1. 55 ("anti-diarrhea preparations"); col. 6, 11. 52-60 ("Examples of controlled drying processes include ... hot air impingement across the bottom substrate and bottom heating plates ... controlled radiation drying ... such as infrared and radio frequency radiation ...."); col. 7, lines 5 through 16 ("This may be achieved by applying heat to the bottom surface of the film ... or alternatively by the introduction of controlled microwaves to evaporate the water. . .. air currents directed at the bottom of the film should desirably be controlled"); col. 27, 11. 53-55 ("The temperature at which the films are dried is about 100°C. or less"); col. 41, 11. 49-50 ("films were dried in an oven at approximately 60° C."). Support for new claims may also be found throughout the '~~337~~080 Patent, including, the Figures ~~and Claims, for example at col. 19,11. 10-25, col. 19,1. 30 through col. 22, ,~~ Tables and Claims, for example at col. 19,11. 10-25, col. 19,1. 30 through col. 22, 1. 28, col. 25, 11. 53-60, ~~1. 28, col. 25, 11.53-65, col. 28, 11. 53-58, col. 18,11.54-59,~~ col. 22, 11. 24-28; col. 28, 11. 1-2; col. 14,11. 63-65; Tables 17 and 18; Figures 6-8, 33, 34 and 35. Many of the claim elements of the new independent claims can be found in original independent claims 1,82, and 161 of the '080 patent.

> "Temperatures that approach 100° C. will generally cause degradation of proteins as well as nucleic acids. For example some glycoproteins will degrade if exposed to a temperature of

70° C. for thirty minutes. Proteins from bovine extract are also known to degrade at such low temperatures. DNA also begins to denature at this temperature. "Applicants have discovered, however, that the films of the present invention may be exposed to high temperatures during the drying process without concern for degradation, loss of activity or excessive evaporation due to the inventive process for film preparation and forming. In particular, the films may be exposed to temperatures that would typically lead to degradation, denaturization, or inactivity of the active component, without causing such problems. According to the present invention, the manner of drying may be controlled to prevent deleterious levels of heat from reaching the active component."

'080 Patent. col. 12, 11. 20-36.

"For instance, the films of the present invention desirably are dried for 10 minutes or less. Drying the films at 80° C. for 10 minutes produces a temperature differential of about 5° C. This means that after 10 minutes of drying, the temperature of the inside of the film is 5° C. less than the outside exposure temperature. In many cases, however, drying times of less than 10 minutes are sufficient, such as 4 to 6 minutes. Drying for 4 minutes may be accompanied by a temperature differential of about 30° C., and drying for 6 minutes may be accompanied by a differential of about 25° C. Due to such large temperature differentials, the films may be dried at efficient, high temperatures without causing heat sensitive actives to degrade."

'080 Patent. col. 13, 11. 23-36.

"The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process."

'080 Patent, col. 16, 1. 62 through col. 17, 1. 3 (emphasis supplied).

"It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and overall appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons."

'080 Patent, col. 28, 1. 66 through col. 29, 1. 6 (emphasis supplied).

"The cut film then may be sampled by removing small pieces from each of the opposed ends of the portion(s), without disrupting the middle of the portion(s) ... . After the end pieces, or sampling sections, are removed from the film portions), they may be tested for uniformity in the content of components between samples. "

'080 Patent, col. 29, 11. 20 through 35 (emphasis supplied).

"An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active."

'080 Patent, col. 32, 11. ~~36~~34-41 (emphasis supplied).

"The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages ofactive, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment.

> Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present."
>
> '080 Patent, col. 2, 11. 27-46 (emphasis supplied).
>
> "Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1 % by weight, or less than 0.5% by weight. "
>
> '080 Patent, col. 15,11. 28-43 (emphasis supplied).

III. Declarations Submitted With This Reply

Along with this Reply, the Patentee is submitting the Declarations of Dr. B. Arlie Bogue (Exhibit A) ("Bogue Declaration") and Dr. ~~Gerald Fuller~~David T. Lin (Exhibit B) ~~both~~("Lin Declaration") under 37 C.F.R. § 1.132. The ~~Declarations~~ Bogue Declaration provides technical results regarding Patentee's commercial pharmaceutical films manufactured in accordance with the '080 Patent and it ~~provide no legal arguments, but rather provides technical opinions and factual statements, and thus~~ should not ~~count~~be counted toward the page limit of 37 C.F.R. § 1.943. The Lin Declaration provides Dr.

Lin's background information, information relating to FDA uniformity of content dosage requirements, and has six (6) numbered paragraphs of statements (¶ ¶ 17-22) relating to a prior art disclosure at pages 5-6, which might at most be counted as two (2) pages toward the page limit of 37 C.F.R. §1.943.

IV. Background of the '080 Patent

The '080 Patent is a continuation of U.S. application Ser. No. *10/856,176,* filed May 28, 2004 now U.S. Pat. No. 7,666,337 (" '337 Patent"), which claims the benefit ofU.S. Provisional Application No. *60/473,902,* filed May 28, 2003 and is a continuation-in-part ofU.S. application Ser. No. *101768,809,* filed Jan. 30, 2004 now U.S. Pat. No. 7,357,891 (" '891 Patent"), which claims benefit to U.S. Provisional Application No. *60/443,741* filed Jan. 30, 2003 and is a continuation-in-part of:

(a) *PCT/US02/32575* filed Oct. 11,2002, which claims priority to: (1) U.S. application Ser. No. *10/074,272,* filed Feb. 14,2002 which claims benefit to U.S. Provisional Application No. *60/328,868,* filed Oct. 12,2001 and (2) U.S. Provisional Application No. *60/386,937,* filed Jun. 7,2002;

(b) *PCT/US02/32594,* filed Oct. 11,2002, which claims priority to: (1) U.S. Provisional Application No. *60/414,276,* filed Sep. 27,2002, (2) U.S. application Ser. No. *10/074,272,* filed Feb. 14,2002, which claims benefit to U.S. Provisional Application No. *60/328,868,* filed Oct. 12,2001 and (3) U.S. Provisional Application No. *60/386,937,* filed Jun. 7, 2002; and

(c) *PCT/US02/32542,* filed Oct. 11,2002, which claims priority to: (1) U.S. Provisional Application No. *60/371,940,* filed Apr. 11,2002, (2) U.S. application Ser. No. *10/074,272,* filed Feb. 14,2002, which claims benefit to U.S. Provisional Application No. *60/328,868,* filed Oct. 12,2001 and (3) U.S. Provisional Application No. *60/386,937,* filed Jun. 7, 2002.

~~The '080 Patent has not been and is not currently involved in litigation.~~

There are pending applications claiming the benefit ofthe priority of all and/or some of the above.

The '891 Patent is involved in a U.S. litigation wherein Patentee has alleged that the Third Party Requester, BioDelivery Sciences International, Inc. ("BDSI") has infringed its '891 Patent. The litigation is Civil Action No. 10-cv-5695 in the U.S. District Court in the District of New Jersey. In the litigation, Patentee also alleged that the Third Party Requester infringed two other of Patentee's patents, U.S. 7,425,292 (" '292 Patent") and U.S. 7,824,588 (" '588 Patent").

Third Party Requester requested reexamination of the '891 Patent *(90/012,098),* the '292 Patent *(90/012,097)* and the '588 Patent *(95/001,753)* as well. Both the '292 and the '891 Patent successfully exited reexamination. The Examiner on January 23,2013 issued a Right of Appeal Notice ("RAN") for the '588 Patent reexamination. ~~Finally,~~In response, Patentee filed a Notice of Appeal, a Petition Under 37 C.F.R. § 1.183 Requesting Waiver of the Prohibition of an Extension of Time for Filing an Appeal Brief and for an Extension of Time for Filing an Appeal Brief, and a Petition Under 37 C.F.R. § 1.182 Requesting Continued Reexamination.

Third Party Requester requested reexamination ~~ofthe '080 Patent and~~of another of Patentee's related patents namely U.S. Pat. No. 7,666,337 (Control No. *95/002,171),* reexamination was ordered, an Office Action issued ~~and,~~ Patentee ~~is preparing a response thereto~~Replied, and Third Party Requester submitted its Comments.

Finally, Third Party Requester requested the reexamination herein of the '080 Patent.

The '080 Patent has not been and is not currently involved in litigation.

'080 Patent Office Action Statements

In connection with the Order Granting Request for Inter Partes Reexamination of the '080 Patent, Control No. *95/002,170* ("Order Granting IPR Request '080 Patent"),

noted above, certain comments were made by the Examiner with respect to Claim 25 ofthe '337 Patent. The statements were made when the Examiner addressed Third Party Requester's request to find that claim 82 of the '080 Patent should be rejected under 35 U.S.C. § 101 double patenting over claim 25 of the '337 Patent. Patentee supports the Examiner's finding that the Third Party Requester had failed to demonstrate a reasonable likelihood of success~~, in that respect, with at~~ of arriving at the subject matter of at least one claim ofthe '080 Patent. However, Patentee respectfully disagrees with the Examiner's statements interpreting "uniform" and "substantially uniform" therein. In particular, Patentee disagrees that "the active is uniformly distributed (i.e. no variance of active)" in the matrix. Certainly a uniform distribution does not require a state of "no variance". See pages 21 and 22 of the Order Granting IPR Request '080 Patent~~:~~. "Uniform" and "substantially uniform" are indeed different, but "uniform" from a practical standpoint must of necessity allow for some variance, albeit less than "substantially uniform". ~~The concept of "no variance" of anything has little practical value in the real physical world and in the '337 Patent, where the phrase does not appear. The '337 Patent makes no claim to some form of absolute 100% uniformity, it discloses, *inter alia,* uniformity ofactive and substantial uniformity of active both with no more than 10% variance. As used in the '337 Patent, while a "uniform distribution of active" has little variance in active, and in particular, less variance in active than a "substantially uniform distribution ofactive", Patentee does not claim its processes involve obtaining absolute uniformity of composition or content uniformity of no variance. The variance in uniformity may be very small but that is not the same as saying that a uniform distribution has no variance in the distribution. As the Examiner can appreciate, manufacturing processes never result in "no variance" in the quantitative compositional makeup ofproducts made therefrom. In short, "uniform" and "substantially uniform" are indeed different, but "uniform" from a practical standpoint,. Must of necessity allow for some variance, albeit less than "substantially uniform".~~

V. The Patented Invention

The present invention is directed to novel and non-obvious processes for manufacturing pharmaceutical and bioactive active containing films, suitable for commercialization and U.S. Food and Drug Administration ("FDA") approval. As noted in the Bogue Declaration, ¶ 4, one manufactured lot of such resulting film can contain 2,000,000 individual dosage units. The claimed processes accomplish this feat while providing the necessary narrow ranges in the amount of active in individual dosage units. As claimed, the '080 Patent, at least, requires a uniformity of content in amount of active (i) in individual dosage units sampled from a resulting film of 10% or less (independent claims 1,82,161, and 316-318, see Appendix A, Bogue Declaration), and (ii) in individual dosage units sampled from two or more resulting films of 10% or less as a percent difference from a desired amount (independent claim 315, see Appendix B, Bogue Declaration).

One conceptual approach to understanding (i) and (ii) is as follows. A baker has a good recipe or process for making bread. The recipe includes the ingredients and the controlled baking conditions. On Monday the baker bakes a loaf of bread strictly following the recipe. On Friday the baker bakes a loaf of bread again strictly following the recipe. The loaves are cut into individual slices. When tasted, all the slices from Monday's loaf taste almost the same, indeed the tastes differs by only 10% between slices from Monday's loaf. In the same fashion, when tasted, all the slices from Friday's loaf taste almost the same, indeed the tastes differs by only 10% between slices from Friday's loaf. However, when a slice from Monday's loaf is compared to a slice from Friday's loaf, the difference in taste is more pronounced than between individual slices from the same loaf. Since the baker follows the same recipe for all his/her bread the baker expects that all slices from all loaves should taste alike or almost alike. However, the difference in taste between slices from Monday and slices from Friday is greater than the difference between slices in the same loaf. Indeed, the taste difference is now about 10% from what the baker believes all his/her bread should be expected to taste like--that is, 10% from the high quality standard ("desired amount" and/or "target amount") for all the bread baked.

In a similar fashion, the "recipe" of Patentee's claimed processes keep differences between individual dosage units from one manufactured lot very small--e.g. smaller than 10% in amount of pharmaceutical active. See, independent claims 1,82,161 and 316-318. The "recipe" of Patentee's claimed processes also keeps differences between individual dosage units between different manufactured lots small as well, just not necessarily as small--e.g. smaller than a 10% difference from the standard, i.e. desired amount. See, independent claim 315.

~~The present invention is directed to a novel and non-obvious method of manufacturing an ingestible therapeutic active delivery system and uses thereof. The patented invention, as explicitly claimed, covers a process for manufacturing a resulting film suitable for commercialization and regulatory approval said film having a~~Thus, in the case of a resulting film from one manufacturing lot, the substantially uniform distribution ~~of a pharmaceutical active components, wherein substantially uniform distribution ofthe pharmaceutical~~of the active is indicated through analytical chemical tests ~~for active~~which indicate that uniformity of content ~~of~~in the amount of the active in substantially equal sized individual dosage units sampled from the resulting film varies by no more than 10%. ~~Hence the commercially~~See Appendix A from Bogue Declaration copied below and Bogue Declaration, ¶ 9, where this is shown to be true for 73 separately manufactured ~~'337 Patent~~lots of film ~~is both a~~, all manufactured by Patentee in accordance with the claimed invention.

APPENDIX A (Bogue Declaration)

(THE GRAPH WAS REMOVED FOR THE SAKE OF BREVITY)

In the case of resulting films from different manufacturing lots the substantially

uniform distribution of the active is indicated through analytical chemical tests which indicate that uniformity of content in the amount of the active varies by no more than 10% from a desired amount. See Appendix B from Bogue Declaration copied below and Bogue Declaration, ¶ 10, where this is shown to be true across 73 separately manufactured lots of film, all manufactured by Patentee in accordance with the claimed invention. 100.0% indicating the desired amount.

APPENDIX B (Bogue Declaration)

(THE GRAPH WAS REMOVED FOR THE SAKE OF BREVITY)

Hence, the manufacturing process of the '080 Patent as claimed is a commercially viable ~~product as well as a product which can and does meet, for example,~~processes which yields commercial viable products meeting FDA regulations, including active assaying requirements. This should be compared to the laboratory produced films described in the prior art relied on by the Examiner. In the cited prior art, terms such as uniformity, substantial uniformity, and homogeneity~~,~~ are all accepted without real support. They cannot be relied upon. What is missing is the support for the statements~~,~~ -- that is, having had the amount of active tested by analytical chemical testing, including assaying. *See* Lin Declaration, ¶17-22 (statements about insufficient disclosure in cited prior art reference). Patentee uses the '~~337~~080 Patent invention to manufacture commercially acceptable ~~pharmaceutical~~ products for which Patentee must establish ~~the content~~ uniformity of content in the amount of active in its products by such analytical chemical testing as required by regulatory agencies, such as the FDA. Dr. Bogue's Declaration describes such testing on Patentee's products produced in accordance with the invention and the results which are consistent with the '~~337~~080 Patent's claims for ~~active~~uniformity of content ~~of substantially equal sized~~ in the amount of active (i) in

individual dosage units sampled from ~~the~~a resulting film ~~varies by no more than~~of 10% or less, and (ii) in individual dosage units sampled from two or more resulting films of 10% or less as a percent difference from a desired amount. Bogue Declaration, ¶¶ 4~~-r, r 5-13~~11.

PATENTEE'S CLAIMS

Patentee's instant claims ~~recited~~recite additional ~~detail~~details about its processes for manufacturing a resulting pharmaceutical film suitable for commercialization and regulatory approval. Some of the details include: forming a flowable polymer matrix~~;~~ comprising a polymer, a solvent and an active, said matrix having a substantially uniform distribution of said ~~pharmaceutical~~ active; casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps ~~and~~; controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to ~~rapidly~~ form a visco-elastic film, having said ~~pharmaceutical~~ active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying ~~within about the first 4 minutes~~ to maintain said substantially uniform distribution of said ~~pharmaceutical~~ active by locking-in or substantially preventing migration of said ~~pharmaceutical~~ active within said visco-elastic film~~,~~ wherein the polymer matrix temperature is 100°C or less; forming ~~the~~said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of ~~pharmaceutical~~said active by said locking-in or substantially preventing migration of said ~~pharmaceutical~~ active is maintained, ~~wherein~~ performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film from one lot, said tests indicating that uniformity of content in the amount ofthe active varies by no more than 10% and said resulting film is suitable for ~~commercialization~~commercial and regulatory approval~~; sampling the resulting film at~~

~~different locations of the resulting film in order to perform the analytical chemical tests for content uniformity ofsaid pharmaceutical active and thus establish for commercialization and regulatory purposes the substantially uniform distribution of the pharmaceutical active throughout the film product at a desired/required degree of uniformity, i.e., vary by~~, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and, in the case of more than one resulting film lot, repeating the process for forming one film lot such that uniformity of content in the amount of said active across all said resulting film lots varies no more than 10% from the desired amount ofthe active as indicated by said analytical chemical tests.

Additional claim limitations can be found in some of Patentee's narrower independent claims, for example claims 317-318. These claims generally add to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60°C and using air currents, which have forces below the yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising continuing evaporation to a water content of said resulting film of 10% or less. ~~Ofparticular relevance to the Office Action, the patented invention relates to film products and film-containing products, wherein controlling the viscosity of the polymer matrix and controlling the drying process, among other things, ensures that the active components maintain their uniform distribution throughout the film product so that the desired uniformity is found in the resulting product as indicated and/or verified by testing, such as the steps of cutting samples from the resulting film product, dissolving at least portions of the samples and then testing each sample for the actual amount ofactives present using analytical equipment.~~

~~As used throughout the '080 Patent, the resulting visco-elastic product is defined as a product that has maintained the desired uniformity ofcontent of the active after being~~

~~subjected to a coating/deposition step (i.e., casting) and drying. For example, the '080 Patent, at col. 8, lines 64-66, discloses that the stability is important "in the wet film stage until sufficient drying has occurred to lock in the particles and matrix into a sufficiently solid form such that uniformity is maintained." The '080 Patent, at col. 13, lines 53-54 clearly discloses that: "The resulting dried film 1 is a visco-elastic solid, as depicted in Section C. The components desirably are locked into a uniform distribution throughout the film." Thus, as~~As defined in the ~~application as filed and present in the issued claims, a viscoelastic solid~~'080 Patent, a visco-elastic film is one that has been controllably dried to lock its components into a substantially uniform distribution throughout the film while avoiding problems associated with conventional drying methods. By providing a visco-elastic film product having this compositional uniformity or uniformity of content, the user can be assured that the product includes the proper amount of components, such as an active contained therein. ~~Thus, a visco-elastic product is one in which the active contained therein is present in an amount that is substantially uniform in the visco-elastic product.~~ Further, ~~when~~ the process ~~is~~can be used to make commercially viable large-scale film products, such as large rolls of film from which smaller ~~films~~individual dosage units are cut, the user can feel confident that no matter where the large roll of film is cut, the resulting pieces (e.g., individual unit dosages) will have a substantially uniform composition. As noted above, Patentee successfully manufactures pharmaceutical films containing 2,000,000 individual dosage units meeting FDA requirements using the claimed processes. Bogie Declaration, ¶ 4. As claimed, the uniformity of content as a percent difference will be no more than 10% and in some cases less. The need for providing a process for obtaining the desired uniformity of content of the desired amount of active in the resulting products is critically important, particularly for regulated products, such as the claimed pharmaceuticals.

Prior to the present invention, it was known to prepare ~~film products~~films. However, in many cases the end product was merely assumed to be homogeneous, either because the initial components were blended together or because after the blending step the physically observable properties of the resulting film product, for example, its

appearance or weight, were satisfactory. However, these physical properties do not indicate ~~that~~or establish that the uniformity of content of the components is such that, for example, the amount of the active in individual dosage units varies by no more than 10%~~.~~ ~~The only way to actually test for the amount of the active present in individual dosage unit samples, is to use analytical chemical testing and actually test for the presence of the desired amount of active.~~ for a particular film. By contrast, for example, in one instance, "the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix." '080 Patent, col. 18, 11. 37-40.

Nor do physical properties indicate or establish that that the uniformity of content of the components is such that, for example, the amount of the active in individual dosage units from one film to another film varies by no more than 10% from a desired amount. This range of uniformity is disclosed in connection with, for example, the uniformity of content disclosed in the '080 Patent when referencing the FDA and other regulatory requirements. "Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present." '080 Patent, col 2, 11. 43-45. In these cases, the FDA and/or other regulatory agency sets the amount of active that must be present in an individual dosage unit (or dosage form), *i.e.,* the desired amount, and provides for the necessary uniformity of content, in this case the active may vary by 10% from the desired amount. A" desired amount" is an essential concept, as the FDA indicates the required dosage for each drug, and each drug has its own specified dosage amount. Essential to any pharmaceutical and related product is a viable means of actually testing for the amount of the active present in individual dosage unit samples, and that is to use analytical chemical testing and actually test for the presence of the desired amount of active and thereby determine whether the prescribed uniformity of content of active is present. *See* Lin Declaration, ¶¶9-16.

Importantly, the process of forming a proper film product with the claimed levels of uniformity of content in, for example, the amount of active does not end at the mixing stage. Patentee has discovered that the various steps post-mixing ~~also play an~~play a very

important role in ensuring that the resulting product ~~composition~~complies with the stringent requirements for uniformity of content. For example, one key step in the formation of a film product is the drying step, particularly when heat and/or radiation is used to dry the film. Patentee has discovered that controlled drying methods ~~may be used to prepare a compositionally uniform film product~~is essential in meeting these claimed requirements. Controlled drying includes methods that ~~do not include~~avoid, for example, the formation of bubbles, or uncontrolled air currents that may cause movement of particles within the visco-elastic film forming matrix. Controlled drying, as required by the invention as claimed, may be effectuated through evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100°C or less.

It is important to understand that compositional uniformity or uniformity ofcontent is not the same as ~~uniform thickness, nor is it the same as~~ having a surface that appears free of defects.

Importantly, having a glossy surface does not equate to a uniform film, ~~since~~because the bottom side of a film product formed on a substrate will take the surface features of the substrate. If the substrate is smooth, the resulting bottom surface will also be smooth and possibly glossy. A product that has a surface that appears free of defects may have experienced significant non-uniformity below the surface, for example due to aggregation and agglomeration of components~~, movement due to the Soret effect, etc~~. It is important to note that just because the surface of a resulting product looks glossy or free of defects does not inherently mean that the actives within the film product ~~are uniform so as~~exhibit the level of uniformity of content necessary to satisfy regulatory requirements and/or deliver the desired amount to the patient. ~~See Fuller Declaration, ~ 11-13.~~

The '080 Patent discloses in a section entitled "Testing Films for Uniformity" (col. 28, 1. 65 through col. 29, 1. 53) that "[i]t may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process". '080 Patent, col. 28, 1. 66 through col. 29, 1. 1. In particular:

> "It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and over all appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons."
>
> '080 Patent, col. 28, 1. 66 through col. 29, 1. 6 (emphasis supplied).

Thus disclosed are two general types of testing, one for physical uniformity, and one for chemical uniformity. The disclosure goes on to provide different ways to test for each.

> "After the end pieces, or sampling sections, are removed from the film portiones), they may be tested for uniformity in the content of components between samples. Any conventional means for examining and testing the film pieces may be employed, such as, for example, visual inspection, use of analytical equipment, and any other suitable means known to those skilled in the art. If the testing results show non-uniformity between film samples, the manufacturing process may be altered. This can save time and expense because the process may be altered prior to completing an entire manufacturing run. For example, the drying conditions, mixing conditions, compositional components and/or film viscosity may be changed. Altering the drying conditions may involve changing the temperature, drying time, moisture level, and dryer positioning, among others."
>
> '080 Patent, col. 29, 11. 33-38 (emphasis supplied).

In this way the '080 Patent provides multiple tests for non-uniformity, which are extremely useful in guiding the commercial manufacture of films. For example,

manufacturing runs of films which appear to exhibit "non-uniformity" may be adjusted early in the run with less waste of materials, thus saving time and expense associated with the possibility of a non-uniform film. Physical tests, such as observational tests, are insufficient to determine the ~~degree of uniformity. However, especially in the case ofindividual doses of actives, for example, pharmaceutical actives, the actual uniformity of content in the amount of active is essential and must be quantified through analytical chemical testing. For example,~~level of uniformity of content disclosed and claimed by the '080 Patent--they do not determine the actual amount of active in samples.

The '080 Patent discloses testing to determine the appropriate degree ~~ofcontent uniformity of the~~of uniformity of content of the resulting film ~~for commercial scale and regulatory compliance may involve~~involving sampling substantially equal sized individual dosage units of the resulting film, dissolving ~~at least a portion ofthe~~the active in the sampled resulting film, and testing for the amount of active present in the sampled resulting film. Thus, the '080 Patent discloses that uniformity of the active is demonstrated through testing.

> "An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain ~~.~~substantially the same amount of active."
>
> '080 Patent, col. 32, 11. 36-41 (emphasis supplied).

In this respect the Examiner, in his Scope of Claims section has mistakenly included physical uniformity type tests, used to quickly and/or easily suggest non-uniformity, with chemical uniformity type tests involving analytic equipment, that is, the actual testing of the uniformity of content for the amount of active. In the Scope of Claims section of the Office Action (pp. 3-7), the Examiner refers to two different portions of the '080 Patent's "EXAMPLES" section as follows:

> "An alternative means for evaluating uniformity is to cut the

> films into individual doses and measure the weight of the doses (col. 31, line 46 through col. 32, line 45). The '080 patent notes that "films of substantially similar size cut from different locations of the same film contain substantially the same amount of active." (col. 32, lines 37-39)."
>
> Office Action, p. 7.

~~Unfortunately~~Significantly, the two sentences are not related to each other, other than that both deal with examples and with cutting the film into dosage forms. The first is from a physical test, the second, relating to actives, is from an analytical chemical test for uniformity of content of active.

First is the physical test which refers to uniformity in mass.

> "Uniformity was also measured by first cutting the film into individual dosage forms. Twenty-five dosage forms of substantially identical size were cut from the film of inventive composition (E) above from random locations throughout the film. Then eight of these dosage forms were randomly selected and additively weighed. The additive weights of eight randomly selected dosage forms, are as shown in Table 2 below:
>
> [Table omitted.]
>
> "The individual dosages were consistently 0.04 gm, which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages forms from the same film of substantially equal dimensions, will contain the same mass."
>
> '080 Patent, col. 31, 1. 46 through col. 32, 1. 34 (emphasis supplied).

In accordance with this test, if the masses are unequal that would be an indication of mass nonuniformity.

Immediately after the above quoted disclosure, the '080 Patent discloses

essentially that to demonstrate uniformity of content for active, the amount of active in each substantially similarly sized sample must be determined.

> "An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active."
>
> '080 Patent, col. 32, 11. 35-40 (emphasis supplied).

The Examiner also relies on the paragraph at '080 Patent, col. 31, 11. 38-45 for support that physical type tests, in this case observational tests, are sufficient to establish uniformity of content of active.

> "The uniform distribution of the components within the film was apparent by examination by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another. Therefore, there was substantially no disparity among the amount of active found in any portion of the film."
>
> '080 Patent, col. 31, 11. 38-45

However, it is one thing to have films which appear to be substantially free of aggregation and rely on that to say there is substantially no disparity among the amount of active in any portion of the film, and it is a totally different thing to demonstrate ~~by testing for the active that its distribution among film samples of the same size establishes a~~the presence of the required level of uniformity of content ~~within a desired range~~in the amount of active by analytical chemical testing and determining the actual amount of active in samples.

This paragraph, again, from the '080 Patent's section on "EXAMPLES", sets the

stage for disclosing both the physical and chemical type tests referred to above at '080 Patent, col. 31, 1. 46 through col. ~~32,1~~32, 1. 40, which follows this paragraph (see citation). Moreover, this paragraph itself follows the manufacture of the film of Examples A-I and starts with what would be ~~a~~an expected quick and inexpensive procedure of looking at the film right after making ~~the film taking a look at~~ it~~,~~ to see if it appears non-uniform~~. That is, look at the film and see if it looks like everything is~~ or uniform~~ and, if it does, then test the film to make sure it is~~. Such an observational test is at a macro level and does not indicate the degree of uniformity. Even if the film appears uniform, analytical chemical tests must then be conducted to verify uniformity of content at the prescribed level. What followed next were the two other tests discussed above.

Importantly, the first test is obviously a physical type test needed to rely on assumptions to reach its conclusion of substantially no disparity among the amount of active found in any portion of the film. Namely, by "viewing the films it was apparent that they were substantially free of aggregation. .. . Therefore, there was substantially no disparity among the amount of active found in any portion of the film." Based on physical observations a conclusion was drawn. The second, another physical test, concluded "individual dosages forms from the same film of substantially equal dimensions will contain the same mass;" again, referring to mass not uniformity of content of active. Again, no simple declarative statement~~,~~ that the amount of active in each sample was substantially the same~~. [If we modify the independent claim to include test for the active, we should refer to that here~~ or that the actual amount of active was determined.~~]~~

It was only the third test, the analytical chemical type test that could directly establish that "films of substantially similar size cut from different locations on the same film contain substantially the same amount of active". This is to be expected as only the chemical based tests could provide the necessary assurance for the statement that substantially the same amount of active was present in each dose. Thus, ~~it is wrong to~~one cannot solely rely on physical tests in prior art disclosures to "establish" that the prior art films actually possessed the ~~uniformity ofactive required~~levels of uniformity of content

as claimed by the '080 Patent ~~as determined by actual~~. However, analytical chemical testing ~~for the active. In fact, such physical tests would not result in the type of quantitative assay which would yield the percent (%) variance as recited in the claims.~~ is used in the '080 Patent to establish the actual amount of active in samples. In one example, in the '080 Patent analytical chemical testing was used to test for the amount of one component, a red dye, and in so doing established that the uniformity of content of the component fell well within the 10% level, particularly, it was 4%. See, '080 Patent, col. 33, l. 10 through col. 34, l. 24 (example M). ~~The resulting product of the present invention is a useful, active-containing, visco-elastic film product that has a substantially uniform distribution ofactive components after formation, such that uniformity of content of the resulting film varies no more than 10% with respect to the desired amount of the active present in substantially equally sized individual dosage units sampled from different locations ofthe resulting film. Importantly, in accordance with the invention the patented processes can be used in the manufacture of commercial products.~~

VI. Arriving at the Invention

The inventors of the ~~'337~~'080 Patent are the first to not only identify the problems associated with manufacturing commercially and pharmaceutically viable active containing film individual dosage units or forms, but also to solve those problems, especially as same relate to obtaining required levels of uniformity of content. Although many prior publications discussed the use of film as a dosage form for drugs, none of the publications identified nor solved the problems and complications associated with their manufacture. These early publications focused on the compositional and qualitative aspects of the films only and merely treated the manufacturing, if mentioned at all, as being simple, such as exposing the cast wet film to a conventional hot air circulating oven. However, especially in a commercial manufacturing setting, drying an active-containing cast wet film (even if the wet film is homogenous), in a conventional hot air circulating oven does not necessarily produce a film that is commercially viable, or

deliver a film with the prescribed degree of uniformity of content in said setting. The '~~337~~080 Patent does. *See*

Bogue Declaration, ¶[~~5~~4-~~13~~11.

A. Recognition of the Problem

The inventors ~~have~~ discovered that it is not commercially viable to manufacture therapeutic-active-containing films using conventional drying methods. Even when a wet film matrix is properly formed so as to have a substantially uniform distribution of active within it, there are numerous factors which can destroy that uniformity of content during later processing such as casting and drying. The present specification describes many of these problems, which include
(i) self-aggregation and agglomeration of active; (ii) skinning of the surface (a barrier through which remaining solvent must penetrate) before the thickness of the film is sufficiently dried, resulting in ripping and re-forming of the surface; (iii) forming of ripples on the surface; (iv) formation of air bubbles, which result in voids or air spaces within the film product; (v) maintaining the active in a substantially stable and uniformly dispersed state; ~~or~~ (vi) movement of active particles due to uncontrolled air currents during drying; (vii) using air currents which create forces which overcome the yield value of the polymer matrix, or which would disturb or break the surface of the polymer matrix, or which overcome the inherent viscosity of the polymer matrix. See, for example, col. ~~3,~~ ~~I~~3,1. 33 through col. 4, ~~I~~1. 6, and col. 11, ll. 14-25, the '080 Patent.

B. Solving the Problem

The inventors not only were the first to identify all the problems described above, but the first to solve them. Failure to solve one or more of these problems results in a film product that lacks the desired degree of uniformity of content of active per unit dose of film and therefore when equal dosage sizes are cut from the bulk film product, the desired amount of active per dosage lacks the desired and/or required degree of uniformity of

content of active. The inventive methods and processes of the '080 Patent maintain the desired uniformity of content of active by, *inter alia,* controlling polymer matrix viscosity and controlling the drying processes so as to avoid the aforementioned problems. Thereby, forming a visco-elastic film that locks-in the substantially uniform distribution of actives) during the drying steps. As described in the specification and claims, the present invention ~~substantially~~ maintains the ~~uniformity~~claimed levels of uniformity of content of active from the formation of the initial matrix through the final drying process, such that the pharmaceutical active varies by no more than 10% within a film lot, and by no more than 10% when sampled from different film lots.

The Examiner has cited several references, which will be discussed in further detail below. For ease of understanding, the Patentee will briefly discuss the primary cited references herein. During the discussion, it is important to keep in mind that statements from these sources regarding uniformity of content of components, especially actives, are not based on analytical chemical testing for the amount of active present in equally sized samples, but are at best assumptions, generally based on physically observable properties of the film in its intact state. The below discussion is supported by the Bogue Declaration and the Fuller Declaration.

VIII. The Claim Rejections.

The Examiner's rejection of the claims begins on page 7 of the Office Action.

A. Claims 1-299 were improperly rejected.

Claims 1-299 were rejected as allegedly anticipated under 35 U.S.C. §102(b), or, in the alternative under 35 U.S.C. § 103(a), as obvious over, each of the following references: Chen (WO *00/42992)* ("Chen"), Staab (U.S. 5,393,528) ("Staab"), Le Person *(Chemical Engineering and Processing,* Vol. 37, pp. 257-263 (1998)) ("Le Person") and Horstmann (U.S. 5,629,003) ("Horstmann") or some combination thereof as set forth in the Office Action. These rejections relied on the Examiner's findings that material claim elements of the '080 Patent's only independent claims in reexamination, Claims 1, 82 and

161, were inherent in the cited references. Two limitations were of paramount importance, namely the limitations of "substantially uniform distribution of components" and of "locking-in or substantially preventing migration of" active ~~component~~.

Patentee maintains that the foregoing claim limitations are sufficient in themselves to establish patentability. Nevertheless, to advance prosecution, Patentee has explicitly added to all the independent claims herein presented specified levels of uniformity of content in the amount of active. Either a 10% limitation on the amount by which an active can vary between individual dosage units sampled from a particular film, and/or a 10% limitation by which the amount of active can vary from a desired amount among individual dosage units sampled from more than one film, which specified levels of uniformity of content in the amount of active are not disclosed expressly nor are they inherent in the art of record. Patentee has also explicitly required manufacturing resulting pharmaceutical and/or bioactive active-containing films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units. Additional aspects not present in the art of record include, *inter alia,* viscosity ranges, controlled drying, conveying, applying air currents which have forces below the yield value of the polymer matrix during drying, forming a visco-elastic film in about 4 minutes, keeping the polymer matrix temperature below 100°C, wherein resulting film has a water content of 10% or less. And the foregoing was just a partial listing of new claim elements. Hence, independent claims 1,82 and 161, as amended, and all the new independent claims, claims ~~321~~315-~~324~~318, are not ~~explictly, implicitly or inherently~~ disclosed ~~or suggested~~and/or made obvious, explictly or inherently, in the cited prior art. ~~In particular, the prior art ofrecod does not disclose, forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a pharmaceutical active, said matrix having a uniform distribution ofsaid pharmaceutical active, casting said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps and conveying said polymer matrix through a drying apparatus and evaporating at least a portion ofsaid solvent to rapidly form a visco-elastic film having~~

~~said pharmaceutical active uniformly distributed throughout by rapidly increasing the viscosity ofsaid polymer matrix upon initiation ofdrying within about the first 4 minutes to maintain said uniform distribution ofsaid pharmaceutical active by locking in or substantially preventing migration ofsaid pharmaceutical active within said visco-elastic film wherein the polymer matrix temperature is 100°C or less, forming the resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said uniform distribution ofpharmaceutical active by said locking in or substantially preventing migration ofsaid pharmaceutical active is maintained, wherein said resulting film is suitable for commercialization and regulatory approval, sampling the resulting film at different locations ofthe resulting film, in order to perform the analytical chemical tests for content uniformity ofsaid pharmaceutical active, and thus establish for commercialization and regulatory purposes the substantially uniform distribution of the pharmaceutical active throughout the film product, and/or where the required degree ofuniformity is such that the amount ofactive does not vary by more than 10%.~~

The Examiner ~~basically~~ relies on the Declaration ofEdward D. Cohen, Ph.D. under 37 C.F.R. § 1.132, dated September 6,2012 ("Cohen Declaration) ~~for his~~to support the assumption that it would be difficult for a person of ordinary skill in the thin film art not to obtain a film that has uniform content of active. Office Action, pp. 14 and 43. However, Dr. Cohen's assumption is dead wrong on its face or does not apply to the '080 Patent. Importantly, Dr. Cohen does not discuss the degree of uniformity of content. He refers generally to "substantial uniformity of content of active" and "uniform content of active" per unit dosage. Cohen Declaration, ¶¶ 8-10. Dr. Cohen's statement about uniform content of active, without providing the degree of uniformity of content cannot be applied to the '080 Patent's invention. Especially now that the claims of the '080 Patent expressly ~~claims~~require a degree of uniformity of content, namely, that uniformity of content of the resulting ~~film~~film(s) varies (i) no more than 10% with respect to the amount of active within a film (claims 1,82,161,316-318) and/or (ii) no more than 10% from a desired amount ~~ofthe active present~~with respect to the amount of active; said active sampled from

different films in substantially equally sized individual dosage units sampled from different locations of the ~~resulting film~~relevant film(s) (claim 315). ~~Moreover, the Declaration of Dr. Fuller on the other hand provides, at paragraphs 6-10, a basis and opinion for a conclusion much different from that provided by Dr. Cohen.~~

~~"6. It is my opinion that the film process as described by Chen at commercial scale would not inherently result in a film having a uniform distribution ofactive in the film. In particular, it is also my opinion that the film process of Chen would not inherently result in a film having a uniformity ofcontent of active in substantially equal sized individual dosage units sampled from Chen's resultant film, where the active in the dosage units varies no more than 10%. The process described by Chen does not describe how to dry in a manner that would avoid redistribution and inhomogeneity of a dissolved solute or suspended actives due to well known thermodiffusive effects. The effects, also referred to as the Soret effect, can drive inhomogeneities during the drying ofa previously homogeneous mixture. In other words, even ifa solution containing a solute or suspended actives is spatially homogeneous in that constituent, the act of drying the solution to create a solid film can cause redistribution ofthe solute or suspended actives through the creation oftemperature variations. This is the result oftemperature gradients within the polymer film matrix causing the solute or suspended actives in the film to migrate and accumulate in different locations even ifthe solute or suspended actives were initially uniformly distributed. The Soret effect, which was described in 1800's, is a classical phenomenon, and is well-known to the chemical process industry. (see Appendix II)~~

~~"8. Dr. Cohen's assumption that Chen's process wi11lead to films that are spatially homogeneous in composition is flawed because it does not recognize that thermodiffusive effects can result in spatial redistribution of constituents even if they were initially homogeneous prior to the application of heating during the process of film formation. Because Chen does not describe the film drying process, it cannot be assumed that any resulting temperature gradients within the polymer film matrix during the drying process will not lead to thermodiffusion and spatial inhomogeneity.~~

~~9. Chen does not discuss the development of viscoelasticity in the film during the drying process. Chen discloses the use of hydro colloids and it is wellestablished that these materials can increase viscosity but will not necessarily enhance viscoelasticity. It is well known that viscosity is only one property within the general description of viscoelasticity. Even though these materials, such as Carbopol®, can lead to shear thinning materials, they are often inelastic and purely viscous. Chen does not recognize the mechanism of viscoelasticity of a film undergoing drying needs to be effectuated to retain the spatial uniformity of the constituents ofthat film. The development of viscoelasticity has the ability of arresting processes such as the Soret effect that can induce inhomogeneities. The Monosol process that creates a viscoelastic film within the first four (4) minutes ofdrying has the important benefit of locking in a spatially homogeneous distribution ofcomponents by inhibiting the effects of thermodiffusion to obtain active uniformity that does not vary more than 10% in the amount of active present in substantially equal sized individual dosage units.~~

~~"10. Dr. Cohen is incorrect in his assumption that simply increasing the viscosity of a hydrocolloid material through film drying will retain spatial uniformity of the constituents ofa film. In the absence of conditions which rapidly build viscoelasticity, components can diffuse spatially in a viscous media in response to thermodiffusive effects. The development of a rapid viscoelastic network formation is able to spatially constrain the diffusion of components and inhibit thermodiffusivity and retain spatial uniformity to the desired degree."~~

Moreover, as set forth in the Bogue Declaration, ¶¶~~10~~4-~~14~~11, 730 samples of individual dosage units, ten each from 73 ~~separate manufacturing~~separately manufactured lots of resulting films produced in accordance with Patentee's invention, were tested for active content. The results were that the active content of each individual dosage unit remained well within the control limits of 90% to 110% of the desired amount.

> "The results shown in the appendices establish that the resulting films produced by the inventive method of the '080 Patent as disclosed and claimed have the required uniformity of

content based on analytical chemical testing. First, the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film. See Appendix A. Second, the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active. See Appendix B. Finally, the uniformity of content of the 73 lots of resulting film meets even more stringent standards, for example, the data shows: (i) 46 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 5%; (ii) 15 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 4%; 4 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 3%; and 1 lot of resulting film wherein the uniformity of content of active is shown with the amount of active varying by only 2%. See Appendix C .."

~~"It can be seen from Appendix A that the active content ofeach individual dosage unit remains well within the control limits of90% to 110%. The target or desired amount is 8.00 mg ofactive per individual dosage unit. The range of analytical chemical testing results among those 730 individual dosage units was 93.50% (7.48 mg) to 105.80% (8.47 mg) ofthe target or desired amount ofactive. This uniformity ofcontent level is consistent with that described in the '337 Patent."~~

Bogue Declaration, ¶ ~~12~~11.

As noted, the FDA requires that the amount ~~ofactive~~of active vary from dose to dose by no more than a prescribed percentage from the desired amount of active, essentially prescribing a degree of uniformity of content ~~uniformity~~in the amount of active which must be met. *See* Lin declaration, ¶9-16. Dr. Cohen provides no support for any prescribed degree of uniformity, and certainly not for the prescribed degree of uniformity of content in the amount of active explicitly recited by Patentee's claims under examination to meet commercial and/or regulatory requirements, or the degree of uniformity present in resulting films manufactured in accordance with Patentee's invention, as clearly demonstrated by the Bogue Declaration.

As held by the Court of Appeals for the Federal Circuit ("Federal Circuit") inherency requires much more than probabilities, possibilities, or for that matter assumptions~~, such as, that by starting with so called "uniform" mix ofmaterials, stirring them, then casting and drying inherently results in the processes claimed in the '080 Patent~~. In *Crown Operations Intern., Ltd. V. Solutia Inc.,* 289 F.3d 1367 (Fed.Cir. 2002) *("Crown"),* the patents at issue related to layered films used to create safety and solar control glass. The multi-layer film added properties to the glass assembly, such as impact resistance. An inner layer had solar control properties to reflect, absorb (and thus convert to heat), or transmit defined percentages of certain wavelengths oflight. *Crown,* at 1370. The district court had held the only relevant independent claim ofone ofthe patents, the '511 patent, not invalid on the grounds of anticipation and obviousness. It claimed a composite solar/safety film, comprised ofa solar control film "wherein said solar control film contributes no more than about 2% visible reflectance". *Crown,* at 1372.

> "Crown [the declaratory judgment plaintiff] argued that U.S. Patent No. 4,017,661 to Gillery (the "Gillery patent") anticipates the '511 patent. The district court held otherwise, because, while the Gillery patent discloses the first three limitations of claim ~~1~~1 ofthe'511 patent, it does not disclose the two percent visible reflectance limitation. The court found that neither the Gillery patent claims nor its description expressly disclose a two percent limit on reflectance contribution from the solar control film layer. Crown argued that the two percent limitation was inherently present in the Gillery patent's teachings because the Gillery patent disclosed an assembly with PVB layers, substrate layer, and substrate metalcoating - arguably of the same composition and thickness of the films disclosed by the '511 patent. Thus, Crown argued, because the structure, thickness and materials ofthe assembly were the same or within the same range(s), the Gillery patent must inherently disclose a two percent limitation. The district court rejected this argument because it found that none of the embodiments disclosed by the Gillery patent meet the two percent visible light reflectance limit."
>
> *Crown,* at 1372.

The Federal Circuit, in upholding the decision of the District Court as well as the

validity of the '511 patent, discussed the application ofinherency to validity that is most relevant here.

> "Regarding alleged anticipation by the Gillery patent, on its face the Gillery patent does not disclose or discuss a two percent limitation for the reflectance contribution of the solar control film. Crown maintains that the'511 patent merely claims a preexisting property inherent in the structure disclosed in the prior art. Crown urges us to accept the proposition that if a prior art reference discloses the same structure as claimed by a patent, the resulting property, in this case, two percent solar control film reflectance, should be assumed. We decline to adopt this approach because this proposition is not in accordance with our cases on inherency. If the two percent reflectance limitation is inherently disclosed by the Gillery patent, it must be necessarily present and a person of ordinary skill in the art would recognize its presence. In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed.Cir.1999); Continental Can, 948 F.2d at 1268, 20 USPQ2d at 1749. Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." Id. at 1269,20 USPQ2d at 1749 (quoting In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981)) (emphasis supplied)."

The alleged inherency of the art cited by the Examiner and discussed below has not been established other than by statements of probabilities and/or possibilities and/or just statements that things are uniform without providing any degree of uniformity that must be present. For example, the assumption that by starting with so-called "uniform" mix of materials, stirring them, then casting and drying as alleged to be disclosed in the prior art is insufficient to establish inherency. Again, inherency requires that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. Importantly, the mere possibility that some of the films produced as disclosed by the art cited might result in some type of "uniform" film is not sufficient.

1. Chen's alleged inherency.

> "The claimed "substantially uniform distribution of components" and "locking-in or substantially preventing migration" of the active in independent claims 1,82 and 161, and the variation of active content of 10% or less in dependent claims 254-255,272-273 and 290-291, are inherent in Chen's exemplified films and process. Inherency is based on the following: As discussed above, Chen uses the same materials and method as here claimed. Chen's ingredients are mixed until they are uniformly dispersed or dissolved in the hydrocolloid (p. 17, lines 8-11). Chen uses the same criteria discussed above with respect to the '080 patent in the Scope of Claims section for evaluation of substantial uniform distribution, i.e., weight of dosages and visual inspection."
>
> Office Action, p. 13.

The criteria used by Chen as cited by the Examiner for evaluation of "substantial uniform distribution" are physical observations. Such "observations" cannot be used, either inherently or otherwise, to establish the uniformity ofcontent in the actual amount of active in equally sized samples in Chen's examples. Absent, statements or data based on analytical chemical testing, not weighing or visual inspection, for the amount ofactive present in the film, Chen does not and cannot inherently disclose Patentee's resulting film having ~~uniformity ofcontent, with respect to the amount ofthe active present in substantially equally sized individual dosage units sampled from different locations ofthe resulting film, which varies by no more than 10% from the desired amount ofthe active~~the claimed levels of uniformity of content. Moreover, even if Chen disclosed, which it does not, the use of the same materials and methods as the '080 Patent, the mere fact that a certain thing may result from a given set of circumstances is not sufficient to support inherency. *Crown, supra,* at 1378.

Moreover, Third Party Requester has not provided any proof that Chen's process examples when followed exactly, with all the components exactly as listed, and all other conditions of Chen exactly met, will provide a process suitable for commercial manufacture, a process which produces products which are regulatory approvable by the FDA, and which exhibit the levels of uniformity of content in actual amount of active

claimed by Patentee's processes. Indeed, FIG. 5 of Chen describes a release profile of almost 120% of active from a film, which certainly exceeds the levels of uniformity of content in the amount of active that Patentee claims. This single active content result voids all claims to Chen's alleged inherency regarding same.

> "Finally, Chen's patent discloses the release profiles of four active agents from films. See Chen, Figure 5. The release profile data presented in Figure 5 show a high degree of variability at each data point. For example, the release profile for nicotine containing film product show that the amount of nicotine released at the 5 minute and 8 minute time point can be as high as approximately 115-120%. This level of active agent is greater than the 110% level (from an expected amount of 100%) that is considered acceptable to FDA for regulatory approval of a product that purports to be manufactured consistently with acceptable content uniformity. These data indicate that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film."
>
> Lin Declaration, ¶ 22.

The Examiner states that the films made in accordance with the claims as issued are inherent in Chen. This conclusion is based on the belief that Chen uses the "same materials and method" as the Patentee, but even if true, much more is required. Patentee respectfully submits that this conclusion is incorrect, and particularly incorrect ~~with the amended claims. The examiner~~in light of the claims as amended. The Examiner erroneously states that Chen "uses the same criteria" as the '080 Patent that issued in evaluating substantial uniform distribution, i.e. weights of dosages and visual inspection." Although, a number of ways to test films in the patent are disclosed, in order to test content uniformity ~~ofan~~of an FDA regulated film product, it is necessary to assay using analytical chemical tests for drug or therapeutic active content of unit film doses. *See,* Lin declaration, ¶ 9-16. This is necessary to ensure the amount of active is within acceptable guidelines. Visual observation and physical measurements such as weight is insufficient

to determine the active amount in equally sized dosage units~~. Almost all~~ at the level of uniformity of content required.

All of Patentees' ~~amended~~ claims now require analytical chemical testing and~~/or~~ that the films have ~~uniformity~~levels of uniformity in the amount of active which varies by no more than 10% ~~variance~~from film to film and/or no more than 10% from a desired amount across several films. The Examiner's assumption that visual inspection and weight measurements ~~provide this information~~establish these levels of uniformity of content in and by themselves is therefore incorrect~~.~~, in so far at least as is required by the FDA, for example. Moreover, "Chen's disclosure is lacking, both explicitly and inherently, the disclosure necessary to provide for the manufacture of drug-containing films with the uniformity of content in amount of drug (active) in individual dosage units to make FDA approvable film products." Lin Declaration, ¶21.

~~Fuller Declaration, especially at " 6-14, provides further reasoning regarding this incorrect assumption and lack of inherency. According to Dr. Fuller, "the film process as described by Chen would not inherently result in a film having a uniform distribution of active in the film ... [or] a uniformity ofcontent of active in substantially equal sized individual dosage units sampled from Chen's resultant film, where the active in the dosage units varies no more than 10%." Fuller Declaration, , 6. Moreover, Chen disclosure exhibits a lack ofunderstanding and more importantly any teaching "to describe the drying operation that would cause it to avoid redistribution and inhomogeneity ofa dissolved solute or suspended actives due to well known thermodiffusive effects. The effects, also referred to as the Soret effect can drive inhomogeneities during the drying ofa previously homogeneous mixture. In other words, even if a solution containing an active ingredient is spatially homogeneous in that constituent, the act of drying the solution to create a solid film can cause redistribution of the solute through the creation of temperature variations." Fuller Declaration, ~ 7. "Chen does not recognize that the mechanism ofviscoelasticity of a film undergoing drying to retain the spatial uniformity of the constituents of that film. The development of~~

~~viscoelasticity has the ability of arresting processes such as the Soret effect that can induce inhomogeneities. The Monosol process that creates a viscoelastic film within the first four minutes of drying has the important benefit of locking in a spatially homogeneous distribution of components by inhibiting the effects of thermodiffusion." Fuller Declaration, ~ 9.~~

Finally, ~~Dr. Fuller's Declaration addresses the~~there is a misplaced reliance on the physical terms "glossy" and "transparent" in the Office Action, which the Examiner use to establish the presence of "uniformity" in Chen's films. However, ~~as Dr. Fuller declares,~~ the ~~"~~term ~~'~~"glossy~~'~~" is purely a visual characteristic ("surface luster or brightness") and is not interchangeable with nor equivalent to the uniformity of content of components of a film, nor the content uniformity of an active in the film. *See,* www.merriam-webster.comldictionary/glossy. It is also not interchangeable with ~~a specific variation ofactive~~specified levels of uniformity of content in ~~unit dosage samples taken~~amount ofactive in individual dosage units sampled from a film~~...~~ or sampled from different films. The term ~~'~~transparent~~'...~~ is also a purely visual appearance characteristic ~~that is neither~~("transmitting light without appreciable scattering ... "). *See,* www.merriam-webster.coml dictionary/transparent. It is not indicative ~~nor suggestive of the~~of the uniformity of content ~~of the~~of the film~~. In particular, this term does not necessarily provide any indication or suggestion of a specific variance of active per unit dose of film sampled therefrom." Fuller Declaration, ~~~ 12-13. As such the Chen's films~~. As such, Chen can neither ~~inherently~~ anticipate, explicitly or inherently, nor make obvious the '~~337~~080 Patent claims, see discussion below.

2. Staab's alleged inherency.

> "Staab also discloses that "[t]he device of the invention thus is composed of a biologically-compatible material that has been blended homogeneously" with the drug (see col. 6, lines 5-10). In the Example at cols. 11-12, Staab prepares a four foot wide film which is then cut into two inch by two inch films each weighing 190 mg and containing 19 mg of benzalkonium

chloride as the active agent (see col. 11, line 52 through col. 12, line 3). Accordingly, Staab's films inherently have the instantly claimed substantially uniform distribution of components and active. Also, in view of the fact that each film contains 19 mg of benzalkonium chloride and in view of said homogeneous blending, the variation of active in the dosage units is 0% (sic 10%), as per claims 254, 255, 272, 273, 290 and 291."

Office Action, p. 29.

"In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Staab uses the same hydrocolloid as in the '080 patent, i.e. said HPMC. Accordingly, Staab's film in the Example at cols. 11-12 is inherently viscoelastic before drying. Accordingly, after drying for about 10 minutes, a viscoelastic film having less water that before drying is formed."

Office Action, p. 30.

"While Staab does not discuss viscoelasticity or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the active, Staab, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process."

Office Action, p. 31.

Again, as with Chen, absent statements based on testing ~~and/or a determination ofthe actual~~to determine the actual uniformity of content in the amount of active present in the film, so as to meet FDA approval, Staab does not and cannot inherently disclose Patentee's resulting film having ~~uniformity~~the claimed levels of uniformity of content, with respect to the amount of the active present in substantially equally sized individual

dosage units sampled from different locations of the resulting film~~, which varies no more than 10% from the desired amount ofthe active~~ and/or of different resulting films. Staab does not and cannot inherently form a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content within ~~this~~the recited ~~10% variance~~levels of uniformity of content.

Moreover, even if Staab disclosed, which it does not, the use of the same materials and methods as the '~~337~~080 Patent, the mere fact that a certain thing may result from a given set of circumstances is not sufficient to support inherency. *Crown, supra,* at 1378. Moreover, Staab just states that there is 19 mg of benzalkonium chloride present in each sample weighing 190 mg. However, ~~however~~ Staab does not disclose testing to determine the amount of benzalkonium chloride present in the final film product or even how each and every sample turned out to be 19 mg. Staab, ~~coL 11, L~~col. 11,1. 35 ~~through coL 12, L~~-col. 12, 1. 3. Staab's resulting structure is a foam rather than ~~a substantially solid~~the recited visco-elastic ~~structure~~film formed within 4 minutes and Staab also would not inherently have the recited degree of uniformity of amount of active in substantially equal sized dosage units. Moreover, Staab starts with a composition having 10% by weight of benzalkonium chloride (50% aqueous)~~. Yet~~ yet allegedly obtains a resulting film with 19 mg benzalkonium chloride in a 190 mg film, to once again obtain a 10% benzalkonium chloride resulting composition. A perfect yield must always be considered suspect. Inherency should never be based on a suspect disclosure. As such, Staab can neither anticipate, explicitly nor inherently, nor make obvious the '080 Patent claims, see discussion below.

3. Le Person's alleged inherency.

> "Le Person discloses that after 5 min of the drying, 'the polymeric network is not turgescent and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [i.e., pharmaceutical or drug] when the system reequilibrates.' (See p. 262, coL 2, third full paragraph.) Le Person also teaches that '[b]etween the 5th and 10th min of drying the heavy solvent migrates ... active substance, slowed

down in its migration, stays in the bottom of the layer.' (See the last four lines at page 262, coL 2). It is noted that the heavy solvent only accounts for 2% of the wet composition of the coating (see page 258, Table 1). As such, within 5-10 minutes, the solvent has been sufficiently evaporated such that, inherently, a substantial uniform distribution of the active is locked-in and migration is substantially prevented within the film, as here claimed. The active material homogenizes and a quasi-equilibrium is obtained for the components of the Page 38 active phase, taking into account evaporation of the heavy solvent (p. 263, col. 1, lines 8-13), and thus, there is a variation of active content of less than 10%, as per claims 272, 273, 290 and 291.

Office Action, pp. 37-38.

"While Le Person does not discuss viscoelasticity or that the films in its process have a 'substantially uniform distribution of components' or disclose 'locking-in or substantially preventing migration' of the active, Le Person, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 82,89-91,161,171-173,272-274 and 290-292, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a)."

Office Action, p. 38.

Le Person is entirely devoid of any details with respect to its process and materials. For example, nowhere does Le Person discuss what type of acrylic polymer he uses~~,~~ nor the molecular weight of the polymer. Thus, Le Person allows for materials which may have such a low molecular weight that forming a visco-elastic film may not be possible. Moreover, Le Person lacks sufficient enabling disclosure to be an effective reference as applied in view of the amended claims. Such deficiencies cannot be used in support of an inherency argument.

Again, absent statements and data based on testing for the amount of active present in the film with results establishing a substantial uniformity ~~ofcontent, which~~

~~active varies by no more than 10%~~of content at the claimed levels and suitable for FDA approval, Le Person does not and cannot inherently disclose Patentee's resulting film~~, having uniformity of content, with respect to the amount ofthe active present in substantially equally sized individual dosage units sampled from different locations of the resulting film, varying by no more than 10% from the desired amount ofthe active. .~~. Moreover, Le Person does not and cannot inherently form a viscoelastic film in about 4 minutes which locks-in the claimed uniformity of content ~~within this recited 10% variance~~in the amount of active.

~~Moreover, Le~~ Le Person discloses ~~.~~very little about the acrylic polymer, such as the molecular weight. If the molecular weight was low enough it may not become a viscoelastic material. Patentee asks, how could Le Person anticipate and/or make obvious the '080 Patent which is directed to the commercial manufacture of a regulatory approvable resulting film ~~with a~~meeting required specified ~~content uniformity of~~levels of uniformity of content in the amount of the active, where Le Person's goal, as noted in its abstract, was devoted to determining "cases ~~of mal distribution of the~~of maldistribution of the active substance," in connection with different drying methods, and not to providing a process for manufacturing films with ~~active~~ uniformity of ~~the~~content of the desired amount of an active. Importantly, Patentee has added several additional process steps not in the prior art. These new process steps present in the amended independent claim, as well as the new independent claims, further distance Patentee's patent from the prior art~~, by negating any anticipation and obviousness assertions.~~. As such, Le Person can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

4. Horstmann's alleged inherency.

> "The claimed substantially uniform distribution of components and active, and locking-in or substantially preventing migration of active, and the variance of active content of 10% or less in dependent claims 254, 272 and 290 are also inherent in Horstmann's Examples 1,3 and 4. In particular, Horstmann's

> films before drying are described as being uniform and homogeneous (see col. .3, line 11-19,29-34 and 37-41; col. 5, lines 1 and 50), and as noted above, Horstmann uses the same components and process steps as here claimed. The '080 patent notes that Horstmann addressed the problem of self-aggregation and nonuniformity by increasing the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film (see col. 2, line 60 through col. 3, line 1).
>
> Office Action, p. 43.
>
> "While Horstmann does not discuss viscoelasticity, water content of its dried films or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the, active, Horstmann, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 1,5,7-10,12-1423,63,64,82,84,86-89,91-93,102,142,143,161, 166, 168-171, 173-175, 184,224,225,249,254,267,272,285 and 290, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a)."
>
> Office Action, pp. 43-44.

Horstmann forms a gel, rather than a solid film as in the present invention. Thus the gel rheological properties of Horstmann are very different than a solid visco-elastic film having a water content of 10% or less. Moreover, Horstmann specifically teaches protecting the gels from drying up by placing the cut out gel shapes in a water vapor impermeable sealing material. See Horstmann, col. 5, 11. 11-13. This is a direct teaching away from drying to a water content of 10% or less. ~~Moreover,~~ Horstmann at col. 2, 11. 25-29, suggests drying may not be necessary.

Again, absent statements based on testing for the amount of active present in the film with results establishing a ~~substantial uniformity of content, with no more than 10% variation from a desired amount ofthe active~~the claimed levels of uniformity of content in the amount of active, suitable for FDA approval, Horstmann does not and cannot

inherently disclose Patentee's resulting film ~~having said uniformity of content which varies no more than 10% with respect to the desired amount ofthe active present in substantially equally sized individual dosage units sampled from different locations ofthe resulting film.~~claiming the specified levels of uniformity of content in the amount of active.

Additionally, as the Examiner admits, Horstmann discloses only that its film is alleged to be uniform at a point prior to drying. Horstmann, col. 3, 11.37-41. Horstmann says nothing about the uniformity of the product during or after drying. Again, *Crown* holds that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* A disclosure of some unspecified degree of uniformity of a film prior to drying in Horstmann does not establish that the product after drying is uniform, let alone the degree of uniformity as claimed by the '080 Patent. As noted throughout the '080 Patent, controlled drying is required for ensuring~~, among other things, [that uniformity of content ofthe resulting film varies no more than 10% with respect to the desired amount ofthe active present in substantially equally sized individual dosage units sampled from different locations ofthe resulting film].~~ the claimed levels of uniformity of content. As such, Horstmann can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

Importantly, Patentee has added several additional process steps also not in the prior art. See above. These new process steps present in the amended independent claims, as well as the new independent claims, further distance Patentee's patent from the prior art, by negating any anticipation and obviousness assertions. Even without the additional process steps, even if it were possible that a resulting film with the proper ~~uniformity~~levels of uniformity of content in the amount of active might possibly result from some manipulations of the disclosures given in any of Chen, Staab, Le Person and/or Horstmann, it is incorrect to rely on these references in an attempt to show they inherently disclosed Patentee's resulting film. See *Crown,* at 1377-1378, *supra.*

As the absence of inherency in and of itself removes Chen, Staab, Le Person and

Horstmann as viable prior art for rejecting Patentee's claims under ~~either~~ 35 U.S.C. § 102, the Examiner should withdraw his rejections of Patentee's claims ~~claims~~ 1,82 and 161 based on same. For the same reasons new independent claims ~~321~~315-~~324~~318 are allowable. Moreover, these references for the same reasons discussed above, as well as the reason discussed below, do not support any finding of obviousness, and thus the rejections of claims 1,82, and 161 ~~rejections~~ based on 35

U.S.C. § 103 should be withdrawn as well. For the same reasons new independent claims ~~321324~~315-318 are not obvious in light of the prior art. Finally, Patentee's claims 2 through 81, 83 through 160, ~~163~~162 through 299 and 300 through ~~320 and 325 through 628~~314 as they depend from independent claims ~~1,82, 161, and 321-324~~1,82,161 should all be allowed as well, with any rejections withdrawn.

B. Third Party Requester's Wherein Argument is Wrong

Patentee finds it necessary to address Third Party Requester's attempt to vitiate the '080 Patent's claim language beginning with "wherein". Third Party Requester cites to the Federal Circuit for the premise that "a whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." *Minton* v. *Nat'l Ass'n o/Securities Dealers, Inc.,* 336 F.3d 1373, 1381 (Fed.Cir.2003). Third Party Requester's Request for Inter Partes Reexamination ("The Request"), p. 16.

However, the Federal Circuit has also strongly held that "when the 'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." *Hoffer* v. *Microsoft Corp.,* 405 F. 3d 1326, 1329 (Fed. Cir. 2005). Essentially, Requester proposes that with elimination of the "whereby" clauses, the claims 1, 82 and 161 (before the amendments herein) would not require "wherein said resulting film has a water content of 10% or less and said uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained." The Request, p. 20.

~~Patentee's fundamental invention concerns among other things making a film having a substantially uniform distribution~~

~~ofcomponents or, as now claimed a uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film is such that uniformity of content of the resulting film varies no more than 10% with respect to the amount ofthe active present in substantially equally sized individual dosage units sampled from different locations of the resulting film.~~

As noted above, "when the whereby clause states a condition that is material to patentability, it cannot be ignored to change the substance of the invention." *Hoffer* v. *Microsoft Corp.,* 405 F.3d 1326 (Fed. Cir. 2005); *see also Fantasy Sports Properties, Inc.* v. *Sportsline.com, Inc.,* 287 F.3d 1108, 1111-16 (Fed. Cir. 2002); *Griffin* v. *Bertina,* 285 F.3d 1029, 1034 (Fed. Cir. 2002). In *Griffin,* for example, the court found that "wherein" clauses were claim limitations "because they relate back to and clarify what is required by the count. Each 'wherein' clause ... expresses the inventive discovery [and] ... elaborates the meaning of the preamble." *Griffin,* 285 F. 3d at 1033-34. Further, "the allegedly inherent properties of the 'wherein clauses' provide the necessary purpose to the steps." *Id.* See also, MPEP, § 2111.04.

The ~~original~~ '080 Patent independent claims' wherein clause limitations cannot be disregarded. The '080 Patent claims processes for manufacturing ~~pharmaceutical films with a substantial uniform distribution ofcomponents~~resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the u.s. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films. The ability to make such films with the required ~~amount~~level of uniformity in ~~distribution~~content of active is the essence of Patentee's invention. Thus ~~any~~, such wherein ~~clause~~clauses which ~~expresses~~express the inventive discovery and elaborates the meaning of the preamble~~, for example, that the uniformity of content of the resulting film varies by no more than 10% with respect to the amount ofthe active present in substantially equally sized individual dosage units sampled from different locations of the~~

~~resulting film, or that such uniformity must be determined by analytical chemical testing in compliance with regulations,~~ cannot be ignored for purposes of patentability.

Finally, Third Party Requester has made many allegations about the '080 Patent and its specifications and claims, and the prior art in The Request. Patent owner believes ~~the amendment to claim 25~~that the amendments to claims 1, 82 and 161 herein clarifying the scope of same~~, obviates~~ and thereby advancing the prosecution of same, obviate the need to address Third Party Requester's allegations or the Examiner's statements made without the benefit of the amendments~~, nevertheless~~. Nevertheless, to the extent that any are not explicitly addressed herein, Patentee hereby asserts they are wrong and unsupported in either fact or law.

C. Claims ~~1,4,5,8-18,20-32,34,36-40,44-47,51,53,54,59~~1,4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84,87-97, 99-111,113,115-119,123-126,130,132,133,138,141-150,161-166,169-179, 181-193,195,197-201,205-208,212,214,215,220,223-232,243,244,246, 247,249-262,264,265,267-280,282,283 and 285-299 were rejected under 35
U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chen. Claims ~~2,3,6,7~~2, 3, 6, 7, 19,33,35,41-43,48-50,52,55-58,60,61,85,86,98, 112, 114, 120~~-122, 127-129, 131, 134-137, 139, 140, 167, 168, 180, 194, 196,202~~122,127-129,131,134-137,139,140,167,168,180,194,196,202-204, 209~~-211, 213, 216-219, 221, 222, 245, 248, 263, 266, 281~~211,213,216-219,221,222,245,248,263,266,281 and 284 were rejected under 35 U.S.C. 103(a) as being unpatentable over Chen.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Chen, WO *00/42992* ("Chen") or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Chen. Patentee incorporates its previous discussions in sections A. and B. above. Chen is a primary reference relied upon by the Examiner in the Office Action. Patentee respectfully traverses the ~~rejection~~above rejections on the basis, among others, that Chen does not disclose ~~the~~as claimed~~: particular drying methods; resulting visco-elastic product~~ in the '080 patent: the recited controlled drying; the recited

viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of ~~pharmaceutical~~ active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of a lot of the resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Chen also fails to disclose, explicitly or inherently, the additional elements found in Claim 317. Claim 317 generally adds, *inter alia,* conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60°C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30°C between polymer matrix inside temperature and outside exposure temperature.

Chen discloses two methods of forming a film product, a solvent casting method and an extrusion method. The extrusion method does not rely upon putting a hydrocolloid in a solvent, nor does the extrusion method use a drying oven and is apparently preferred by Chen over the solvent method. Chen, page 15, lines 9-21. In the solvent casting method, Chen states that a hydrocolloid is dissolved or dispersed in water, and mixed to form a homogeneous solution. The active agent and other ingredients may be added and dispersed or dissolved uniformly in the hydrocolloid solution. The coating solution with a

solid content of 5-50% and a viscosity of 500-15000cps is degassed and coated onto a polyester film and "dried under aeration" at a temperature between 40-100°C to avoid destabilizing the agents. Chen, p. 15,11. 19-29. The dry film formed by this process is described to be a "glossy, stand alone, self supporting, non-tacky and flexible film". Chen, p. 15, 11, 30-31. These very general statements are all that are given by Chen as to the formation and drying of Chen's film product. These statements cannot support either anticipation ~~nor~~or obviousness rejections. ~~See, e.g., Fuller Declaration, ~~ 6-13.~~

Chen's drying process is so general and devoid of detail so as to provide no guidance other than that to dry, one places a film in a conventional hot air circulating oven at temperatures ~~of from~~of from 40-100°C and leaves it for a period of time. ~~As shown in Patentee's photographs (Figures 9-16), drying in a hot air oven does not produce uniform films through the locking in of the active in a substantially uniform distribution throughout the visco-elastic film. Again, it is important to note that while physical testing and observations such as Patentee's photographs (Figures 9-16) may be generally relied on to show non-uniformity, direct establishment of the uniformity ofcontent for the amount ofactive is by testing for the active needed to demonstrate that the amount of active is substantially uniform throughout the film. Importantly, Chen's "tests" for uniformity, except perhaps for water content, are for physical uniformity, that is, appearance (glossy, transparent), weight, density, thickness and not the relevant testing of the active itself to demonstrate the desired uniformity ofcontent ofthe desired amount ofactive per unit dosage as required by the claims in reexamination. Fuller Declaration, ~ 11-13.~~

Chen does not disclose any other drying methods beyond drying "under aeration", nor does Chen disclose any controlled drying processes whatsoever. Chen showed no recognition of the complexities involved in the commercial manufacturing of films, as Chen's focus relates solely to the ingredients and mechanical properties, not the process. Without any recognition of the problems, and without any appreciation of the difficulties in preventing the settling, migration and/or aggregation or agglomeration of active(s) in the cast flowable mass, Chen neither sought nor found the solution to creating

commercial scale films having ~~substantial~~ uniformity ~~ofactive(s) per unit dose or per unit of film~~of content of pharmaceutical and bioactive actives per individual dosage unit and meet FDA requirements regarding same. Chen lacks substantial disclosure in view ~~of the '337~~of the '080 Patent. Among its deficiencies, Chen lacks any disclosure as to specific processing means (beyond generally drying in a generic oven) or the formation of a visco-elastic film state. Chen only discloses the apparent homogeneity of a blended matrix, and this is prior to the addition of actives. There is no disclosure or suggestion as to how to create a substantially uniform distribution of the pharmaceutical or biological ~~active~~ active in the blended matrix and then cast that matrix to maintain uniformity, and then ~~convey~~control drying through among other processes conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to rapidly form a visco-elastic film having said pharmaceutical active uniformly distributed throughout by rapidly increasing the viscosity of said polymer matrix upon initiation of drying within about the first 4 to maintain said uniform distribution of said pharmaceutical or biological active by locking-in or substantially preventing migration of said· pharmaceutical active within said visco-elastic film and then test it to establish the substantially uniform distribution of pharmaceutical or biological active content, in compliance with FDA regulations.

~~Thus, among~~Among other things, the '~~337~~080 Patent claims are directed to locking-in ~~the~~an active such as a pharmaceutical or biological active, by controlling drying to form a viscoelastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes. The Examiner has stated in the Reexamination, Reasons for Patentability/Confirmation *("RFP/C"),* in connection with both the '292 Patent and the '891 Patent reexaminations that "Chen does not discuss what happens within the first 4 minutes of drying." Moreover, in the '891 Patent *RFP/C* the Examiner goes on to state that: "Chen does not discuss uniformity of pharmaceutical or biological active components in its doses. Table 4 of Chen gives the grams per unit dosage film and density for Example 1 with standard deviation based on three or four measurements, but does not give compositional uniformity." Additionally, Chen's

Example 1 contains only food flavorings and a sweetener.

Chen does not disclose that the resulting products are compositionally uniform, but only that they are "glossy". ~~Glossy~~As stated above, glossy does not imply or establish compositionally ~~uniform. Fuller Declaration, ~~ 11-13~~uniformity. **In** fact, Chen's Figure 5 (Examples 5-8) clearly shows a lack of compositional uniformity of active. ~~While~~Although statistics are not defined in the text, the error bars represent either high or low values, standard deviation or some measure of variation. Given that the compositions of Examples 5-8 are the same, except for the amount of active, it is reasonable to ~~assume~~conclude that the active is not uniformly present in the individual films due to the wide variation of release of active from the same film compositions. For example, with regard to the release of nicotine in the same film compositions, the release reaches in excess of ~~100%. It is reasonable to conclude that a major reason for these release differences is that~~118%. Certainly there is neither disclosure of, nor inherency in, the that the level uniformity of content in the amount of active ~~in each film tested varies by more than the claimed 10%, despite the identical film-forming compositions.~~as sampled in individual dosage units of the same film be 10% or less. "The release profile data presented in Figure 5 show a high degree of variability at each data point. This indicates that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film." Lin Declaration, ¶ 22.

~~Patentee's claims are directed to the formation of a suitable visco-elastic product, prepared through the methods of the invention. As used throughout the application, the formation of a suitable commercial and regulatory compliant product is the desired goal, and a suitable product is one that is substantially uniform in active content to the extent required by said commercial and regulatory concerns. For example, those regulations and directions provided by the FDA for pharmaceuticals and biologic actives. As used throughout the application, the resulting visco-elastic product is defined as a product that has maintained the desired compositional uniformity after being subjected to a~~

~~coating/deposition step and drying. For example, the '080 Patent at col. 8, 11. 64-66 states that the stability is important "in the wet film stage until sufficient drying has occurred to lock in the particles and matrix into a sufficiently solid form such that uniformity is maintained." The '080 Patent at col. 13,11. 53-59 even more clearly states that: "The resulting dried film 1 is a viscoelastic solid, as depicted in Section C. The components desirably are locked into a uniform distribution throughout the film."~~

~~Thus, as~~As defined in the specification for the '~~337~~080 Patent as filed, a visco-elastic solid is one that has been sufficiently dried to lock its active components into a substantially uniform distribution throughout the film. The '~~337~~080 Patent claims require that this be done within about the first 4 minutes or less. The Examiner has previously ~~stated~~acknowledged that Chen does not disclose that the resulting film product has any compositional uniformity of pharmaceutical or biological active at that point in time. See '891 Patent *RFP/C.* ~~The Examiner cannot point to any portion of~~Neither Chen~~, or~~ nor the other references~~, that teaches~~ teach this step.

As explained throughout the '080 Patent and as summarized above, the present invention is based upon the discovery that certain process parameters, such as, viscosity and controlled drying methods to avoid non-uniformity of content in the amount of active must be employed to provide a commercially and FDA viable film product. Chen does not disclose or suggest such a resulting product. *See* Lin Declaration, ¶¶ 17-22. Chen discloses that various components (absent the active) are combined and that the mixture is blended to form a "uniform" solution. (Chen, p. 20, 11. 19-20). ~~While~~although even the formation of a uniform solution in a blender is beneficial, it is not the end of the process by any means~~. Chen's initial blend (without the active) may be mixed to be homogeneous, but there is absolutely no disclosure whatsoever of forming a homogeneous mixture containing an active and casting and drying to maintain such uniformity in the resulting film~~. Further, as explained above, conventional drying methods do not inherently provide uniform films and, in fact, would not be expected to provide resulting films having ~~compositional~~ the claimed uniformity of content in the amount of active. ~~uniformity or uniformity of content of active. See Fuller Declaration,~~

~~ 6-10.

In addition, use ofnon-controlled drying methods such as described in the '080 Patent specification can lead to compositional non-uniformity, as explained above, due to the number of problems associated with conventional drying, see col. 3,11. 13-57 ofthe '080 Patent. In fact, as explained in the '080 Patent, depending upon the drying methods used, various "hot spots" can form due to uneven air flow and temperatures, which destroy the compositional uniformity of the resulting product. See the '080 Patent, col. 13,11.6-16, as well as, Figs. 9-16. Chen's drying methods, such as the use ofuncontrolled hot air circulating ovens, do not inherently provide compositionally uniform films. In fact, the Patentee has demonstrated quite the contrary occurs.

See also, Fuller Declaration, ~~ 6-10.

Patentee's claimed process isprocesses are not present in Chen, either literallyexpressly or inherently, and it Chen cannot anticipate the claims as pending. Moreover, one of ordinaryof ordinary skill in the art, considering the teachings of the cited Chen reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Chen does not render obvious the pending claims ofthis rejection.

D. Claims 2, 3,16,32,55,72-81,95,111,134,151-160,177,193,216 and 233-242 were rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teaching of Chen and Staab.

The Office Action rejected the above claims under 35 U.S.C. § 103(a), as being unpatentable over the combined teaching of Chen and Staab, U.S. 5,393,528 ("Staab").

Patentee incorporates its previous discussions in sections A., B. and C., above, and DE., below and traverses all said rejections thereon. As all the above claims depend from one of the independent claims, claims 1,82 and 161, they are allowable for all the reasons provided in the sections dealing with Chen, above, and Staab, below and even combined Chen and Staab do not render obvious the pending claims ofthis rejection.

E. Claims 1-5, 10, 12-16,21,24,25,32,44-46,54,55,59,63-70,72-75,78-84, 89, 91-~~95,100,103,104,111,123-125,133,134,138~~95, 100, 103, 104,111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171,173-177,182,185,186,193,205-207,215,216, 220, 224-231, 233-236, 239242,249-252,254,255,257-260,267-270,272,273,275-278,285-288,290,291 and 293-299 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Staab. Claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170,237 and 238 were rejected under 35 U.S.C. 103(a) as being unpatentable over Staab.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102 (b) by Staab, or, under 35 U.S.C. § 1 03(a), as obvious or unpatentable over Staab. Patentee incorporates its previous discussions in sections A., B., C. and D., above, Patentee respectfully traverses the rejection on the basis, among others, that Staab does not disclose ~~the~~as claimed~~: particular drying methods; resulting visco-elastic product~~ in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution ~~ofcomponents; casting a flowable polymer matrix_having a viscosity from about 400 to about 100,000 cps~~of components; or locking-in or substantially preventing migration of the pharmaceutical and/or bioactive active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution ~~ofpharmaceutical active~~of active, such that uniformity of content of the resulting film ~~vary~~varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of one lot of the resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Staab certainly does not disclose, explicitly or inherently, the additional claim elements of Claim 317. Claim 317 generally adds to the above, *inter alia,* conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60°C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said viscoelastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5°C to 30°C between polymer matrix inside temperature and outside exposure temperature.

~~Staab teaches the benefits ofusing a "gas foamed film" or films. Staab, col. 5, 11.33-35; col. 8,11.33. Staab also teaches away from the '337 Patent by teaching that air bubbles are necessary, which are contraindicated in Patentee's invention requiring the uniform distribution of active. Staab instead teaches that gas bubbles must be added to the polymer/drug mixture prior to casting. .~~

> ~~"It should be noted that heretofore, the significance ofthe addition ofgases in the formation ofthe film to alter the texture and solubility ofthe film has not been recognized. "~~
>
> ~~Staab, col. 3, 11. 15-20.~~

~~"The fine tuning of dissolution rates and delivery of agent material, by the addition of gases and by altering the grades or mixtures of polymer materials or layers, is an important aspect of the present invention.~~

~~"On addition ofthe gas, preferably nitrogen, a web is formed ofthe final formulation and the gas. The resultant structure can be described as a foam with various sized air bubbles trapped in the matrix. There is a dual benefit that has~~

~~been surprisingly observed in this connection, namely that not only can the size of the bubbles in the foam alter the dissolution rates and correct what is a serious flaw in standard polymer films, it also offers to the user a perceptible softness to the film which enables the delivery of many types of drugs to tender mucosal tissues. It has been observed that the formation of this web ofthe polymer/drug formulation and the gas must be made just prior to casting on the glass or steel plates. This offers precise control over the microbubbles and resultant control over the dissolution,~~

~~"Without this web formation, the quick release of drug was heretofore not possible.•This frothy foam mixture or web can also be added to a mold to provide a formed device such as a barrier delivery system which completely dissolves upon use in a body cavity, e.g. the vagina.~~

> ~~"The gases, for example, air or nitrogen are introduced near the point of application of the liquid polymer material to the stainless steel casting sheet. The gases are added in a closed system by mixing with whipping blades or a motor driven homogenizer to homogenize the mixture of polymer, active material and gas to form a frothy foam. The final mixture then sets up or gels as a foam. It is also possible to pour the frothy foam mixture into a mold. The mold is then deformed and the formed device such as a diaphragm, is removed." Staab, col. 8, 11. 29-64 (emphasis supplied). In direct conflict with Staab's teaching, the '080 Patent teaches the use ofanti-foamingagents to prevent gas bubble formation. "Therefore, there is a need for methods and compositions for film products, which use a minimal number of materials or components, and which rovide a substantially non-self-aggregating uniform heterogeneity throughout the area ofthe films .... Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product."~~
>
> ~~'080 Patent, col. 4, 11.5-21 (emphasis supplied).~~

~~"A number of techniques may be employed in the mixing stage~~

~~to prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed. Additionally, the speed ofthe mixture is desirably controlled to prevent cavitation of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film."~~

~~'080 Patent, col. 9,11.56-65 (emphasis supplied).~~

~~See also section of '080 Patent entitled "Anti-foaming and De-foaming Compositions" ('080 Patent, col. 22, 1. 47 through col. 23, 1. 53).~~

~~Staab addresses the fine tuning ofdissolution rates and delivery of active agent, by teaching the addition of gases as an important aspect ofhis invention (Staab, col. 8,11.30-34).~~

~~Staab is silent with respect to the claimed uniformity ofcontent, the essence of the '080 Patent. The '080 Patent in connection with achieving said unifonnity of content teaches the removal of such gases and bubbles ('080 Patent, col. 9, 11. 56-65). Moreover, Staab uses conventional drying (Staab, col. 11, 11. 64-65) rather than the particular drying methods used to ensure the unifonnity of content claimed by the '080 Patent.~~

~~Staab provides absolutely no teaching or suggestion as to how to arrive at a final product that contains the recited level of active unifonnity. Similar to the discussion of Chen above, Staab teaches general drying methods that would be expected to subject the material to similar air forces as in Chen's air drying oven, but does not teach the fonnation of and maintenance of a film having a substantially unifonn active content. Again, as explained above, Staab provides absolutely no teaching or suggestion as to how to arrive at a final product that includes the claimed content unifonnity. Similar to the discussion of Chen above, Staab teaches general drying methods that are likely to subject~~

~~the material to similar air forces as in a conventional air drying oven, but does not teach the fonnation ofand maintenance ofa film having a substantially unifonn active content.~~

~~The presently claimed process is not present in Staab, either literally or inherently, and it cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings ofthe cited reference as a whole, would not predictably or rationally arrive at the limitations ofthe present claims. For these reasons, Staab does not render obvious the pending claims ofthis rejection. Patentee respectfully traverses the rejection on the basis, among others, that Staab does not disclose the claimed: particular drying methods; resulting visco-elastic product; substantially unifonn distribution ofcomponents; casting a flowable polymer matrix having a viscosity from about 400 to about 100,000 cps; or locking-in or substantially preventing migration ofthe active; or said unifonn distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidily increasing the viscosity ofthe polymer matrix upon initiation ofdrying within about 4 minutes to maintain said unifonn distribution ofpharmaceutical active, such that unifonnity of Patent No.: US 7,897,080 content of the resulting film's variation in amount ofthe active present in substantially equally sized individual dosage units sampled from different locations ofthe resulting film is in compliance with regulations governing same.~~

Moreover, Staab teaches the benefits ofusing a "gas foamed film" or films. Staab, col. 5, 11.33-35; col. 8, 11. 33. Staab ~~also~~thus teaches away from the '~~337~~080 Patent by teaching that air bubbles are necessary, which are contraindicated ~~for the patented~~ in Patentee's invention requiring a substantially uniform ~~compositional~~ distribution of active. Staab instead teaches that gas bubbles must be added to the polymer/drug mixture prior to casting~~.~~

> "It should be noted that heretofore, the significance ofthe addition of gases in the formation of the ~~mm~~film to alter the texture and solubility ofthe film has not been recognized. "

Staab, col. 3, 11. 15-20.

"The fine tuning of dissolution rates and delivery of agent material, by the addition of gases and by altering the grades or mixtures of polymer materials or layers, is an important aspect of the present invention.

* * * *

~~"On addition ofthe gas, preferably nitrogen, a web is formed ofthe final formulation and the gas. The resultant structure can be described as a foam with various sized air bubbles trapped in the matrix. There is a dual benefit that has been surprisingly observed in this connection, namely that not only can the size of the bubbles in the foam alter the dissolution rates and correct what is a serious flaw in standard polymer films, it also offers to the user a perceptible softness to the film which enables the delivery ofmany types ofdrugs to tender mucosal tissues. It has been observed that the formation ofthis web ofthe polymer/drug formulation and the gas must be made just prior to casting on the glass or steel plates. This offers precise control over the microbubbles and resultant control over the dissolution, "Without this web formation, the quick release ofdrug was heretofore not possible.•This frothy foam mixture or web can also be added to a mold to provide a formed device such as a barrier delivery system which completely dissolves upon use in a body cavity, e.g. the vagina.~~

"The gases, for example, air or nitrogen are introduced near the point of application of the liquid polymer material to the stainless steel casting sheet. The gases are added in a closed system by mixing with whipping blades or a motor driven homogenizer to homogenize the mixture of polymer, active material and gas to form a frothy foam. The final mixture then sets up or gels as a foam. It is also possible to pour the frothy foam mixture into a mold. The mold is then deformed and the formed device such as a diaphragm, is removed." Staab, col. 8, 11. 29-64 (emphasis supplied).

In direct conflict with Staab's teaching, the '~~337~~080 Patent teaches the use ofanti-foaming

agents to prevent gas bubble formation~~.~~ and thereby promote uniformity. Importantly, Patentee's processes, in many cases, avoid the formation of bubbles, without the need to use anti-foaming agents.

"~~Therefore, there is a need for methods and compositions for film products, which use a minimal number of materials or components, and which provide a substantially non-self-aggregating uniform heterogeneity throughout the area of the films ....~~

> Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product."

'~~337~~080 Patent, col. 4, 11. 5-21 (emphasis supplied).

> "A number of techniques may be employed in the mixing stage to prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed.~~ Additionally, the speed ofthe mixture is desirably controlled to prevent cavitation of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film."~~."

'~~337~~080 Patent, col. 9, 11.56-65 (emphasis supplied).

See also section of '~~337~~080 Patent entitled "Anti-foaming and De-foaming Compositions" ('~~337~~ 080 Patent, col. 22, 1. 47 through col. 23, 1. 53).

Staab addresses the fine tuning of dissolution rates and delivery of active agent ~~material~~, by teaching the addition of gases as an important aspect of his invention (Staab, col. 8,11.30-34). Staab is silent with respect to the ~~claimed uniformity~~recited levels of uniformity of content~~, the essence of the '337 Patent~~. The '~~337~~080 Patent in connection with achieving ~~said~~ uniformity of content in the amount of active teaches avoiding bubble

formation and the removal of such gases and bubbles ('~~337~~080 Patent, col. 9, 11. 56-65). Moreover, Staab uses conventional drying (Staab, col. 11,11.64-65) rather than the particular drying methods used to ensure the uniformity of content claimed by the '~~337~~080 Patent.

~~Staab provides absolutely no teaching or suggestion as to how to arrive at a final product that contains the recited level ofactive uniformity. Similar to the discussion of Chen above, Staab teaches general drying methods that would be expected to subject the material to similar air forces as in Chen's air drying oven, but does not teach the formation of and maintenance ofa film having a substantially uniform active content. Again, as explained above, Staab provides absolutely no teaching or suggestion as to how to arrive at a final product that includes the claimed content uniformity. Similar to the discussion of Chen above, Staab teaches general drying methods that are likely to subject the material to similar air forces as in a conventional air drying oven, but does not teach the formation of and maintenance of a film having a substantially uniform active content.~~

The presently claimed process is not ~~present~~disclosed in Staab, either ~~literally~~expressly or inherently, and ~~it cannot~~Staab does not anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Staab does not render obvious the pending claims ~~of this rejection~~of the above rejections.

F. Claims 82, 89-~~91, 161, 171~~91,161,171-173,272-274 and 290-292 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Le Person.

Claims 92 and 174 were rejected under 35 U.S.C. 103(a) as being unpatentable over Le Person.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Le Person, Chemical Engineering and Processing, Vol. 37, pp. 257-263 (1998) ("Le Person") or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Le Person. Patentee incorporates its previous discussions in sections A., B., C., D. and E., above,

Patentee respectfully traverses the rejection on the basis, among others, that Le Person does not disclose ~~the~~as claimed~~: particular drying methods to provide a substantially uniform distribution ofcomponents; resulting visco-elastic product~~ in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution ~~of components; casting a flowable polymer matrix_having a viscosity from about 400 to about 100,000 cps~~of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of ~~pharmaceutical~~ active, such that uniformity of content of the resulting ~~films vary~~film varies by no more than 10% in ~~the~~ amount of the active present in substantially equally sized individual dosage units sampled from different locations of one lot of ~~the~~ resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same. ~~Le Person discloses that~~

Le Person certainly does not disclose, either explicitly or inherently, the additional claim elements found in Claim 317. Claim 317 generally adds to the above, *inter alia,* conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60°C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized

individual dosage units, sampled from different locations of said viscoelastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30°C between polymer matrix inside temperature and outside exposure temperature.

Le Person does disclose that the drying step used plays a role in the final product, but fails to disclose or suggest how to achieve a uniform final product. In fact, Le Person discloses methods that result in a non-uniform product prior to and at 10 minutes. According to Le Person, the resulting product dried in 9 minutes would not have claimed uniformity of content of active.

Le Person's goal was to determine "cases of maldistribution of the active substance," in connection with different drying methods, said mal distribution having consequences on storage and delivery of a drug and proposes the use of Laser Scanning Confocal Microscopy on the active substance and the heavy solvent to determine same. (Le Person, Abstract). Le Person acknowledges that in the formation of a film product, "drying is the essential unit operation necessary to form the final product." (Le Person, p. 257). ~~In Le Person's experiment, a coating mixture includes a polymer, three light solvents, a heavy solvent, and a pharmaceutical active substance. Le Person stated that the drying process used must evacuate the light solvent and preserve the heavy solvent.~~ Le Person's experimental set-up was composed of two parts, "the drying cell and the wind tunnel. . . . [wherein] the wind tunnel is a conventional drying rig ...." Le Person, p. 258, col. 2 & Fig. 1. Le Person's disclosure of the use of a wind tunnel further negates any argument that Le Place inherently anticipates or makes obvious Patentee's invention.

~~Le Person conducted experiments on drying conditions. At the 5 minute mark, Le Person noted that intense moisture removal through the exposed surface ofthe layer to radiation during the first three minutes of drying produced a stress on the polymer and caused "displacement of the active phase towards the bottom ofthe layer." (Le Person, p. 261). Le Person noted that, initially, the constituents of the active phase are apparantly homogeneously distributed, but during a drying process, the active substance separated and sunk to the bottom. (Le Person, p. 262). Le Person noted that, between 5 and 10~~

~~minutes ofdrying, the heavy solvent migrates towards the top surface and the active substance stays in the bottom layer. (Le Person, p. 262). After 15 minutes, Le Person notes that the active substance crystallizes, due to the lack of solvent contained therein. (Le Person, p. 263). Eventually, the active substance homogenizes, and only after 15 minutes a quasi equilibrium is obtained for the active phase, taking into account the evaporation ofheavy solvent. (Le Person, p. 263). Thus, Le Person acknowledged that the drying step ofa film formation is critical, and noted the non-homogeneity ofthe film product it produced during drying.~~

It is important to note that Le Person simply recognized the overall, general difficulty in obtaining films with a substantially uniform distribution of active. ~~However~~Le Person did not try to solve this problem, only to determine means to identify it. Thus, Le Person did not recognize the specific reasons therefor, nor did Le Person recognize the solutions needed to overcome this difficulty. Le Person's goal was to find ways to best determine whether or not there was homogeneity of film product. ~~Le Person uses water with a heavy solvent (see abstract and Table 1), and does not complete its drying, and in particular removal of the heavy solvent, until after 15 minutes (see Le Person, pp. 261-263). After 10 minutes, Le Person's heavy solvent has migrated to the exposed surface; and after 15 minutes, a quasi-equilibrium is obtained for the components of the active phase, taking into account the evaporation ofthe heavy solvent (see Le Person, p. 263).~~

However, the point of Le Person is that, in the time period (i.e., less than 10 minutes), there is non-uniformity of the product. Le Person even states that "intense moisture removal through the exposed surface of the layer to the radiation, during the first 3 min of drying (Le Person, Fig. 7) produces a stress on the polymer skeleton ... and as a result the acrylic polymer becomes more and more dense in the upper part of the layer (exposed surface)." (Le Person, p. 261). As a result, this "intense" shrinkage results in displacement of the active phase. As such, Le Person's disclosure ~~,~~is not directed towards achievement of a film having a substantially uniform ~~film~~distribution of an

active through drying, and in fact, if anything, teaches away from achieving ~~such content~~ uniformity of content in the amount of an active.

The presently claimed ~~process is~~processes are not present in Le Person, either ~~literally~~expressly or inherently, and ~~it cannot~~Le Person does not anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Le Person does not render obvious the pending claims ~~of this rejection~~.

G. Claims 1,5,7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166,168-171,173-175,184,224,225,249,254,267,272,285 and 290 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hortsmann.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Horstman, et al. U.S. 5,629,003 ("Horstmann") or, in the alternative under 35 U.S.C.

§ 103(a), as obvious over Horstmann. Patentee incorporates its previous discussions in sections A., B., C., D., E. and F., above, Patentee respectfully traverses the rejection on the basis, among others, that Horstmann does not disclose ~~the~~as claimed~~: particular drying methods to provide a substantially uniform distribution of components; resulting visco-elastic product~~in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components~~; casting a flowable polymer matrix having a viscosity from about 400 to about 100,000 cps~~; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of ~~pharmaceutical~~ active, such that uniformity of

content of the resulting ~~films vary~~film varies by no more than 10% in ~~the~~ amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film, by no more than 10% from the desired amount across different resulting films, and is in compliance with FDA regulations governing same.

Horstmann certainly does not disclose, either explicitly or inherently, the additional claim elements of Claim 317. Claim 317 generally adds to the above, *inter alia,* conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60°C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said viscoelastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30°C between polymer matrix inside temperature and outside exposure temperature.

Moreover, the '080 Patent's description of the differences between Horstmann and Patentee's invention claimed in the '080 Patent is relevant to the Examiner's current rejections as well. For example:

> "In one attempt to overcome non-uniformity, U.S. Pat. No. 5,629,003 to Horstmann ... incorporated additional ingredients, i.e. gel formers and polyhydric alcohols respectively, to increase the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film. These methods have the disadvantage of requiring additional components, which translates to additional cost and manufacturing steps. Furthermore, both methods employ the use the conventional time-consuming drying methods such as a high temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The long length of drying time aids in promoting the aggregation of the active and other adjuvant, notwithstanding the use of viscosity modifiers."

'080 Patent, col. 2, 1. 63 to col. 3,1. 9.

Horstmann's use of conventional drying methods and need for gel formers teaches away from obtaining a resulting film with the desired ~~uniformity~~levels of uniformity of content ~~ofactive ofno more than 10% variation~~in the amount of active. Horstmann does not disclose the degree of uniformity of content, merely, for example, in Example 2, referring to film sections containing "approximately" 3 mg of active and a weight of "approximately" 80 mg. Horstmann, col. 5, 11. 15-36. Horstmann does not disclose that these amounts are based on any testing, or for that matter what they are based upon, or that they comply with FDA requirements relating to drug products.

The presently claimed process is not present in Horstmann, either ~~literally~~expressly or inherently, and ~~it~~Horstmann cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Horstmann does not render obvious the pending claims~~of this rejection~~.

IX. Conclusion

No reference, either alone or in combination with other references, teaches the processes claimed by the '080 Patent. Entry of the amendments herein is respectfully requested. Patentee traverses all rejections of its claims. For at least the reasons set forth above, independent claims 1, 82, 161, and ~~321~~315-~~324~~318 are allowable. Claims 2 -81,83 -160, 162 -~~320, and 325-628~~314 are allowable at least based on their dependencies, whether direct or indirect, from independent Claims 1, 82, ~~161,321 and 322~~161 . Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejections to same~~. Fees for addition of 4 new independent claims and 324 new dependent claims are due with this submission, and the Commissioner is authorized to charge this fee to Deposit Account No. 08-2461. Should any additional fees be due, the Commissioner is authorized to charge any additional fees, such as fees for extensions of time or additional claims, to Deposit Account No. 08-2461~~. Should the Examiner have any questions regarding this response, the undersigned would be pleased to address them.

Electronic Patent Application Fee Transmittal

Application Number:	95002170
Filing Date:	10-Sep-2012
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Filer:	Danielle L. Herritt
Attorney Docket Number:	117744-00023

Filed as Large Entity

inter partes reexam Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
PETITION IN REEXAM PROCEEDING	1824	1	1940	1940
Petition fee- 37 CFR 1.17(f) (Group I)	1462	1	400	400
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2340**

Electronic Acknowledgement Receipt

EFS ID:	15337222
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	22-MAR-2013
Filing Date:	10-SEP-2012
Time Stamp:	22:44:33
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2340
RAM confirmation Number	6177
Deposit Account	504876
Authorized User	

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Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		117744_0023_Petition_to_Expedite.PDF	12606 4ab6e559f42569b5a68aa49ea6bf40c43b78549b	yes	3
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Receipt of Petition in a Reexam		1	2	
	Reexam Certificate of Service		3	3	
Warnings:					
Information:					
2		117744_00023_Petition_to_Deny_Entry_of_Supp_Resp.PDF	35522 1edc91f633aa74c00eb9edd1dfbd45a8f88ff4f5	yes	8
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Receipt of Petition in a Reexam		1	7	
	Reexam Certificate of Service		8	8	
Warnings:					
Information:					
3	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Exhibit_A.PDF	12648302 8d8dea68dbe9138f1f7495717e4341166119e11c	no	205
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
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4	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Exhibit_B.PDF	6235292 b01d153dde8db3d40aaace72394663b6d681a580	no	117
Warnings:					
Information:					
5	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Exhibit_C.PDF	663537 0ab69cceab75f118a5a6617717a6f74019d0ec64	no	146

Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	31786 7b9c4d0d113a565d33ce49a60dd4345454df316e	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	19627045	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	March 13, 2013	M&E Docket:	117744-00023

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Central Reexamination Unit
Commissioner for Patents
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P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on March 13, 2013
Signed: Michael I. Chakansky /Michael I Chakansky/

REPLY BY PATENTEE TO A NON-FINAL OFFICE ACTION PURSUANT TO 37 C.F.R. §1.111

Madame:

In compliance with the Notice Re Defective Paper in *Inter Partes* Reexamination, mail date February 26, 2013, Patent owner MonoSol Rx, LLC ("Patentee" and/or "MonoSol") hereby presents its re-drafted response to the Office Action in the above-identified *Inter Partes* Reexamination, dated November 29, 2012 ("Office Action"), a reply to which is due March 13, 2013. Please amend U.S. Patent No. 7,897,080 ("the '080 Patent") in reexamination as set forth hereinbelow. The present amendments are being made in accordance with 37 C.F.R. §1.530(d)–(j). Patentee has previously paid fees for the addition of 4 new independent claims and 324 new dependent in connection with this reexamination. Accordingly, no claim fees are believed to be due with this submission. If, however, there are any fees due in connection with this submission, authorization to charge such fees, including any claim fees, and authorization to credit any overpayments, to Deposit Account No. 08-2461 are hereby provided.

Amendment to the Claims begins on page 2 of this paper.

Remarks begin on page 42 of this paper.

Amendment to the Claims

1. (Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less; [and]

(e) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(f) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

2. (Original) The process of claim 1, wherein said pre-determined amount of master batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.

3. (Original) The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.

4. (Original) The process of claim 1, wherein said water-soluble polymer comprises polyethylene oxide.

5. (Original) The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

6. (Original) The process of claim 5, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl

cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

7. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

8. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

9. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

10. (Original) The process of claim 1, wherein said solvent is selected from the group

consisting of water, polar organic solvent, and combinations thereof.

11. (Original) The process of claim 10, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

12. (Cancelled)

13. (Amended) The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-

spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

14. (Amended) The process of claim 1, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

15. (Original) The process of claim 1, wherein said active is a bioactive active.

16. (Cancelled)

17. (Original) The process of claim 1, wherein said active is an opiate or opiate-derivative.

18. (Original) The process of claim 1, wherein said active is an anti-emetic.

19. (Original) The process of claim 1, wherein said active is an amino acid preparation.

20. (Original) The process of claim 1, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

21. (Original) The process of claim 1, wherein said active is a protein.

22. (Original) The process of claim 1, wherein said active is insulin.

23. (Original) The process of claim 1, wherein said active is an anti-diabetic.

24. (Original) The process of claim 1, wherein said active is an antihistamine.

25. (Original) The process of claim 1, wherein said active is an anti-tussive.

26. (Original) The process of claim 1, wherein said active is a non-steroidal anti-inflammatory.

27. (Original) The process of claim 1, wherein said active is an anti-asthmatics.

28. (Amended) The process of claim 1, wherein said active is an anti-diarrhea preparation.

29. (Original) The process of claim 1, wherein said active is an alkaloid.

30. (Original) The process of claim 1, wherein said active is an anti-psychotic.

31. (Original) The process of claim 1, wherein said active is an anti-spasmodic.

32. (Original) The process of claim 1, wherein said active is a biological response modifier.

33. (Original) The process of claim 1, wherein said active is an anti-obesity drug.

34. (Original) The process of claim 1, wherein said active is an H_2-antagonist.

35. (Original) The process of claim 34, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

36. (Original) The process of claim 1, wherein said active is a smoking cessation aid.

37. (Original) The process of claim 1, wherein said active is an anti-parkinsonian agent.

38. (Original) The process of claim 1, wherein said active is an anti-depressant.

39. (Original) The process of claim 1, wherein said active is an anti-migraine.

40. (Original) The process of claim 1, wherein said active is an anti-Alzheimer's agents.

41. (Original) The process of claim 1, wherein said active is a dopamine receptor agonist.

42. (Original) The process of claim 1, wherein said active is a cerebral dilator.

43. (Original) The process of claim 1, wherein said active is a psychotherapeutic agent.

44. (Original) The process of claim 1, wherein said active is an antibiotic.

45. (Original) The process of claim 1, wherein said active is an anesthetic.

46. (Original) The process of claim 1, wherein said active is a contraceptive.

47. (Original) The process of claim 1, wherein said active is an anti-thrombotic drug.

48. (Original) The process of claim 1, wherein said active is diphenhydramine.

49. (Original) The process of claim 1, wherein said active is nabilone.

50. (Original) The process of claim 1, wherein said active is albuterol sulfate.

51. (Original) The process of claim 1, wherein said active is an anti-tumor drug.

52. (Original) The process of claim 1, wherein said active is a glycoprotein.

53. (Original) The process of claim 1, wherein said active is an analgesic.

54. (Original) The process of claim 1, wherein said active is a hormone.

55. (Original) The process of claim 1, wherein said active is a decongestant.

56. (Original) The process of claim 1, wherein said active is a loratadine.

57. (Original) The process of claim 1, wherein said active is dextromethorphan.

58. (Original) The process of claim 1, wherein said active is chlorpheniramine maleate.

59. (Original) The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

60. (Original) The process of claim 1, wherein said active is an appetite stimulant.

61. (Original) The process of claim 1, wherein said active is a gastrointestinal agent.

62. (Original) The process of claim 1, wherein said active is a hypnotic.

63. (Original) The process of claim 1, wherein said active is taste-masked.

64. (Original) The process of claim 1, wherein said active is taste-masked using a flavor.

65. (Original) The process of claim 1, wherein said active is coated with a controlled release composition.

66. (Original) The process of claim 65, wherein said controlled release composition provides an immediate release.

67. (Original) The process of claim 65, wherein said controlled release composition provides a delayed release.

68. (Original) The process of claim 65, wherein said controlled release composition provides a sustained release.

69. (Original) The process of claim 65, wherein said controlled release composition provides a sequential release.

70. (Original) The process of claim 1, wherein said active is a particulate.

71. (Original) The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.

72. (Original) The process of claim 1, further comprising a step of providing a second film layer.

73. (Original) The process of claim 72, wherein said second film layer is coated onto said resulting film.

74. (Original) The process of claim 72, wherein said second film layer is spread onto said resulting film.

75. (Original) The process of claim 72, wherein said second film layer is cast onto said resulting film.

76. (Original) The process of claim 72, wherein said second film layer is extruded onto said resulting film. .

77. (Original) The process of claim 72, wherein said second film layer is sprayed onto said resulting film.

78. (Original) The process of claim 72, wherein said second film is laminated onto said resulting film.

79. (Original) The process of claim 72, further comprising laminating said resulting film to another film.

80. (Original) The process of claim 72, wherein said second film layer comprises an active.

81. (Amended) The process of claim [72]80, wherein said active in said second film is different than said active in said resulting film.

82. (Amended) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives[, drugs, medicaments] and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%; [and]

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

83. (Original) The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.

84. (Original) The process of claim 82, wherein said polymer comprises a polymer selected

from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

85. (Original) The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

86. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

87. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

88. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol

copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

89. (Original) The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

90. (Original) The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

91. (Cancelled)

92. (Amended) The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management

agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

93. (Amended) The process of claim 82, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

94. (Original) The process of claim 82, wherein said active is a bioactive active.

95. (Cancelled)

96. (Original) The process of claim 82, wherein said active is an opiate or opiate-derivative.

97. (Original) The process of claim 82, wherein said active is an anti-emetic.

98. (Original) The process of claim 82, wherein said active is an amino acid preparation.

99. (Original) The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

100. (Original) The process of claim 82, wherein said active is a protein.

101. (Original) The process of claim 82, wherein said active is insulin.

102. (Original) The process of claim 82, wherein said active is an anti-diabetic.

103. (Original) The process of claim 82, wherein said active is an antihistamine.

104. (Original) The process of claim 82, wherein said active is an anti-tussive.

105. (Original) The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.

106. (Original) The process of claim 82, wherein said active is an anti-asthmatics.

107. (Amended) The process of claim 82, wherein said active is an anti-diarrhea preparation.

108. (Original) The process of claim 82, wherein said active is an alkaloid.

109. (Original) The process of claim 82, wherein said active is an anti-psychotic.

110. (Original) The process of claim 82, wherein said active is an anti-spasmodic.

111. (Original) The process of claim 82, wherein said active is a biological response modifier.

112. (Original) The process of claim 82, wherein said active is an anti-obesity drug.

113. (Original) The process of claim 82, wherein said active is an H_2-antagonist.

114. (Amended) The process of claim [82]113, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

115. (Original) The process of claim 82, wherein said active is a smoking cessation aid.

116. (Original) The process of claim 82, wherein said active is an anti-parkinsonian agent.

117. (Original) The process of claim 82, wherein said active is an anti-depressant.

118. (Original) The process of claim 82, wherein said active is an anti-migraine.

119. (Original) The process of claim 82, wherein said active is an anti-Alzheimer's agents.

120. (Original) The process of claim 82, wherein said active is a dopamine receptor agonist.

121. (Original) The process of claim 82, wherein said active is a cerebral dilator.

122. (Original) The process of claim 82, wherein said active is a psychotherapeutic agent.

123. (Original) The process of claim 82, wherein said active is an antibiotic.

124. (Original) The process of claim 82, wherein said active is an anesthetic.

125. (Original) The process of claim 82, wherein said active is a contraceptive.

126. (Original) The process of claim 82, wherein said active is an anti-thrombotic drug.

127. (Original) The process of claim 82, wherein said active is diphenhydramine.

128. (Original) The process of claim 82, wherein said active is nabilone.

129. (Original) The process of claim 82, wherein said active is albuterol sulfate.

130. (Original) The process of claim 82, wherein said active is an anti-tumor drug.

131. (Original) The process of claim 82, wherein said active is a glycoprotein.

132. (Original) The process of claim 82, wherein said active is an analgesic.

133. (Original) The process of claim 82, wherein said active is a hormone.

134. (Original) The process of claim 82, wherein said active is a decongestant.

135. (Original) The process of claim 82, wherein said active is a loratadine.

136. (Original) The process of claim 82, wherein said active is dextromethorphan.

137. (Original) The process of claim 82, wherein said active is chlorpheniramine maleate.

138. (Original) The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

139. (Original) The process of claim 82, wherein said active is an appetite stimulant.

140. (Original) The process of claim 82, wherein said active is a gastrointestinal agent.

141. (Original) The process of claim 82, wherein said active is a hypnotic.

142. (Original) The process of claim 82, wherein said active is taste-masked.

143. (Original) The process of claim 82, wherein said active is taste-masked using a flavor.

144. (Original) The process of claim 82, wherein said active is coated with a controlled release composition.

145. (Original) The process of claim 144, wherein said controlled release composition provides an immediate release.

146. (Original) The process of claim 144, wherein said controlled release composition provides a delayed release.

147. (Original) The process of claim 144, wherein said controlled release composition provides a sustained release.

148. (Original) The process of claim 144, wherein said controlled release composition provides a sequential release.

149. (Original) The process of claim 82, wherein said active is a particulate.

150. (Original) The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.

151. (Original) The process of claim 82, further comprising a step of providing a second film layer.

152. (Original) The process of claim 151, wherein said second film layer is coated onto said resulting film.

153. (Original) The process of claim 151, wherein said second film layer is spread onto said resulting film.

154. (Original) The process of claim 151, wherein said second film layer is cast onto said resulting film.

155. (Original) The process of claim 151, wherein said second film layer is extruded onto said resulting film.

156. (Original) The process of claim 151, wherein said second film layer is sprayed onto said resulting film.

157. (Original) The process of claim 151, wherein said second film layer is laminated onto said resulting film.

158. (Original) The process of claim 151, further comprising laminating said resulting film to another film.

159. (Original) The process of claim 151, wherein said second film comprises an active.

160. (Amended) The process of claim [151]159, wherein said active in said second film is different than said active in said resulting film.

161. (Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said[making a] film capable of being administered to a body surface and having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; [and]

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration, and

[(e)](f) administering said resulting film to a body surface.

162. (Original) The process of claim 161, wherein said body surface is a mucous membrane.

163. (Original) The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.

164. (Original) The process of claim 161, wherein said body surface is the surface of a wound.

165. (Original) The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.

166. (Original) The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

167. (Original) The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

168. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic

acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

169. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

170. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

171. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

172. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

173. (Cancelled)

174. (Amended) The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

175. (Amended) The process of claim 161, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,

]vitamins and combinations thereof.

176. (Original) The process of claim 161, wherein said active is a bioactive active.

177. (Cancelled)

178. (Original) The process of claim 161, wherein said active is an opiate or opiate-derivative.

179. (Original) The process of claim 161, wherein said active is an anti-emetic.

180. (Original) The process of claim 161 wherein said active is an amino acid preparation.

181. (Original) The process of claim 161, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

182. (Original) The process of claim 161, wherein said active is a protein.

183. (Original) The process of claim 161, wherein said active is insulin.

184. (Original) The process of claim 161, wherein said active is an anti-diabetic.

185. (Original) The process of claim 161, wherein said active is an antihistamine.

186. (Original) The process of claim 161, wherein said active is an anti-tussive.

187. (Original) The process of claim 161, wherein said active is a non-steroidal anti-inflammatory.

188. (Original) The process of claim 161, wherein said active is an anti-asthmatics.

189. (Amended) The process of claim 161, wherein said active is an anti-diarrhea preparation.

190. (Original) The process of claim 161, wherein said active is an alkaloid.

191. (Original) The process of claim 161, wherein said active is an anti-psychotic.

192. (Original) The process of claim 161, wherein said active is an anti-spasmodic.

193. (Original) The process of claim 161, wherein said active is a biological response modifier.

194. (Original) The process of claim 161, wherein said active is an anti-obesity drug.

195. (Original) The process of claim 161, wherein said active is an H_2-antagonist.

196. (Original) The process of claim 195, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

197. (Original) The process of claim 161, wherein said active is a smoking cessation aid.

198. (Original) The process of claim 161, wherein said active is an anti-parkinsonian agent.

199. (Original) The process of claim 161, wherein said active is an anti-depressant.

200. (Original) The process of claim 161, wherein said active is an anti-migraine.

201. (Original) The process of claim 161, wherein said active is an anti-Alzheimer's agents.

202. (Original) The process of claim 161, wherein said active is a dopamine receptor agonist.

203. (Original) The process of claim 161, wherein said active is a cerebral dilator.

204. (Original) The process of claim 161, wherein said active is a psychotherapeutic agent.

205. (Original) The process of claim 161, wherein said active is an antibiotic.

206. (Original) The process of claim 161, wherein said active is an anesthetic.

207. (Original) The process of claim 161, wherein said active is a contraceptive.

208. (Original) The process of claim 161, wherein said active is an anti-thrombotic drug.

209. (Original) The process of claim 161, wherein said active is diphenhydramine.

210. (Original) The process of claim 161, wherein said active is nabilone.

211. (Original) The process of claim 161, wherein said active is albuterol sulfate.

212. (Original) The process of claim 161, wherein said active is an anti-tumor drug.

213. (Original) The process of claim 161, wherein said active is a glycoprotein.

214. (Original) The process of claim 161, wherein said active is an analgesic.

215. (Original) The process of claim 161, wherein said active is a hormone.

216. (Original) The process of claim 161, wherein said active is a decongestant.

217. (Original) The process of claim 161, wherein said active is a loratadine.

218. (Original) The process of claim 161, wherein said active is dextromethorphan.

219. (Original) The process of claim 161, wherein said active is chlorpheniramine maleate.

220. (Original) The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

221. (Original) The process of claim 161, wherein said active is an appetite stimulant.

222. (Original) The process of claim 161, wherein said active is a gastrointestinal agent.

223. (Original) The process of claim 161, wherein said active is a hypnotic.

224. (Original) The process of claim 161, wherein said active is taste-masked.

225. (Original) The process of claim 161, wherein said active is taste-masked using a flavor.

226. (Original) The process of claim 161, wherein said active is coated with a controlled release composition.

227. (Original) The process of claim 226, wherein said controlled release composition provides an immediate release.

228. (Original) The process of 226, wherein said controlled release composition provides a delayed release.

229. (Original) The process of claim 226, wherein said controlled release composition

provides a sustained release.

230. (Original) The process of claim 226, wherein said controlled release composition provides a sequential release.

231. (Original) The process of claim 161, wherein said active is a particulate.

232. (Original) The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.

233. (Original) The process of claim 161, further comprising a step of providing a second film layer.

234. (Original) The process of claim 233, wherein said second film layer is coated onto said resulting film.

235. (Original) The process of claim 233, wherein said second film layer is spread onto said resulting film.

236. (Original) The process of claim 233, wherein said second film layer is cast onto said resulting film.

237. (Original) The process of claim 233, wherein said second film layer is extruded onto said resulting film.

238. (Original) The process of claim 233, wherein said second film layer is sprayed onto said resulting film.

239. (Original) The process of claim 233, wherein said second film layer is laminated onto said resulting film.

240. (Original) The process of claim 233, further comprising laminating said resulting film to another film.

241. (Original) The process of claim 233, wherein said second film comprises an active.

242. (Amended) The process of claim [233]241, wherein said active in said second film is different than said active in said resulting film.

243. (Original) The process of claim 1, said active is an anti-nauseant.

244. (Amended) The process of claim 1, said active is an erectile dysfunction drug.

245. (Original) The process of claim 1, said active is a vasoconstrictor.

246. (Original) The process of claim 1, said active is a stimulant.

247. (Original) The process of claim 1, said active is a migraine treatment.

248. (Original) The process of claim 1, said active is granisetron hydrochloride.

249. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

250. (Original) The process of claim 1, wherein said resulting film provides administration of said active through gingival application of said individual.

251. (Original) The process of claim 1, wherein said resulting film provides administration of said active through sublingual application of said individual.

252. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

253. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

254. (Cancelled)

255. (Cancelled)

256. (Original) The method of claim 1, wherein said resulting film contains less than about 6% by weight solvent.

257. (Cancelled)

258. (Original) The method of claim 1, wherein said resulting film is orally administrable.

259. (Original) The method of claim 1, wherein said active is in the form of a particle.

260. (Original) The method of claim 1, wherein said matrix comprises a dispersion.

261. (Original) The process of claim 82, said active is an anti-nauseant.

262. (Amended) The process of claim 82, said active is an erectile dysfunction drug.

263. (Original) The process of claim 82, said active is a vasoconstrictor.

264. (Original) The process of claim 82, said active is a stimulant.

265. (Original) The process of claim 82, said active is a migraine treatment.

266. (Original) The process of claim 82, said active is granisetron hydrochloride.

267. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

268. (Original) The process of claim 82, wherein said resulting film provides administration of said active through gingival application of said individual.

269. (Original) The process of claim 82, wherein said resulting film provides administration of said active through sublingual application of said individual.

270. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

271. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

272. (Cancelled)

273. (Cancelled)

274. (Original) The method of claim 82, wherein said resulting film contains less than about 6% by weight solvent.

275. (Cancelled)

276. (Original) The method of claim 82, wherein said resulting film is orally administrable.

277. (Original) The method of claim 82, wherein said active is in the form of a particle.

278. (Original) The method of claim 82, wherein said matrix comprises a dispersion.

279. (Original) The process of claim 161, said active is an anti-nauseant.

280. (Amended) The process of claim 161, said active is an erectile dysfunction drug.

281. (Original) The process of claim 161, said active is a vasoconstrictor.

282. (Original) The process of claim 161, said active is a stimulant.

283. (Original) The process of claim 161, said active is a migraine treatment.

284. (Original) The process of claim 161, said active is granisetron hydrochloride.

285. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

286. (Original) The process of claim 161, wherein said resulting film provides administration of said active through gingival application of said individual.

287. (Original) The process of claim 161, wherein said resulting film provides administration of said active through sublingual application of said individual.

288. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

289. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

290. (Cancelled)

291. (Cancelled)

292. (Original) The method of claim 161, wherein said resulting film contains less than about 6% by weight solvent.

293. (Cancelled)

294. (Original) The method of claim 161, wherein said resulting film is orally administrable.

295. (Original) The method of claim 161, wherein said active is in the form of a particle.

296. (Original) The method of claim 161, wherein said matrix comprises a dispersion.

297. (Original) The method of claim 1, wherein said matrix comprises an emulsion, a colloid or a suspension.

298. (Original) The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.

299. (Original) The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.

300. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

301. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

302. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

303. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

304. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

305. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

306. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

307. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

308. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

309. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

310. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

311. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

312. (New) The process of claim 1, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

313. (New) The process of claim 82, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

314. (New) The process of claim 161, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

315. (New) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes

by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%;

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of said active as indicated by said analytical chemical tests.

316. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

317. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus using air currents, which have forces below a yield value of said flowable polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by no more than 10%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling drying by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said

active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

318. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus at a temperature of about 60 °C and using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-

elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by less than 5%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by less than 5% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

REMARKS

I. Description of the Patent and the Applicant's Reply

The above-identified U.S. Patent No. 7,897,080 (" '080 Patent") is presently under reexamination. Claims 1-299 were issued in the '080 Patent. Claims 1-299, subject to reexamination, were rejected in the Office Action. Claims 16, 95 and 177, have been canceled herein as they are identical to claims 32, 111 and 193, respectively. See Office Action, p. 7. Claims 12, 91, 173, 254, 255, 257, 272, 273, 275, 290, 291, and 293 have also been canceled purely for clarity. Claims 300 through 318 are new.

While the Examiner's rejection of all the claims is respectfully traversed in all respects, claims 1, 82 and 161 of the '080 Patent have been amended in an effort to advance the prosecution of the present reexamination. Claims 1, 82 and 161 are hereby amended in accordance with 37 C.F.R. §1.530(d) (2) and (f). In accordance with 35 U.S.C. § 314(a), the amendments to claims 1, 82 and 161, new independent claims 315-318, and new dependent claims 300-314 do not enlarge the scope of the claims of the '080 Patent. Explanation of the support for these claims appears below. Entry of this amendment and reconsideration is respectfully requested.

II. Status of Claims and Support for Claim Changes Pursuant to 37 C.F.R. §1.530(e)

The status of the claims as of the date of this amendment is as follows: Claims 1-299 were issued in the '080 Patent and are subject to reexamination. Claims 1-299, subject to reexamination, were rejected in the Office Action. Claims 300 through 318 are new and are subject to examination. Please cancel claims 16, 95 and 177, as they are identical to claims 32, 111 and 193, respectively. See Office Action, p. 7. Please cancel Claims 12, 91, 173, 254, 255, 257, 272, 273, 275, 290, 291, and 293, for clarity, including some limitations which now appear in the independent claims from which some depend.

In compliance with 37 C.F.R. § 1.530(j), the amendments to claims 1, 82 and 161 do not enlarge their scope or the scope of the original claims or introduce new matter, nor do the

amendments adding new claims 300 through 318 enlarge the scope of the original claims or introduce new matter.

Support for the amendments to claims 1, 82 and 161 and new claims 300 through 318 may be found throughout the '080 Patent, including, the Abstract, Specification, Figures and Claims, for example, at col. 13, ll. 23-36, col. 16, l. 62 through col. 17, l. 3, col. 28, l. 66 through col. 29, l. 6; col. 29, ll. 20-35 and 38; col. 32, ll. 34-41; col. 2, ll. 27-46; col. 15, ll. 28-43, and the Abstract; quoted in detail below; col. 3, ll. 58-60 ("the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval"); col. 19, l. 30 through col. 21, l. 31 (actives including pharmaceutical actives, bioactive actives, and combinations thereof); col. 6, ll. 49-52 ("These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process."); Figures 6, 7, 8, 35 and 36 and col. 14, ll. 20-25 ("drying" and "drying apparatus"); col. 11, ll. 17-19 ("Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition"); col. 11, ll. 21-23 ("yield values . . . force"); col. 12, ll. 20-36, col. 13, ll. 37-38 ("After mechanical mixing, the film may be placed on a conveyor"); col. 29, ll. 11-13 ("As the film is conveyed through the manufacturing process, for example on a conveyor belt apparatus"); col. 33, l. 10 through col. 34, l. 24 (example M); col. 44, 11. 9-13 ("the controlled drying process of the present invention allows for uniform drying to occur, whereby evaporative cooling and thermal mixing contribute to the rapid formation of viscoelastic film and the 'locking-in' of uniformity of content throughout the film"); col. 4, l. 8; col. 6, ll. 46-52; col. 13, ll. 36-43; col. 26, ll. 9-27; col. 28, ll. 24-58; col. 29, ll. 8-10; col. 20, ll. 65-66 ("Erectile dysfunction . . . drugs"); col. 19, l. 55 ("anti-diarrhea preparations"); col. 6, ll. 52-60 ("Examples of controlled drying processes include . . . hot air impingement across the bottom substrate and bottom heating plates . . . controlled radiation drying . . . such as infrared and radio frequency radiation . . . ."); col. 7, lines 5 through 16 ("This may be achieved by applying heat to the bottom surface of the film . . . or alternatively by the introduction of controlled microwaves to evaporate the water . . . . air currents directed at the bottom of the film should desirably be controlled"); col. 27, ll. 53-55 ("The temperature at which the films are dried is about 100°C. or less"); col. 41, ll. 49-50 ("films were dried in an oven at approximately 60° C."). Support for new claims may also be found throughout the '080 Patent, including, the Figures, Tables and

Claims, for example at col. 19, ll. 10-25, col. 19, l. 30 through col. 22, l. 28, col. 25, ll. 53-60, col. 22, ll. 24-28; col. 28, ll. 1-2; col. 14, ll. 63-65; Tables 17 and 18; Figures 6-8, 33, 34 and 35. Many of the claim elements of the new independent claims can be found in original independent claims 1, 82, and 161 of the '080 patent.

> "Temperatures that approach 100° C. will generally cause degradation of proteins as well as nucleic acids. For example some glycoproteins will degrade if exposed to a temperature of 70° C. for thirty minutes. Proteins from bovine extract are also known to degrade at such low temperatures. DNA also begins to denature at this temperature.
>
> "Applicants have discovered, however, that the films of the present invention may be exposed to high temperatures during the drying process without concern for degradation, loss of activity or excessive evaporation due to the inventive process for film preparation and forming. In particular, the films may be exposed to temperatures that would typically lead to degradation, denaturization, or inactivity of the active component, without causing such problems. According to the present invention, the manner of drying may be controlled to prevent deleterious levels of heat from reaching the active component."
>
> '080 Patent. col. 12, ll. 20-36.
>
> "For instance, the films of the present invention desirably are dried for 10 minutes or less. Drying the films at 80° C. for 10 minutes produces a temperature differential of about 5° C. This means that after 10 minutes of drying, the temperature of the inside of the film is 5° C. less than the outside exposure temperature. In many cases, however, drying times of less than 10 minutes are sufficient, such as 4 to 6 minutes. Drying for 4 minutes may be accompanied by a temperature differential of about 30° C., and drying for 6 minutes may be accompanied by a differential of about 25° C. Due to such large temperature differentials, the films may be dried at efficient, high temperatures without causing heat sensitive actives to degrade."
>
> '080 Patent. col. 13, ll. 23-36.
>
> "The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process."

'080 Patent, col. 16, l. 62 through col. 17, l. 3 (emphasis supplied).

"It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and overall appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons."

'080 Patent, col. 28, l. 66 through col. 29, l. 6 (emphasis supplied).

"The cut film then may be sampled by removing small pieces from each of the opposed ends of the portion(s), without disrupting the middle of the portion(s). . . . After the end pieces, or sampling sections, are removed from the film portion(s), they may be tested for uniformity in the content of components between samples."

'080 Patent, col. 29, ll. 20 through 35 (emphasis supplied).

"An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active."

'080 Patent, col. 32, ll. 34-41 (emphasis supplied).

"The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage

units based on films, this virtually mandates that uniformity in the film be present."

'080 Patent, col. 2, ll. 27-46 (emphasis supplied).

"Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight. "

'080 Patent, col. 15, ll. 28-43 (emphasis supplied).

III. Declarations Submitted With This Reply

Along with this Reply, the Patentee is submitting the Declarations of Dr. B. Arlie Bogue (Exhibit A) ("Bogue Declaration") and Dr. David T. Lin (Exhibit B) ("Lin Declaration") under 37 C.F.R. §1.132. The Bogue Declaration provides technical results regarding Patentee's commercial pharmaceutical films manufactured in accordance with the '080 Patent and it should not be counted toward the page limit of 37 C.F.R. §1.943. The Lin Declaration provides Dr. Lin's background information, information relating to FDA uniformity of content dosage requirements, and has six (6) numbered paragraphs of statements (¶¶ 17-22) relating to a prior art disclosure at pages 5-6, which might at most be counted as two (2) pages toward the page limit of 37 C.F.R. §1.943.

IV. Background of the '080 Patent

The '080 Patent is a continuation of U.S. application Ser. No. 10/856,176, filed May 28, 2004 now U.S. Pat. No. 7,666,337 (" '337 Patent"), which claims the benefit of U.S. Provisional Application No. 60/473,902, filed May 28, 2003 and is a continuation-in-part of U.S. application Ser. No. 10/768,809, filed Jan. 30, 2004 now U.S. Pat. No. 7,357,891 (" '891 Patent"), which claims benefit to U.S. Provisional Application No. 60/443,741 filed Jan. 30, 2003 and is a continuation-in-part of:

(a) PCT/US02/32575 filed Oct. 11, 2002, which claims priority to: (1) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002 which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (2) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002;

(b) PCT/US02/32594, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/414,276, filed Sep. 27, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002; and

(c) PCT/US02/32542, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/371,940, filed Apr. 11, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002.

There are pending applications claiming the benefit of the priority of all and/or some of the above.

The '891 Patent is involved in a U.S. litigation wherein Patentee has alleged that the Third Party Requester, BioDelivery Sciences International, Inc. ("BDSI") has infringed its '891 Patent. The litigation is Civil Action No. 10-cv-5695 in the U.S. District Court in the District of New Jersey. In the litigation, Patentee also alleged that the Third Party Requester infringed two other of Patentee's patents, U.S. 7,425,292 (" '292 Patent") and U.S. 7,824,588 (" '588 Patent").

Third Party Requester requested reexamination of the '891 Patent (90/012,098), the '292 Patent (90/012,097) and the '588 Patent (95/001,753) as well. Both the '292 and the '891 Patent successfully exited reexamination. The Examiner on January 23, 2013 issued a Right of Appeal Notice ("RAN") for the '588 Patent reexamination. In response, Patentee filed a Notice of Appeal, a Petition Under 37 C.F.R. § 1.183 Requesting Waiver of the Prohibition of an Extension of Time for Filing an Appeal Brief and for an Extension of Time for Filing an Appeal Brief, and a Petition Under 37 C.F.R. § 1.182 Requesting Continued Reexamination.

Third Party Requester requested reexamination of another of Patentee's related patents namely U.S. Pat. No. 7,666,337 (Control No. 95/002,171), reexamination was ordered, an Office Action issued, Patentee Replied, and Third Party Requester submitted its Comments.

Finally, Third Party Requester requested the reexamination herein of the '080 Patent. .

The '080 Patent has not been and is not currently involved in litigation.

'080 Patent Office Action Statements

In connection with the Order Granting Request for Inter Partes Reexamination of the '080 Patent, Control No. 95/002,170 ("Order Granting IPR Request '080 Patent"), noted above, certain comments were made by the Examiner with respect to Claim 25 of the '337 Patent. The statements were made when the Examiner addressed Third Party Requester's request to find that claim 82 of the '080 Patent should be rejected under 35 U.S.C. § 101 double patenting over claim 25 of the '337 Patent. Patentee supports the Examiner's finding that the Third Party Requester had failed to demonstrate a reasonable likelihood of success of arriving at the subject matter of at least one claim of the '080 Patent. However, Patentee respectfully disagrees with the Examiner's statements interpreting "uniform" and "substantially uniform" therein. In particular, Patentee disagrees that "the active is uniformly distributed (i.e. no variance of active)" in the matrix. Certainly a uniform distribution does not require a state of "no variance". See pages 21 and 22 of the Order Granting IPR Request '080 Patent. "Uniform" and "substantially uniform" are indeed different, but "uniform" from a practical standpoint must of necessity allow for some variance, albeit less than "substantially uniform".

V. The Patented Invention

The present invention is directed to novel and non-obvious processes for manufacturing pharmaceutical and bioactive active containing films, suitable for commercialization and U.S. Food and Drug Administration ("FDA") approval. As noted in the Bogue Declaration, ¶ 4, one manufactured lot of such resulting film can contain 2,000,000 individual dosage units. The claimed processes accomplish this feat while providing the necessary narrow ranges in the amount of active in individual dosage units. As claimed, the '080 Patent, at least, requires a uniformity of content in amount of active (i) in individual dosage units sampled from a resulting film of 10% or less (independent claims 1, 82, 161, and 316-318, see Appendix A, Bogue Declaration), and (ii) in individual dosage units sampled from two or more resulting films of

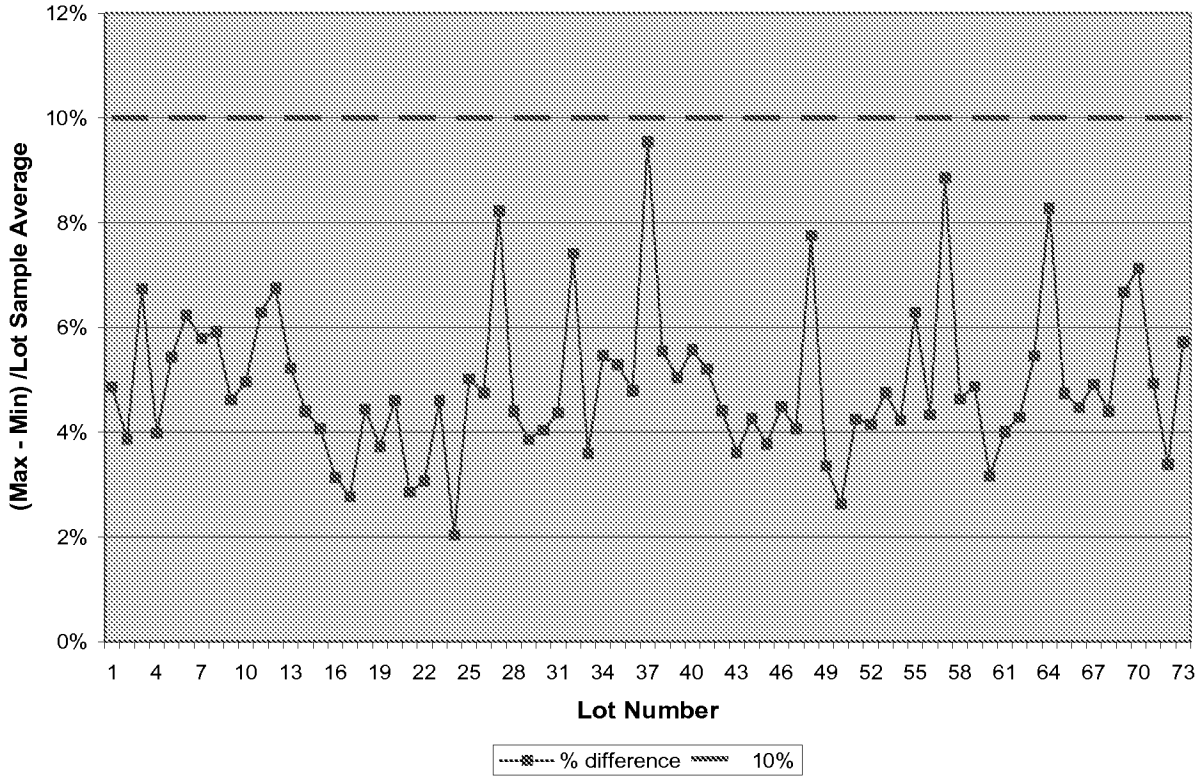
10% or less as a percent difference from a desired amount (independent claim 315, see Appendix B, Bogue Declaration).

One conceptual approach to understanding (i) and (ii) is as follows. A baker has a good recipe or process for making bread. The recipe includes the ingredients and the controlled baking conditions. On Monday the baker bakes a loaf of bread strictly following the recipe. On Friday the baker bakes a loaf of bread again strictly following the recipe. The loaves are cut into individual slices. When tasted, all the slices from Monday's loaf taste almost the same, indeed the tastes differs by only 10% between slices from Monday's loaf. In the same fashion, when tasted, all the slices from Friday's loaf taste almost the same, indeed the tastes differs by only 10% between slices from Friday's loaf. However, when a slice from Monday's loaf is compared to a slice from Friday's loaf, the difference in taste is more pronounced than between individual slices from the same loaf. Since the baker follows the same recipe for all his/her bread the baker expects that all slices from all loaves should taste alike or almost alike. However, the difference in taste between slices from Monday and slices from Friday is greater than the difference between slices in the same loaf. Indeed, the taste difference is now about 10% from what the baker believes all his/her bread should be expected to taste like-- that is, 10% from the high quality standard ("desired amount" and/or "target amount") for all the bread baked.

In a similar fashion, the "recipe" of Patentee's claimed processes keep differences between individual dosage units from one manufactured lot very small-- e.g. smaller than 10% in amount of pharmaceutical active. See, independent claims 1, 82, 161 and 316-318. The "recipe" of Patentee's claimed processes also keeps differences between individual dosage units between different manufactured lots small as well, just not necessarily as small-- e.g. smaller than a 10% difference from the standard, i.e. desired amount. See, independent claim 315.

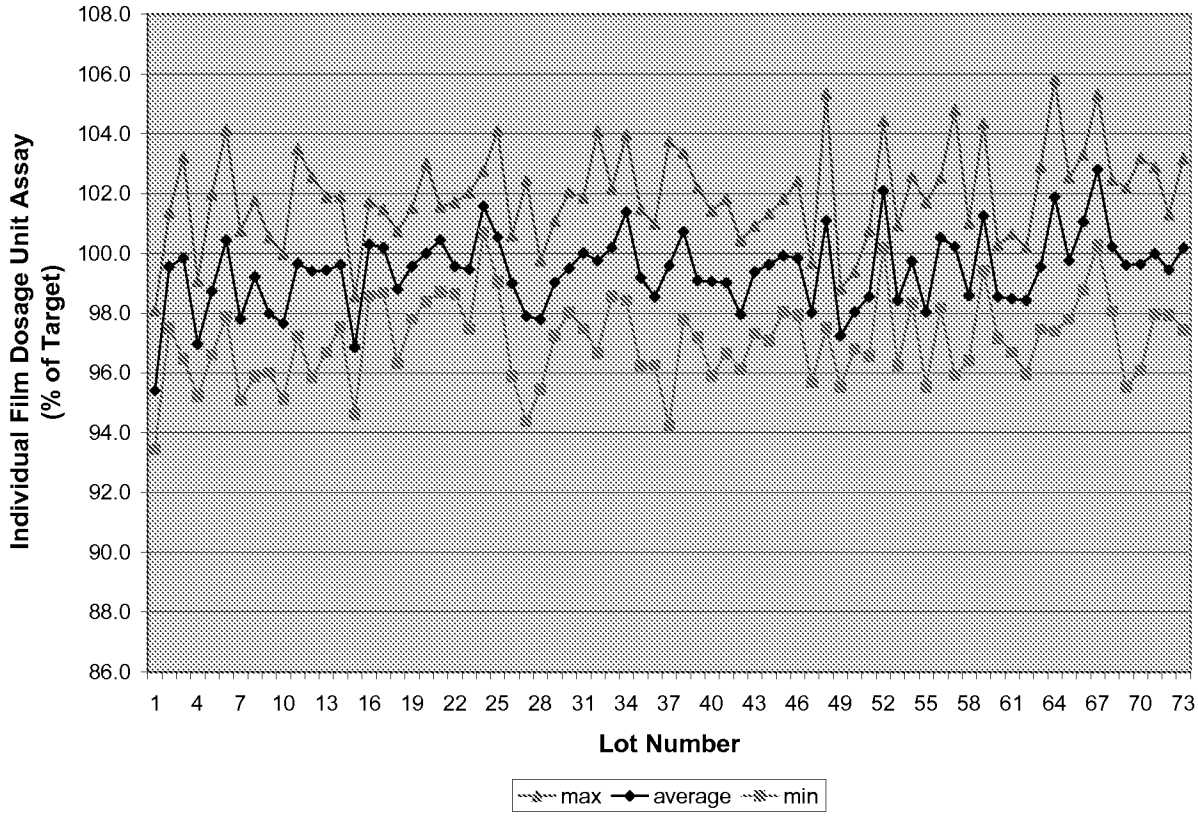
Thus, in the case of a resulting film from one manufacturing lot, the substantially uniform distribution of the active is indicated through analytical chemical tests which indicate that uniformity of content in the amount of the active in substantially equal sized individual dosage units sampled from the resulting film varies by no more than 10%. See Appendix A from Bogue Declaration copied below and Bogue Declaration, ¶ 9, where this is shown to be true for 73 separately manufactured lots of film, all manufactured by Patentee in accordance with the claimed invention.

APPENDIX A (Bogue Declaration)



In the case of resulting films from different manufacturing lots the substantially uniform distribution of the active is indicated through analytical chemical tests which indicate that uniformity of content in the amount of the active varies by no more than 10% from a desired amount. See Appendix B from Bogue Declaration copied below and Bogue Declaration, ¶ 10, where this is shown to be true across 73 separately manufactured lots of film, all manufactured by Patentee in accordance with the claimed invention. 100.0% indicating the desired amount.

APPENDIX B (Bogue Declaration)



Hence, the manufacturing process of the '080 Patent as claimed is a commercially viable processes which yields commercial viable products meeting FDA regulations, including active assaying requirements.

This should be compared to the laboratory produced films described in the prior art relied on by the Examiner. In the cited prior art, terms such as uniformity, substantial uniformity, and homogeneity are all accepted without real support. They cannot be relied upon. What is missing is the support for the statements -- that is, having had the amount of active tested by analytical chemical testing, including assaying. *See* Lin Declaration, ¶¶ 17-22 (statements about insufficient disclosure in cited prior art reference). Patentee uses the '080 Patent invention to manufacture commercially acceptable products for which Patentee must establish uniformity of content in the amount of active in its products by such analytical chemical testing as required by regulatory agencies, such as the FDA. Dr. Bogue's Declaration describes such testing on

Patentee's products produced in accordance with the invention and the results which are consistent with the '080 Patent's claims for uniformity of content in the amount of active (i) in individual dosage units sampled from a resulting film of 10% or less, and (ii) in individual dosage units sampled from two or more resulting films of 10% or less as a percent difference from a desired amount. Bogue Declaration, ¶¶ 4-11.

PATENTEE'S CLAIMS

Patentee's instant claims recite additional details about its processes for manufacturing a resulting pharmaceutical film suitable for commercialization and regulatory approval. Some of the details include: forming a flowable polymer matrix comprising a polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active; casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps; controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less; forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film from one lot, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and, in the case of more than one resulting film lot, repeating the process for forming one film lot such that uniformity of content in the amount of said active across all said resulting film lots varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

Additional claim limitations can be found in some of Patentee's narrower independent claims, for example claims 317-318. These claims generally add to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising continuing evaporation to a water content of said resulting film of 10% or less.

As defined in the '080 Patent, a visco-elastic film is one that has been controllably dried to lock its components into a substantially uniform distribution throughout the film while avoiding problems associated with conventional drying methods. By providing a visco-elastic film product having this compositional uniformity or uniformity of content, the user can be assured that the product includes the proper amount of components, such as an active contained therein. Further, the process can be used to make commercially viable large-scale film products, such as large rolls of film from which smaller individual dosage units are cut, the user can feel confident that no matter where the large roll of film is cut, the resulting pieces (e.g., individual unit dosages) will have a substantially uniform composition. As noted above, Patentee successfully manufactures pharmaceutical films containing 2,000,000 individual dosage units meeting FDA requirements using the claimed processes. Bogie Declaration, ¶ 4. As claimed, the uniformity of content as a percent difference will be no more than 10% and in some cases less. The need for providing a process for obtaining the desired uniformity of content of the desired amount of active in the resulting products is critically important, particularly for regulated products, such as the claimed pharmaceuticals.

Prior to the present invention, it was known to prepare films. However, in many cases the end product was merely assumed to be homogeneous, either because the initial components were blended together or because after the blending step the physically observable properties of the resulting film product, for example, its appearance or weight, were satisfactory. However,

these physical properties do not indicate or establish that the uniformity of content of the components is such that, for example, the amount of the active in individual dosage units varies by no more than 10% for a particular film. By contrast, for example, in one instance, "the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix." '080 Patent, col. 18, ll. 37-40.

Nor do physical properties indicate or establish that that the uniformity of content of the components is such that, for example, the amount of the active in individual dosage units from one film to another film varies by no more than 10% from a desired amount. This range of uniformity is disclosed in connection with, for example, the uniformity of content disclosed in the '080 Patent when referencing the FDA and other regulatory requirements. "Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present." '080 Patent, col 2, ll. 43-45. In these cases, the FDA and/or other regulatory agency sets the amount of active that must be present in an individual dosage unit (or dosage form), *i.e.,* the desired amount, and provides for the necessary uniformity of content, in this case the active may vary by 10% from the desired amount. A "desired amount" is an essential concept, as the FDA indicates the required dosage for each drug, and each drug has its own specified dosage amount. Essential to any pharmaceutical and related product is a viable means of actually testing for the amount of the active present in individual dosage unit samples, and that is to use analytical chemical testing and actually test for the presence of the desired amount of active and thereby determine whether the prescribed uniformity of content of active is present. *See* Lin Declaration, ¶¶ 9-16.

Importantly, the process of forming a proper film product with the claimed levels of uniformity of content in, for example, the amount of active does not end at the mixing stage. Patentee has discovered that the various steps post-mixing play a very important role in ensuring that the resulting product complies with the stringent requirements for uniformity of content. For example, one key step in the formation of a film product is the drying step, particularly when heat and/or radiation is used to dry the film. Patentee has discovered that controlled drying methods is essential in meeting these claimed requirements. Controlled drying includes methods that avoid, for example, the formation of bubbles, or uncontrolled air currents that may cause

movement of particles within the visco-elastic film forming matrix. Controlled drying, as required by the invention as claimed, may be effectuated through evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less.

It is important to understand that compositional uniformity or uniformity of content is not the same as having a surface that appears free of defects. Importantly, having a glossy surface does not equate to a uniform film, because the bottom side of a film product formed on a substrate will take the surface features of the substrate. If the substrate is smooth, the resulting bottom surface will also be smooth and possibly glossy. A product that has a surface that appears free of defects may have experienced significant non-uniformity below the surface, for example due to aggregation and agglomeration of components. It is important to note that just because the surface of a resulting product looks glossy or free of defects does not inherently mean that the actives within the film product exhibit the level of uniformity of content necessary to satisfy regulatory requirements and/or deliver the desired amount to the patient.

The '080 Patent discloses in a section entitled "Testing Films for Uniformity" (col. 28, l. 65 through col. 29, l. 53) that "[i]t may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process". '080 Patent, col. 28, l. 66 through col. 29, l. 1. In particular:

> "It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and over all appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons."
>
> '080 Patent, col. 28, l. 66 through col. 29, l. 6 (emphasis supplied).

Thus disclosed are two general types of testing, one for physical uniformity, and one for chemical uniformity. The disclosure goes on to provide different ways to test for each.

> "After the end pieces, or sampling sections, are removed from the film portion(s), they may be tested for uniformity in the content of components between samples. Any conventional means for examining and testing the film pieces may be employed, such as, for example, visual inspection, use of analytical equipment, and any other suitable means known to those skilled in the art. If the testing results show non-uniformity between film samples, the manufacturing process may be altered. This can save time and expense because the process may be altered prior to completing an entire manufacturing run. For example, the drying conditions, mixing conditions, compositional components and/or film viscosity may be changed. Altering the drying conditions may involve changing the temperature, drying time, moisture level, and dryer positioning, among others."
>
> '080 Patent, col. 29, ll. 33-38 (emphasis supplied).

In this way the '080 Patent provides multiple tests for non-uniformity, which are extremely useful in guiding the commercial manufacture of films. For example, manufacturing runs of films which appear to exhibit "non-uniformity" may be adjusted early in the run with less waste of materials, thus saving time and expense associated with the possibility of a non-uniform film. Physical tests, such as observational tests, are insufficient to determine the level of uniformity of content disclosed and claimed by the '080 Patent-- they do not determine the actual amount of active in samples.

The '080 Patent discloses testing to determine the appropriate degree of uniformity of content of the resulting film involving sampling substantially equal sized individual dosage units of the resulting film, dissolving the active in the sampled resulting film, and testing for the amount of active present in the sampled resulting film. Thus, the '080 Patent discloses that uniformity of the active is demonstrated through testing.

> "An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active."
>
> '080 Patent, col. 32, ll. 36-41 (emphasis supplied).

In this respect the Examiner, in his Scope of Claims section has mistakenly included physical uniformity type tests, used to quickly and/or easily suggest non-uniformity, with chemical uniformity type tests involving analytic equipment, that is, the actual testing of the uniformity of content for the amount of active. In the Scope of Claims section of the Office Action (pp. 3-7), the Examiner refers to two different portions of the '080 Patent's "EXAMPLES" section as follows:

> "An alternative means for evaluating uniformity is to cut the films into individual doses and measure the weight of the doses (col. 31, line 46 through col. 32, line 45). The '080 patent notes that "films of substantially similar size cut from different locations of the same film contain substantially the same amount of active." (col. 32, lines 37-39)."
>
> Office Action, p. 7.

Significantly, the two sentences are not related to each other, other than that both deal with examples and with cutting the film into dosage forms. The first is from a physical test, the second, relating to actives, is from an analytical chemical test for uniformity of content of active.

First is the physical test which refers to uniformity in mass.

> "Uniformity was also measured by first cutting the film into individual dosage forms. Twenty-five dosage forms of substantially identical size were cut from the film of inventive composition (E) above from random locations throughout the film. Then eight of these dosage forms were randomly selected and additively weighed. The additive weights of eight randomly selected dosage forms, are as shown in Table 2 below:
>
> [Table omitted.]
>
> "The individual dosages were consistently 0.04 gm, which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. **Therefore,** when the components of different densities are combined in a uniform manner in a film, as in the present invention, **individual dosages forms from the same film of substantially equal dimensions, will contain the same mass**."
>
> '080 Patent, col. 31, l. 46 through col. 32, l. 34 (emphasis supplied).

In accordance with this test, if the masses are unequal that would be an indication of mass non-uniformity.

Immediately after the above quoted disclosure, the '080 Patent discloses essentially that to demonstrate uniformity of content for active, the amount of active in each substantially similarly sized sample must be determined.

> "An alternative method of determining the uniformity of the active is to cut the film into individual doses. **The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active**."
>
> '080 Patent, col. 32, ll. 35-40 (emphasis supplied).

The Examiner also relies on the paragraph at '080 Patent, col. 31, ll. 38-45 for support that physical type tests, in this case observational tests, are sufficient to establish uniformity of content of active.

> "The uniform distribution of the components within the film was apparent by examination by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another. Therefore, there was substantially no disparity among the amount of active found in any portion of the film."
>
> '080 Patent, col. 31, ll. 38-45

However, it is one thing to have films which appear to be substantially free of aggregation and rely on that to say there is substantially no disparity among the amount of active in any portion of the film, and it is a totally different thing to demonstrate the presence of the required level of uniformity of content in the amount of active by analytical chemical testing and determining the actual amount of active in samples.

This paragraph, again, from the '080 Patent's section on "EXAMPLES", sets the stage for disclosing both the physical and chemical type tests referred to above at '080 Patent, col. 31, l. 46 through col. 32, l. 40, which follows this paragraph (see citation). Moreover, this paragraph

itself follows the manufacture of the film of Examples A-I and starts with what would be an expected quick and inexpensive procedure of looking at the film right after making it to see if it appears non-uniform or uniform. Such an observational test is at a macro level and does not indicate the degree of uniformity. Even if the film appears uniform, analytical chemical tests must then be conducted to verify uniformity of content at the prescribed level. What followed next were the two other tests discussed above.

Importantly, the first test is obviously a physical type test needed to rely on assumptions to reach its conclusion of substantially no disparity among the amount of active found in any portion of the film. Namely, by "viewing the films it was apparent that they were substantially free of aggregation . . . . Therefore, there was substantially no disparity among the amount of active found in any portion of the film." Based on physical observations a conclusion was drawn. The second, another physical test, concluded "individual dosages forms from the same film of substantially equal dimensions will contain the same mass;" again, referring to mass not uniformity of content of active. Again, no simple declarative statement that the amount of active in each sample was substantially the same or that the actual amount of active was determined.

It was only the third test, the analytical chemical type test that could directly establish that "films of substantially similar size cut from different locations on the same film contain substantially the same amount of active". This is to be expected as only the chemical based tests could provide the necessary assurance for the statement that substantially the same amount of active was present in each dose. Thus, one cannot solely rely on physical tests in prior art disclosures to "establish" that the prior art films actually possessed the levels of uniformity of content as claimed by the '080 Patent. However, analytical chemical testing is used in the '080 Patent to establish the actual amount of active in samples. In one example, in the '080 Patent analytical chemical testing was used to test for the amount of one component, a red dye, and in so doing established that the uniformity of content of the component fell well within the 10% level, particularly, it was 4%. See, '080 Patent, col. 33, l. 10 through col. 34, l. 24 (example M).

VI. Arriving at the Invention

The inventors of the '080 Patent are the first to not only identify the problems associated with manufacturing commercially and pharmaceutically viable active containing film individual

dosage units or forms, but also to solve those problems, especially as same relate to obtaining required levels of uniformity of content. Although many prior publications discussed the use of film as a dosage form for drugs, none of the publications identified nor solved the problems and complications associated with their manufacture. These early publications focused on the compositional and qualitative aspects of the films only and merely treated the manufacturing, if mentioned at all, as being simple, such as exposing the cast wet film to a conventional hot air circulating oven. However, especially in a commercial manufacturing setting, drying an active-containing cast wet film (even if the wet film is homogenous), in a conventional hot air circulating oven does not necessarily produce a film that is commercially viable, or deliver a film with the prescribed degree of uniformity of content in said setting. The '080 Patent does. *See* Bogue Declaration, ¶¶ 4-11.

A. Recognition of the Problem

The inventors discovered that it is not commercially viable to manufacture therapeutic–active-containing films using conventional drying methods. Even when a wet film matrix is properly formed so as to have a substantially uniform distribution of active within it, there are numerous factors which can destroy that uniformity of content during later processing such as casting and drying. The present specification describes many of these problems, which include (i) self-aggregation and agglomeration of active; (ii) skinning of the surface (a barrier through which remaining solvent must penetrate) before the thickness of the film is sufficiently dried, resulting in ripping and re-forming of the surface; (iii) forming of ripples on the surface; (iv) formation of air bubbles, which result in voids or air spaces within the film product; (v) maintaining the active in a substantially stable and uniformly dispersed state; (vi) movement of active particles due to uncontrolled air currents during drying; (vii) using air currents which create forces which overcome the yield value of the polymer matrix, or which would disturb or break the surface of the polymer matrix, or which overcome the inherent viscosity of the polymer matrix. See, for example, col. 3, l. 33 through col. 4, l. 6, and col. 11, ll. 14-25, the '080 Patent.

B. Solving the Problem

The inventors not only were the first to identify all the problems described above, but the first to solve them. Failure to solve one or more of these problems results in a film product that lacks the desired degree of uniformity of content of active per unit dose of film and therefore when equal dosage sizes are cut from the bulk film product, the desired amount of active per dosage lacks the desired and/or required degree of uniformity of content of active. The inventive methods and processes of the '080 Patent maintain the desired uniformity of content of active by, *inter alia*, controlling polymer matrix viscosity and controlling the drying processes so as to avoid the aforementioned problems, thereby forming a visco-elastic film that locks-in the substantially uniform distribution of active(s) during the drying steps. As described in the specification and claims, the present invention maintains the claimed levels of uniformity of content of active from the formation of the initial matrix through the final drying process, such that the pharmaceutical active varies by no more than 10% within a film lot, and by no more than 10% when sampled from different film lots.

The Examiner has cited several references, which will be discussed in further detail below. For ease of understanding, the Patentee will briefly discuss the primary cited references herein. During the discussion, it is important to keep in mind that statements from these sources regarding uniformity of content of components, especially actives, are not based on analytical chemical testing for the amount of active present in equally sized samples, but are at best assumptions, generally based on physically observable properties of the film in its intact state. The below discussion is supported by the Bogue Declaration and the Fuller Declaration.

VIII. The Claim Rejections.

The Examiner's rejection of the claims begins on page 7 of the Office Action.

A. Claims 1-299 were improperly rejected.

Claims 1-299 were rejected as allegedly anticipated under 35 U.S.C. §102(b), or, in the alternative under 35 U.S.C. § 103(a), as obvious over, each of the following references: Chen (WO 00/42992) ("Chen"), Staab (U.S. 5,393,528) ("Staab"), Le Person (*Chemical Engineering and Processing*, Vol. 37, pp. 257-263 (1998)) ("Le Person") and Horstmann (U.S.

5,629,003) ("Horstmann") or some combination thereof as set forth in the Office Action. These rejections relied on the Examiner's findings that material claim elements of the '080 Patent's only independent claims in reexamination, Claims 1, 82 and 161, were inherent in the cited references. Two limitations were of paramount importance, namely the limitations of "substantially uniform distribution of components" and of "locking-in or substantially preventing migration of" active.

Patentee maintains that the foregoing claim limitations are sufficent in themselves to establish patentability. Nevertheless, to advance prosecution, Patentee has explicitly added to all the independent claims herein presented specified levels of uniformity of content in the amount of active. Either a 10% limitation on the amount by which an active can vary between individual dosage units sampled from a particular film, and/or a 10% limitation by which the amount of active can vary from a desired amount among individual dosage units sampled from more than one film, which specificed levels of uniformity of content in the amount of active are not disclosed expressly nor are they inherent in the art of record. Patentee has also explicitly required manufacturing resulting pharmaceutical and/or bioactive active-containing films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units. Additional aspects not present in the art of record include, *inter alia*, viscosity ranges, controlled drying, conveying, applying air currents which have forces below the yield value of the polymer matrix during drying, forming a visco-elastic film in about 4 minutes, keeping the polymer matrix temperature below 100 °C, wherein resulting film has a water content of 10% or less. And the foregoing was just a partial listing of new claim elements. Hence, independent claims 1, 82 and 161, as amended, and all the new independent claims, claims 315-318, are not disclosed and/or made obvious, explictly or inherently, in the cited prior art.

The Examiner relies on the Declaration of Edward D. Cohen, Ph.D. under 37 C.F.R. § 1.132, dated September 6, 2012 ("Cohen Declaration) to support the assumption that it would be difficult for a person of ordinary skill in the thin film art not to obtain a film that has uniform content of active. Office Action, pp. 14 and 43. However, Dr. Cohen's assumption is dead wrong on its face or does not apply to the '080 Patent. Importantly, Dr. Cohen does not discuss

the degree of uniformity of content. He refers generally to "substantial uniformity of content of active" and "uniform content of active" per unit dosage. Cohen Declaration, ¶¶ 8-10. Dr. Cohen's statement about uniform content of active, without providing the degree of uniformity of content cannot be applied to the '080 Patent's invention. Especially now that the claims of the '080 Patent expressly require a degree of uniformity of content, namely, that uniformity of content of the resulting film(s) varies (i) no more than 10% with respect to the amount of active within a film (claims 1, 82, 161, 316-318) and/or (ii) no more than 10% from a desired amount with respect to the amount of active; said active sampled from different films in substantially equally sized individual dosage units sampled from different locations of the relevant film(s) (claim 315).

Moreover, as set forth in the Bogue Declaration, ¶¶ 4-11, 730 samples of individual dosage units, ten each from 73 separately manufactured lots of resulting films produced in accordance with Patentee's invention, were tested for active content. The results were that the active content of each individual dosage unit remained well within the control limits of 90% to 110% of the desired amount.

> "The results shown in the appendices establish that the resulting films produced by the inventive method of the '080 Patent as disclosed and claimed have the required uniformity of content based on analytical chemical testing. First, the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film. See Appendix A. Second, the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active. See Appendix B. Finally, the uniformity of content of the 73 lots of resulting film meets even more stringent standards, for example, the data shows: (i) 46 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 5%; (ii) 15 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 4%; 4 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 3%; and 1 lot of resulting film wherein the uniformity of content of active is shown with the amount of active varying by only 2%. See Appendix C.."
>
> Bogue Declaration, ¶ 11.

As noted, the FDA requires that the amount of active vary from dose to dose by no more than a prescribed percentage from the desired amount of active, essentially prescribing a degree

of uniformity of content in the amount of active which must be met. *See* Lin declaration, ¶¶ 9-16. Dr. Cohen provides no support for any prescribed degree of uniformity, and certainly not for the prescribed degree of uniformity of content in the amount of active explicitly recited by Patentee's claims under examination to meet commercial and/or regulatory requirements, or the degree of uniformity present in resulting films manufactured in accordance with Patentee's invention, as clearly demonstrated by the Bogue Declaration.

As held by the Court of Appeals for the Federal Circuit ("Federal Circuit") inherency requires much more than probabilities, possibilities, or for that matter assumptions. In *Crown Operations Intern., Ltd. V. Solutia Inc.*, 289 F.3d 1367 (Fed.Cir. 2002) ("*Crown*"), the patents at issue related to layered films used to create safety and solar control glass. The multi-layer film added properties to the glass assembly, such as impact resistance. An inner layer had solar control properties to reflect, absorb (and thus convert to heat), or transmit defined percentages of certain wavelengths of light. *Crown*, at 1370. The district court had held the only relevant independent claim of one of the patents, the '511 patent, not invalid on the grounds of anticipation and obviousness. It claimed a composite solar/safety film, comprised of a solar control film "wherein said solar control film contributes no more than about 2% visible reflectance". *Crown*, at 1372.

> "Crown [the declaratory judgment plaintiff] argued that U.S. Patent No. 4,017,661 to Gillery (the "Gillery patent") anticipates the '511 patent. The district court held otherwise, because, while the Gillery patent discloses the first three limitations of claim 1 of the '511 patent, it does not disclose the two percent visible reflectance limitation. The court found that neither the Gillery patent claims nor its description expressly disclose a two percent limit on reflectance contribution from the solar control film layer. Crown argued that the two percent limitation was inherently present in the Gillery patent's teachings because the Gillery patent disclosed an assembly with PVB layers, substrate layer, and substrate metal-coating — arguably of the same composition and thickness of the films disclosed by the '511 patent. Thus, Crown argued, because the structure, thickness and materials of the assembly were the same or within the same range(s), the Gillery patent must inherently disclose a two percent limitation. The district court rejected this argument because it found that none of the embodiments disclosed by the Gillery patent meet the two percent visible light reflectance limit."
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> *Crown*, at 1372.

The Federal Circuit, in upholding the decision of the District Court as well as the validity of the '511 patent, discussed the application of inherency to validity that is most relevant here.

> "Regarding alleged anticipation by the Gillery patent, on its face the Gillery patent does not disclose or discuss a two percent limitation for the reflectance contribution of the solar control film. Crown maintains that the '511 patent merely claims a preexisting property inherent in the structure disclosed in the prior art. Crown urges us to accept the proposition that if a prior art reference discloses the same structure as claimed by a patent, the resulting property, in this case, two percent solar control film reflectance, should be assumed. We decline to adopt this approach because this proposition is not in accordance with our cases on inherency. If the two percent reflectance limitation is inherently disclosed by the Gillery patent, it must be necessarily present and a person of ordinary skill in the art would recognize its presence. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed.Cir.1999); *Continental Can*, 948 F.2d at 1268, 20 USPQ2d at 1749. **Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient**." *Id.* at 1269, 20 USPQ2d at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981)) (emphasis supplied)."

The alleged inherency of the art cited by the Examiner and discussed below has not been established other than by statements of probabilities and/or possibilities and/or just statements that things are uniform without providing any degree of uniformity that must be present. For example, the assumption that by starting with so-called "uniform" mix of materials, stirring them, then casting and drying as alleged to be disclosed in the prior art is insufficient to establish inherency. Again, inherency requires that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. Importantly, the mere possibility that some of the films produced as disclosed by the art cited might result in some type of "uniform" film is not sufficent.

1. Chen's alleged inherency.

> "The claimed "substantially uniform distribution of components" and "locking-in or substantially preventing migration" of the active in independent claims 1, 82 and 161, and the variation of active content of 10% or less in dependent claims 254-255,272-273 and 290-291, are inherent in Chen's exemplified films and process. Inherency is based on the following: As discussed above, Chen uses the

> same materials and method as here claimed. Chen's ingredients are mixed until they are uniformly dispersed or dissolved in the hydrocolloid (p. 17, lines 8-11). Chen uses the same criteria discussed above with respect to the '080 patent in the Scope of Claims section for evaluation of substantial uniform distribution, i.e., weight of dosages and visual inspection."
>
> Office Action, p. 13.

The criteria used by Chen as cited by the Examiner for evaluation of "substantial uniform distribution" are physical observations. Such "observations" cannot be used, either inherently or otherwise, to establish the uniformity of content in the actual amount of active in equally sized samples in Chen's examples. Absent statements or data based on analytical chemical testing, not weighing or visual inspection, for the amount of active present in the film, Chen does not and cannot inherently disclose Patentee's resulting film having the claimed levels of uniformity of content. Moreover, even if Chen disclosed, which it does not, the use of the same materials and methods as the '080 Patent, the mere fact that a certain thing may result from a given set of circumstances is not sufficient to support inherency. *Crown, supra*, at 1378.

Moreover, Third Party Requester has not provided any proof that Chen's process examples when followed exactly, with all the components exactly as listed, and all other conditions of Chen exactly met, will provide a process suitable for commercial manufacture, a process which produces products which are regulatory approvable by the FDA, and which exhibit the levels of uniformity of content in actual amount of active claimed by Patentee's processes. Indeed, FIG. 5 of Chen describes a release profile of almost 120% of active from a film, which certainly exceeds the levels of uniformity of content in the amount of active that Patentee claims. This single active content result voids all claims to Chen's alleged inherency regarding same.

> "Finally, Chen's patent discloses the release profiles of four active agents from films. See Chen, Figure 5. The release profile data presented in Figure 5 show a high degree of variability at each data point. For example, the release profile for nicotine containing film product show that the amount of nicotine released at the 5 minute and 8 minute time point can be as high as approximately 115-120%. This level of active agent is greater than the 110% level (from an expected amount of 100%) that is considered acceptable to FDA for regulatory approval of a product that purports to be manufactured consistently with acceptable content uniformity. These data indicate that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity

between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film."

Lin Declaration, ¶ 22.

The Examiner states that the films made in accordance with the claims as issued are inherent in Chen. This conclusion is based on the belief that Chen uses the "same materials and method" as the Patentee, but even if true, much more is required. Patentee respectfully submits that this conclusion is incorrect, and particularly incorrect in light of the claims as amended. The Examiner erroneously states that Chen "uses the same criteria" as the '080 Patent that issued in evaluating substantial uniform distribution, i.e. weights of dosages and visual inspection." Although, a number of ways to test films in the patent are disclosed, in order to test content uniformity of an FDA regulated film product, it is necessary to assay using analytical chemical tests for drug or therapeutic active content of unit film doses. *See*, Lin declaration, ¶¶ 9-16. This is necessary to ensure the amount of active is within acceptable guidelines. Visual observation and physical measurements such as weight is insufficient to determine the active amount in equally sized dosage units at the level of uniformity of content required.

All of Patentees' claims now require analytical chemical testing and that the films have levels of uniformity in the amount of active which varies by no more than 10% from film to film and/or no more than 10% from a desired amount across several films. The Examiner's assumption that visual inspection and weight measurements establish these levels of uniformity of content in and by themselves is therefore incorrect, in so far at least as is required by the FDA, for example. Moreover, "Chen's disclosure is lacking, both explicitly and inherently, the disclosure necessary to provide for the manufacture of drug-containing films with the uniformity of content in amount of drug (active) in individual dosage units to make FDA approvable film products." Lin Declaration, ¶ 21.

Finally, there is a misplaced reliance on the physical terms "glossy" and "transparent" in the Office Action, which the Examiner use to establish the presence of "uniformity" in Chen's films. However, the term "glossy" is purely a visual characteristic ("surface luster or brightness") and is not interchangeable with nor equivalent to the uniformity of content of components of a film, nor the content uniformity of an active in the film. *See,* www.merriam-

webster.com/dictionary/glossy. It is also not interchangeable with specified levels of uniformity of content in amount of active in individual dosage units sampled from a film or sampled from different films. The term transparent is also a purely visual appearance characteristic ("transmitting light without appreciable scattering …"). *See,* www. merriam-webster.com/ dictionary/transparent. It is not indicative of the uniformity of content of the film. As such, Chen can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

2. Staab's alleged inherency.

> "Staab also discloses that "[t]he device of the invention thus is composed of a biologically-compatible material that has been blended homogeneously" with the drug (see col. 6, lines 5-10). In the Example at cols. 11-12, Staab prepares a four-foot wide film which is then cut into two inch by two inch films each weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (see col. 11, line 52 through col. 12, line 3). Accordingly, Staab's films inherently have the instantly claimed substantially uniform distribution of components and active. Also, in view of the fact that each film contains 19 mg of benzalkonium chloride and in view of said homogeneous blending, the variation of active in the dosage units is 0% (*sic* 10%), as per claims 254, 255, 272, 273, 290 and 291."
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> Office Action, p. 29.
>
> "In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Staab uses the same hydrocolloid as in the '080 patent, i.e. said HPMC. Accordingly, Staab's film in the Example at cols. 11-12 is inherently viscoelastic before drying. Accordingly, after drying for about 10 minutes, a viscoelastic film having less water that before drying is formed."
>
> Office Action, p. 30.
>
> "While Staab does not discuss viscoelasticity or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the active, Staab, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process."
>
> Office Action, p. 31.

Again, as with Chen, absent statements based on testing to determine the actual uniformity of content in the amount of active present in the film, so as to meet FDA approval, Staab does not and cannot inherently disclose Patentee's resulting film having the claimed levels of uniformity of content, with respect to the amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film and/or of different resulting films. Staab does not and cannot inherently form a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content within the recited levels of uniformity of content.

Moreover, even if Staab disclosed, which it does not, the use of the same materials and methods as the '080 Patent, the mere fact that a certain thing may result from a given set of circumstances is not sufficient to support inherency. *Crown, supra*, at 1378. Moreover, Staab just states that there is 19 mg of benzalkonium chloride present in each sample weighing 190 mg. However, Staab does not disclose testing to determine the amount of benzalkonium chloride present in the final film product or even how each and every sample turned out to be 19 mg. Staab, col. 11, l. 35 - col. 12, l. 3. Staab's resulting structure is a foam rather than the recited visco-elastic film formed within 4 minutes and Staab also would not inherently have the recited degree of uniformity of amount of active in substantially equal sized dosage units. Moreover, Staab starts with a composition having 10% by weight of benzalkonium chloride (50% aqueous) yet allegedly obtains a resulting film with 19 mg benzalkonium chloride in a 190 mg film, to once again obtain a 10% benzalkonium chloride resulting composition. A perfect yield must must always be considered suspect. Inherency should never be based on a suspect disclosure. As such, Staab can neither anticipate, explicitly nor inherently, nor make obvious the '080 Patent claims, see discussion below.

3. Le Person's alleged inherency.

> "Le Person discloses that after 5 min of the drying, 'the polymeric network is not turgescent and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [i.e., pharmaceutical or drug] when the system reequilibrates.' (See p. 262, col. 2, third full paragraph.) Le Person also teaches that '[b]etween the 5th and 10th min of drying the heavy solvent migrates... active substance, slowed down in its migration, stays in the bottom of the layer.' (See the

> last four lines at page 262, col. 2). It is noted that the heavy solvent only accounts for 2% of the wet composition of the coating (see page 258, Table 1). As such, within 5-10 minutes, the solvent has been sufficiently evaporated such that, inherently, a substantial uniform distribution of the active is locked-in and migration is substantially prevented within the film, as here claimed. The active material homogenizes and a quasi-equilibrium is obtained for the components of the Page 38 active phase, taking into account evaporation of the heavy solvent (p. 263, col. 1, lines 8-13), and thus, there is a variation of active content of less than 10%, as per claims 272, 273, 290 and 291.
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> Office Action, pp. 37-38.
>
> "While Le Person does not discuss viscoelasticity or that the films in its process have a 'substantially uniform distribution of components' or disclose 'locking-in or substantially preventing migration' of the active, Le Person, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 82, 89-91,161,171-173, 272-274 and 290-292, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a)."
>
> Office Action, p. 38.

Le Person is entirely devoid of any details with respect to its process and materials. For example, nowhere does Le Person discuss what type of acrylic polymer he uses nor the molecular weight of the polymer. Thus, Le Person allows for materials which may have such a low molecular weight that forming a visco-elastic film may not be possible. Moreover, Le Person lacks sufficient enabling disclosure to be an effective reference as applied in view of the amended claims. Such deficiencies cannot be used in support of an inherency argument. Again, absent statements and data based on testing for the amount of active present in the film with results establishing a substantial uniformity of content at the claimed levels and suitable for FDA approval, Le Person does not and cannot inherently disclose Patentee's resulting film. Moreover, Le Person does not and cannot inherently form a viscoelastic film in about 4 minutes which locks-in the claimed uniformity of content in the amount of active.

Le Person discloses very little about the acrylic polymer, such as the molecular weight. If the molecular weight was low enough it may not become a viscoelastic material. Patentee asks, how could Le Person anticipate and/or make obvious the '080 Patent which is directed to the commercial manufacture of a regulatory approvable resulting film meeting required specified

levels of uniformity of content in the amount of the active, where Le Person's goal, as noted in its abstract, was devoted to determining "cases of maldistribution of the active substance," in connection with different drying methods, and not to providing a process for manufacturing films with uniformity of content of the desired amount of an active. Importantly, Patentee has added several additional process steps not in the prior art. These new process steps present in the amended independent claim, as well as the new independent claims, further distance Patentee's patent from the prior art. As such, Le Person can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

4. Horstmann's alleged inherency.

> "The claimed substantially uniform distribution of components and active, and locking-in or substantially preventing migration of active, and the variance of active content of 10% or less in dependent claims 254, 272 and 290 are also inherent in Horstmann's Examples 1, 3 and 4. In particular, Horstmann's films before drying are described as being uniform and homogeneous (see col. .3, line 11-19, 29-34 and 37-41; col. 5, lines 1 and 50), and as noted above, Horstmann uses the same components and process steps as here claimed. The '080 patent notes that Horstmann addressed the problem of self-aggregation and nonuniformity by increasing the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film (see col. 2, line 60 through col. 3, line 1).
>
> Office Action, p. 43.
>
> "While Horstmann does not discuss viscoelasticity, water content of its dried films or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the, active, Horstmann, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 1, 5,7-10,12-1423,63,64,82,84,86-89,91-93,102,142,143,161, 166, 168-171, 173-175, 184,224,225,249,254,267,272,285 and 290, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a)."
>
> Office Action, pp. 43-44.

Horstmann forms a gel, rather than a solid film as in the present invention. Thus the gel rheological properties of Horstmann are very different than a solid visco-elastic film having a

water content of 10% or less. Moreover, Horstmann specifically teaches protecting the gels from drying up by placing the cut out gel shapes in a water vapor impermeable sealing material. See Horstmann, col. 5, ll. 11-13. This is a direct teaching away from drying to a water content of 10% or less. Horstmann at col. 2, ll. 25-29, suggests drying may not be necessary.

Again, absent statements based on testing for the amount of active present in the film with results establishing a the claimed levels of uniformity of content in the amount of active, suitable for FDA approval, Horstmann does not and cannot inherently disclose Patentee's resulting film claiming the specified levels of uniformity of content in the amount of active.

Additionally, as the Examiner admits, Horstmann discloses only that its film is alleged to be uniform at a point prior to drying. Horstmann, col. 3, ll. 37-41. Horstmann says nothing about the uniformity of the product during or after drying. Again, *Crown* holds that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* A disclosure of some unspecified degree of uniformity of a film prior to drying in Horstmann does not establish that the product after drying is uniform, let alone the degree of uniformity as claimed by the '080 Patent. As noted throughout the '080 Patent, controlled drying is required for ensuring the claimed levels of uniformity of content. As such, Horstmann can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

Importantly, Patentee has added several additional process steps also not in the prior art. See above. These new process steps present in the amended independent claims, as well as the new independent claims, further distance Patentee's patent from the prior art, by negating any anticipation and obviousness assertions. Even without the additional process steps, even if it were possible that a resulting film with the proper levels of uniformity of content in the amount of active might possibly result from some manipulations of the disclosures given in any of Chen, Staab, Le Person and/or Horstmann, it is incorrect to rely on these references in an attempt to show they inherently disclosed Patentee's resulting film. See *Crown*, at 1377-1378, *supra*.

As the absence of inherency in and of itself removes Chen, Staab, Le Person and Horstmann as viable prior art for rejecting Patentee's claims under 35 U.S.C. § 102, the Examiner should withdraw his rejections of Patentee's claims 1, 82 and 161 based on same. For the same reasons new independent claims 315-318 are allowable. Moreover, these references for

the same reasons discussed above, as well as the reason discussed below, do not support any finding of obviousness, and thus the rejections of claims 1, 82, and 161 based on 35 U.S.C. § 103 should be withdrawn as well. For the same reasons new independent claims 315-318 are not obvious in light of the prior art. Finally, Patentee's claims 2 through 81, 83 through 160, 162 through 299 and 300 through 314 as they depend from independent claims 1, 82, 161 should all be allowed as well, with any rejections withdrawn.

B. Third Party Requester's Wherein Argument is Wrong

Patentee finds it necessary to address Third Party Requester's attempt to vitiate the '080 Patent's claim language beginning with "wherein". Third Party Requester cites to the Federal Circuit for the premise that "a whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." *Minton v. Nat'l Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed.Cir.2003). Third Party Requester's Request for Inter Partes Reexamination ("The Request"), p. 16.

However, the Federal Circuit has also strongly held that "when the 'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." *Hoffer v. Microsoft Corp.*, 405 F. 3d 1326, 1329 (Fed. Cir. 2005). Essentially, Requester proposes that with elimination of the "whereby" clauses, the claims 1, 82 and 161 (before the amendments herein) would not require "wherein said resulting film has a water content of 10% or less and said uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained." The Request, p. 20.

As noted above, "when the whereby clause states a condition that is material to patentability, it cannot be ignored to change the substance of the invention." *Hoffer v. Microsoft Corp.*, 405 F.3d 1326 (Fed. Cir. 2005); *see also Fantasy Sports Properties, Inc. v. Sportsline.com, Inc.*, 287 F.3d 1108, 1111-16 (Fed. Cir. 2002); *Griffin v. Bertina*, 285 F.3d 1029, 1034 (Fed. Cir. 2002). In *Griffin*, for example, the court found that "wherein" clauses were claim limitations "because they relate back to and clarify what is required by the count. Each 'wherein' clause ... expresses the inventive discovery [and] ... elaborates the meaning of the preamble." *Griffin*, 285 F. 3d at 1033-34. Further, "the allegedly inherent properties of the 'wherein clauses' provide the necessary purpose to the steps." *Id.* See also, MPEP, § 2111.04.

The '080 Patent independent claims' wherein clause limitations cannot be disregarded. The '080 Patent claims processes for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films. The ability to make such films with the required level of uniformity in content of active is the essence of Patentee's invention. Thus, such wherein clauses which express the inventive discovery and elaborates the meaning of the preamble cannot be ignored for purposes of patentability.

Finally, Third Party Requester has made many allegations about the '080 Patent and its specifications and claims, and the prior art in The Request. Patent owner believes that the amendments to claims 1, 82 and 161 herein clarifying the scope of same and thereby advancing the prosecution of same, obviate the need to address Third Party Requester's allegations or the Examiner's statements made without the benefit of the amendments. Nevertheless, to the extent that any are not explicitly addressed herein, Patentee hereby asserts they are wrong and unsupported in either fact or law.

C. Claims 1, 4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84,87-97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-262, 264, 265, 267-280, 282, 283 and 285-299 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chen.
Claims 2, 3, 6, 7, 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 85, 86, 98, 112, 114, 120-122, 127-129, 131, 134-137, 139, 140, 167, 168, 180, 194, 196, 202-204, 209-211, 213, 216-219, 221, 222, 245, 248, 263, 266, 281 and 284 were rejected under 35 U.S.C. 103(a) as being unpatentable over Chen.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Chen, WO 00/42992 ("Chen") or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Chen. Patentee incorporates its previous discussions in sections A. and B. above. Chen is a primary reference relied upon by the Examiner in the Office Action. Patentee

respectfully traverses the above rejections on the basis, among others, that Chen does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of a lot of the resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Chen also fails to disclose, explicitly or inherently, the additional elements found in Claim 317. Claim 317 generally adds, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Chen discloses two methods of forming a film product, a solvent casting method and an extrusion method. The extrusion method does not rely upon putting a hydrocolloid in a solvent, nor does the extrusion method use a drying oven and is apparently preferred by Chen over the solvent method. Chen, page 15, lines 9-21. In the solvent casting method, Chen states that a hydrocolloid is dissolved or dispersed in water, and mixed to form a homogeneous solution. The active agent and other ingredients may be added and dispersed or dissolved uniformly in the hydrocolloid solution. The coating solution with a solid content of 5-50% and a viscosity of 500-15000cps is degassed and coated onto a polyester film and "dried under aeration" at a temperature between 40-100°C to avoid destabilizing the agents. Chen, p. 15, ll. 19- 29. The dry

film formed by this process is described to be a "glossy, stand alone, self supporting, non-tacky and flexible film". Chen, p. 15, ll. 30-31. These very general statements are all that are given by Chen as to the formation and drying of Chen's film product. These statements cannot support either anticipation or obviousness rejections.

Chen's drying process is so general and devoid of detail so as to provide no guidance other than that to dry, one places a film in a conventional hot air circulating oven at temperatures of from 40-100°C and leaves it for a period of time. Chen does not disclose any other drying methods beyond drying "under aeration", nor does Chen disclose any controlled drying processes whatsoever. Chen showed no recognition of the complexities involved in the commercial manufacturing of films, as Chen's focus relates solely to the ingredients and mechanical properties, not the process. Without any recognition of the problems, and without any appreciation of the difficulties in preventing the settling, migration and/or aggregation or agglomeration of active(s) in the cast flowable mass, Chen neither sought nor found the solution to creating commercial scale films having uniformity of content of pharmaceutical and bioactive actives per individual dosage unit and meet FDA requirements regarding same. Chen lacks substantial disclosure in view of the '080 Patent. Among its deficiencies, Chen lacks any disclosure as to specific processing means (beyond generally drying in a generic oven) or the formation of a visco-elastic film state. Chen only discloses the apparent homogeneity of a blended matrix, and this is prior to the addition of actives. There is no disclosure or suggestion as to how to create a substantially uniform distribution of the pharmaceutical or biological active in the blended matrix and then cast that matrix to maintain uniformity, and then control drying through among other processes conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to rapidly form a visco-elastic film having said pharmaceutical active uniformly distributed throughout by rapidly increasing the viscosity of said polymer matrix upon initiation of drying within about the first 4 to maintain said uniform distribution of said pharmaceutical or biological active by locking-in or substantially preventing migration of said pharmaceutical active within said visco-elastic film and then test it to establish the substantially uniform distribution of pharmaceutical or biological active content, in compliance with FDA regulations.

Among other things, the '080 Patent claims are directed to locking-in an active such as a pharmaceutical or biological active, by controlling drying to form a viscoelastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes. The Examiner has stated in the Reexamination, Reasons for Patentability/ Confirmation ("RFP/C"), in connection with both the '292 Patent and the '891 Patent reexaminations that "Chen does not discuss what happens within the first 4 minutes of drying." Moreover, in the '891 Patent RFP/C the Examiner goes on to state that: "Chen does not discuss uniformity of pharmaceutical or biological active components in its doses. Table 4 of Chen gives the grams per unit dosage film and density for Example 1 with standard deviation based on three or four measurements, but does not give compositional uniformity." Additionally, Chen's Example 1 contains only food flavorings and a sweetener.

Chen does not disclose that the resulting products are compositionally uniform, but only that they are "glossy". As stated above, glossy does not imply or establish compositionally uniformity. In fact, Chen's Figure 5 (Examples 5-8) clearly shows a lack of compositional uniformity of active. Although statistics are not defined in the text, the error bars represent either high or low values, standard deviation or some measure of variation. Given that the compositions of Examples 5-8 are the same, except for the amount of active, it is reasonable to conclude that the active is not uniformly present in the individual films due to the wide variation of release of active from the same film compositions. For example, with regard to the release of nicotine in the same film compositions, the release reaches in excess of 118%. Certainly there is neither disclosure of, nor inherency in, the that the level uniformity of content in the amount of active as sampled in individual dosage units of the same film be 10% or less. "The release profile data presented in Figure 5 show a high degree of variability at each data point. This indicates that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film." Lin Declaration, ¶ 22.

As defined in the specification for the '080 Patent as filed, a visco-elastic solid is one that has been sufficiently dried to lock its active components into a substantially uniform distribution throughout the film. The '080 Patent claims require that this be done within about the first 4

minutes or less. The Examiner has previously acknowledged that Chen does not disclose that the resulting film product has any compositional uniformity of pharmaceutical or biological active at that point in time. See '891 Patent RFP/C. Neither Chen nor the other references teach this step.

As explained throughout the '080 Patent and as summarized above, the present invention is based upon the discovery that certain process parameters, such as, viscosity and controlled drying methods to avoid non-uniformity of content in the amount of active must be employed to provide a commercially and FDA viable film product. Chen does not disclose or suggest such a resulting product. *See* Lin Declaration, ¶¶ 17-22. Chen discloses that various components (absent the active) are combined and that the mixture is blended to form a "uniform" solution. (Chen, p. 20, ll. 19-20). although even the formation of a uniform solution in a blender is beneficial, it is not the end of the process by any means. Further, as explained above, conventional drying methods do not inherently provide uniform films and, in fact, would not be expected to provide resulting films having the claimed uniformity of content in the amount of active.

Patentee's claimed processes are not present in Chen, either expressly or inherently, and Chen cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited Chen reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Chen does not render obvious the pending claims .

D. Claims 2, 3, 16, 32, 55, 72-81, 95, 111, 134, 151-160, 177, 193, 216 and 233-242 were rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teaching of Chen and Staab.

The Office Action rejected the above claims under 35 U.S.C. § 103(a), as being unpatentable over the combined teaching of Chen and Staab, U.S. 5,393,528 ("Staab"). Patentee incorporates its previous discussions in sections A., B. and C., above, and E., below and traverses all said rejections thereon. As all the above claims depend from one of the independent claims, claims 1, 82 and 161, they are allowable for all the reasons provided in the sections dealing with Chen, above, and Staab, below and even combined Chen and Staab do not render obvious the pending claims of this rejection.

E. Claims 1-5, 10, 12-16, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78- 84, 89, 91-95, 100, 103, 104,111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171,173-177,182,185,186,193,205-207,215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Staab.
Claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 were rejected under 35 U.S.C. 103(a) as being unpatentable over Staab.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Staab, or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Staab. Patentee incorporates its previous discussions in sections A., B., C. and D., above, Patentee respectfully traverses the rejection on the basis, among others, that Staab does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the pharmaceutical and/or bioactive active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of one lot of the resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Staab certainly does not disclose, explicitly or inherently, the additional claim elements of Claim 317. Claim 317 generally adds to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising

drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Moreover, Staab teaches the benefits of using a "gas foamed film" or films. Staab, col. 5, ll.33-35; col. 8, ll. 33. Staab thus teaches away from the '080 Patent by teaching that air bubbles are necessary, which are contraindicated in Patentee's invention requiring a substantially uniform distribution of active. Staab instead teaches that gas bubbles must be added to the polymer/drug mixture prior to casting.

> "It should be noted that heretofore, the significance of the addition of gases in the formation of the film to alter the texture and solubility of the film has not been recognized."
> Staab, col. 3, ll. 15-20.

> "**The fine tuning of dissolution rates and delivery of agent material, by the addition of gases and by altering the grades or mixtures of polymer materials or layers, is an important aspect of the present invention.**
>
> * * * *
>
> **"The gases, for example, air or nitrogen are introduced near the point of application of the liquid polymer material to the stainless steel casting sheet. The gases are added in a closed system by mixing with whipping blades or a motor driven homogenizer to homogenize the mixture of polymer, active material and gas to form a frothy foam. The final mixture then sets up or gels as a foam.** It is also possible to pour the frothy foam mixture into a mold. The mold is then deformed and the formed device such as a diaphragm, is removed."
> Staab, col. 8, ll. 29-64 (emphasis supplied).

In direct conflict with Staab's teaching, the '080 Patent teaches the use of anti-foaming agents to **prevent** gas bubble formation and thereby promote uniformity. Importantly, Patentee's processes, in many cases, avoid the formation of bubbles, without the need to use anti-foaming agents.

> **" Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product."**
>
> '080 Patent, col. 4, ll. 5-21 (emphasis supplied).

> "A number of techniques may be employed in the mixing stage to **prevent bubble inclusions in the final film. To provide a composition mixture with**

substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed.."

'080 Patent, col. 9, ll. 56-65 (emphasis supplied).

See also section of '080 Patent entitled "Anti-foaming and De-foaming Compositions" ('080 Patent, col. 22, l. 47 through col. 23, l. 53).

Staab addresses the fine tuning of dissolution rates and delivery of active agent, by teaching the addition of gases as an important aspect of his invention (Staab, col. 8, ll. 30-34). Staab is silent with respect to the recited levels of uniformity of content. The '080 Patent in connection with achieving uniformity of content in the amount of active teaches avoiding bubble formation and the removal of such gases and bubbles ('080 Patent, col. 9, ll. 56-65). Moreover, Staab uses conventional drying (Staab, col. 11, ll. 64-65) rather than the particular drying methods used to ensure the uniformity of content claimed by the '080 Patent.

The presently claimed process is not disclosed in Staab, either expressly or inherently, and Staab does not anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Staab does not render obvious the pending claims of the above rejections.

F. Claims 82, 89-91, 161, 171-173, 272-274 and 290-292 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Le Person.
Claims 92 and 174 were rejected under 35 U.S.C. 103(a) as being unpatentable over Le Person.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Le Person, Chemical Engineering and Processing, Vol. 37, pp. 257-263 (1998) ("Le Person") or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Le Person. Patentee incorporates its previous discussions in sections A., B., C., D. and E., above, Patentee respectfully traverses the rejection on the basis, among others, that Le Person does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by

locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of one lot of resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Le Person certainly does not disclose, either explicitly or inherently, the additional claim elements found in Claim 317. Claim 317 generally adds to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Le Person does disclose that the drying step used plays a role in the final product, but fails to disclose or suggest how to achieve a uniform final product. In fact, Le Person discloses methods that result in a non-uniform product prior to and at 10 minutes. According to Le Person, the resulting product dried in 9 minutes would not have claimed uniformity of content of active.

Le Person's goal was to determine "cases of maldistribution of the active substance," in connection with different drying methods, said maldistribution having consequences on storage and delivery of a drug and proposes the use of Laser Scanning Confocal Microscopy on the active substance and the heavy solvent to determine same. (Le Person, Abstract). Le Person acknowledges that in the formation of a film product, "drying is the essential unit operation necessary to form the final product." (Le Person, p. 257). Le Person's experimental set-up was composed of two parts, "the drying cell and the wind tunnel. . . . [wherein] the wind tunnel is a conventional drying rig. . . ." Le Person, p. 258, col. 2 & Fig. 1. Le Person's disclosure of the

use of a wind tunnel further negates any argument that Le Place inherently anticipates or makes obvious Patentee's invention.

It is important to note that Le Person simply recognized the overall, general difficulty in obtaining films with a substantially uniform distribution of active. Le Person did not try to solve this problem, only to determine means to identify it. Thus, Le Person did not recognize the specific reasons therefor, nor did Le Person recognize the solutions needed to overcome this difficulty. Le Person's goal was to find ways to best determine whether or not there was homogeneity of film product.

However, the point of Le Person is that, in the time period (i.e., less than 10 minutes), there is non-uniformity of the product. Le Person even states that "intense moisture removal through the exposed surface of the layer to the radiation, during the first 3 min of drying (Le Person, Fig. 7) produces a stress on the polymer skeleton … and as a result the acrylic polymer becomes more and more dense in the upper part of the layer (exposed surface)." (Le Person, p. 261). As a result, this "intense" shrinkage results in displacement of the active phase. As such, Le Person's disclosure is not directed towards achievement of a film having a substantially uniform distribution of an active through drying, and in fact, if anything, teaches away from achieving uniformity of content in the amount of an active.

The presently claimed processes are not present in Le Person, either expressly or inherently, and Le Person does not anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Le Person does not render obvious the pending claims.

G. Claims 1, 5, 7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166, 168-171, 173-175, 184, 224, 225, 249, 254, 267, 272, 285 and 290 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hortsmann.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Horstman, et al. U.S. 5,629,003 ("Horstmann") or, in the alternative under 35 U.S.C. § 103(a), as obvious over Horstmann. Patentee incorporates its previous discussions in sections A., B., C., D., E. and F., above, Patentee respectfully traverses the rejection on the basis, among

others, that Horstmann does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film, by no more than 10% from the desired amount across different resulting films, and is in compliance with FDA regulations governing same.

Horstmann certainly does not disclose, either explicitly or inherently, the additional claime elements of Claim 317. Claim 317 generally adds to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Moreover, the '080 Patent's description of the differences between Horstmann and Patentee's invention claimed in the '080 Patent is relevant to the Examiner's current rejections as well. For example:

> "In one attempt to overcome non-uniformity, U.S. Pat. No. 5,629,003 to Horstmann . . . incorporated additional ingredients, i.e. gel formers and polyhydric alcohols respectively, to increase the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film. These methods have the disadvantage of requiring additional components, which translates to additional cost and manufacturing steps. Furthermore, both methods employ the use the conventional time-consuming drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other

such drying equipment. The long length of drying time aids in promoting the aggregation of the active and other adjuvant, notwithstanding the use of viscosity modifiers. " '080 Patent, col. 2, l. 63 to col. 3, l. 9.

Horstmann's use of conventional drying methods and need for gel formers teaches away from obtaining a resulting film with the desired levels of uniformity of content in the amount of active. Horstmann does not disclose the degree of uniformity of content, merely, for example, in Example 2, referring to film sections containing "approximately" 3 mg of active and a weight of "approximately" 80 mg. Horstmann, col. 5, ll. 15-36. Horstmann does not disclose that these amounts are based on any testing, or for that matter what they are based upon, or that they comply with FDA requirements relating to drug products.

The presently claimed process is not present in Horstmann, either expressly or inherently, and Horstmann cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Horstmann does not render obvious the pending claims.

IX. Conclusion

No reference, either alone or in combination with other references, teaches the processes claimed by the '080 Patent. Entry of the amendments herein is respectfully requested. Patentee traverses all rejections of its claims. For at least the reasons set forth above, independent claims 1, 82, 161, and 315-318 are allowable. Claims 2 - 81, 83 - 160, 162 - 314 are allowable at least based on their dependencies, whether direct or indirect, from independent Claims 1, 82, 161 . Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejections to same. Should the Examiner have any questions regarding this response, the undersigned would be pleased to address them.

Respectfully submitted,

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CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **REPLY BY PATENTEE TO A NON-FINAL OFFICE ACTION PURSUANT TO 37 C.F.R. §1.111** has been served, by first class mail, on March 13, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

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EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	March 13, 2013	M&E Docket:	117744-00023

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I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on
March 13, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, B. Arlie Bogue, Ph.D., do hereby make the following declaration:

I. Technical Background

1. I have worked in the field of pharmaceutical development, and particularly oral dosage form development, for 22 years. I am employed by MonoSol Rx, LLC. ("Patentee" and/or "MonoSol"), the assignee of issued patent U.S. 7,897,080 ("the '080 Patent"), as Senior Director for Manufacturing Strategy and Innovation.

2. I have a BS in Physical Chemistry from Colorado State University and a Ph.D. in Chemical and BioEngineering from Arizona State University. I have participated in postdoctoral studies in Biochemical Engineering at the University of Virginia. During my career, I have been named as an inventor on over 23 U.S. patents and numerous foreign patents directed to the formulation,

processing and/or packaging of pharmaceutical oral disintegrating unit doses (tablets and film strips). I have direct experience with the commercial scale processing of pharmaceutical film systems as well as an understanding of the uniformity of content of active and methods for testing the same.

3. I have read the '080 Patent and the Office Action issued on November 29, 2012 in the reexamination of the '080 Patent ("Office Action") and the references cited therein, and I have also reviewed the amendment as to the independent claims set forth in Patentee's Reply to the Office Action concurrently filed herewith.

II. Producing resulting films in accordance with the '080 Patent

4. Each of the 73 lots of resulting films (Lots 1-73) containing approximately 2,000,000 individual dosage units per lot discussed herein were manufactured: (i) for commercial use and regulatory approval; (ii) in compliance with U.S Food and Drug Administration ("FDA") standards and regulations, including those relating to analytical chemical testing for variation in active in individual dosage units; and (iii) in accordance with the invention disclosed in the '080 Patent, and as claimed by the '080 Patent both as issued and as amended in the Patentee's Reply to the Office Action; by:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a pharmaceutical active, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less;

(d) forming the resulting pharmaceutical film from said visco-elastic film, wherein said resulting pharmaceutical film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting pharmaceutical film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting pharmaceutical film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10%, [see Appendix A] said resulting pharmaceutical film suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

5. Additionally, the uniformity of content in the amount of active as sampled from the 73 lots of resulting film varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests from 4(e) above. [See Appendix B]

III. Analytical Chemical Testing for Uniformity of Content of Patentee's Resulting Films

6. To demonstrate the uniformity of individual dosage unit films, I compiled individual dosage unit assay data for individual Lots 1- 73, all of which were disclosed in MonoSol's 2012 Annual Product Review to the FDA.

7. Ten (10) individual dosage units all having the same dimensions were cut out from different locations of each of the 73 lots of resulting films using a commercial packaging machine, thus providing 730 randomly sampled individual dosage units, ten each from the 73 separate lots. All samples were analyzed by a validated method, in compliance with FDA guidelines and regulations regarding same, using analytical chemical testing, in which the pharmaceutical active

was extracted and analyzed by High Performance Liquid Chromatography (HPLC) against an external standard to quantify the amount of active present in each individual dosage unit.

8. According to the inventive process set forth and claimed in the '080 Patent, and in accordance with FDA nomenclature, I have prepared tables shown as Appendices A, B and C, reflecting the uniformity of content of active of individual dosage units within particular lots and across different lots.

9. First, the uniformity of content of active in a lot is determined through establishing the amount of active ($A_{N(i)}$) actually present in each sampled individual dosage unit from the same lot (N) as determined by taking the difference between the amount of active in the sample with the most active ($Max_{LOT(N)}$) minus the amount of active in the sample with the least amount of active ($Min_{LOT(N)}$) and dividing the difference by the average amount of active in the lot samples ($Lot_{(N)}$ Sample Average). That is: $(Max_{LOT(N} - Min_{LOT(N)}) / ((A_{N(1)} + A_{N(2)} + + + A_{N(10)})/10)$. The results are shown in Appendix A.

10. Second, the uniformity of content across different lots is determined through establishing the amount of active actually present in each sampled individual dosage unit from all 73 lots and comparing that amount of active with a "target" or "desired" amount of active contained therein. The target amount of active, when it is a pharmaceutical, is referred to as the "Label Claim", thus identifying the amount of pharmaceutical active in the film to a user. The desired amount is 100% of the target amount. Each individual dosage unit film cut from any individual lot must have the desired content of pharmaceutical active, varying no more that 10% from the target or desired amount. See Appendix B.

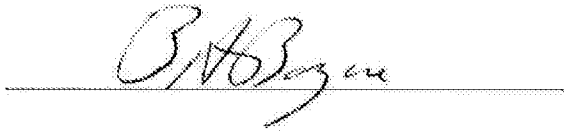
IV. '080 Patent Process Produces Films With Required Uniformity of Content of Active

11. The results shown in the appendices establish that the resulting films produced by the inventive method of the '080 Patent as disclosed and claimed have the required uniformity of content based on analytical chemical testing. First, the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film. See Appendix A.

Second, the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active. See Appendix B. Finally, the uniformity of content of the 73 lots of resulting film meets even more stringent standards, for example, the data shows: (i) 46 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 5%; (ii) 15 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 4%; 4 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 3%; and 1 lot of resulting film wherein the uniformity of content of active is shown with the amount of active varying by only 2%. See Appendix C.

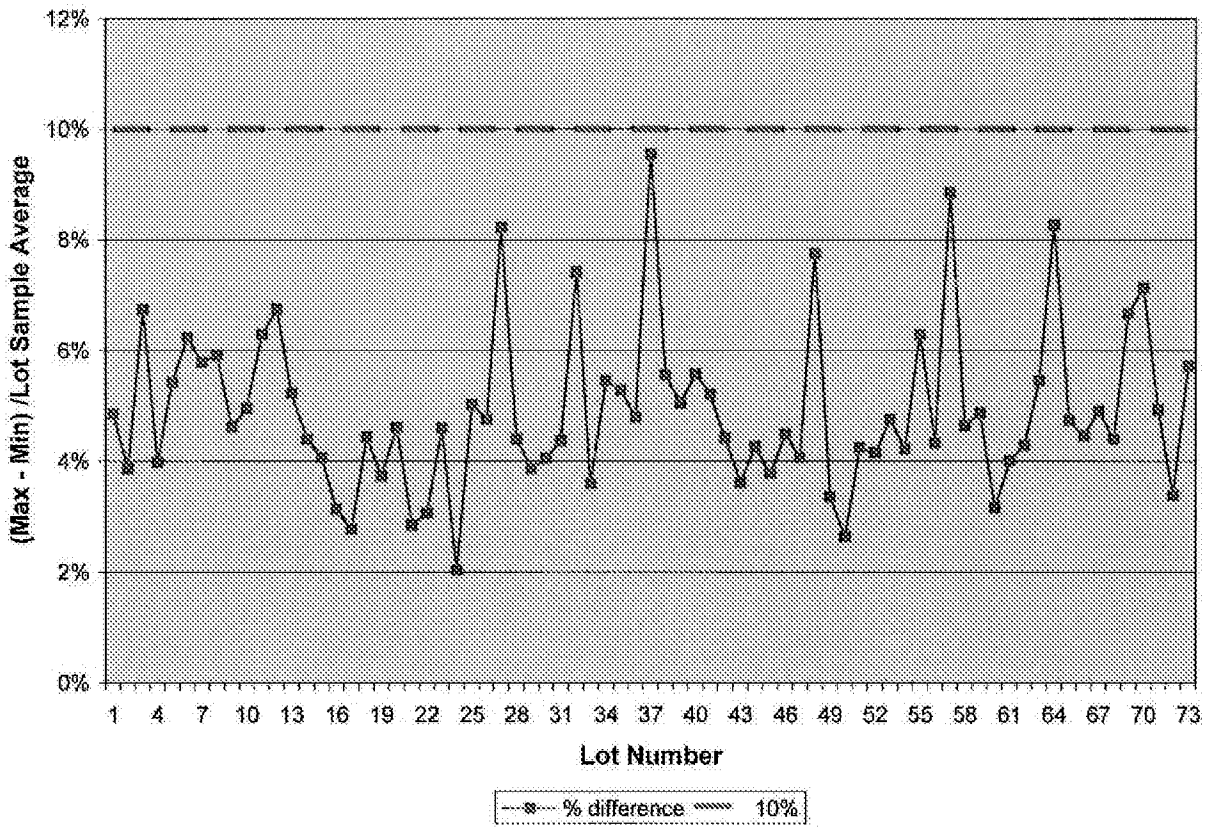
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and. that such statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 13th day of March, 2013

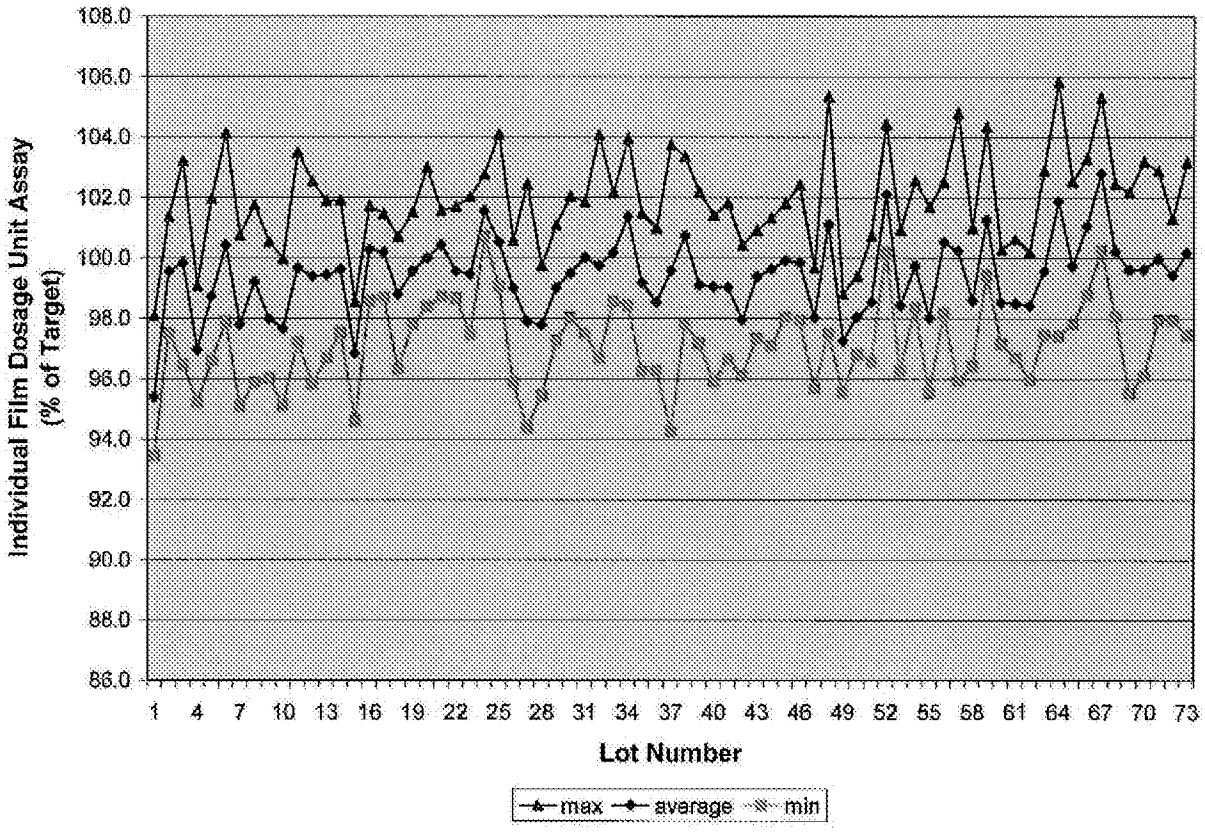


B. Arlie Bogue

APPENDIX A



APPENDIX B



APPENDIX C

Lots less than 5%			lots 5% to 10%	
Lot #	% Difference		Lot #	% Difference
24	2.0%		10	5.0%
45	2.6%		25	5.0%
17	2.8%		39	5.0%
21	2.8%		41	5.2%
22	3.1%		13	5.2%
16	3.1%		35	5.3%
60	3.2%		5	5.4%
50	3.4%		63	5.5%
72	3.4%		34	5.5%
33	3.6%		38	5.6%
43	3.6%		40	5.6%
19	3.7%		73	5.7%
46	3.8%		7	5.8%
29	3.9%		8	5.9%
2	3.9%		6	6.2%
4	4.0%		11	6.3%
61	4.0%		55	6.3%
30	4.0%		69	6.7%
48	4.1%		3	6.7%
15	4.1%		12	6.7%
52	4.2%		70	7.1%
54	4.2%		32	7.4%
51	4.2%		49	7.8%
44	4.3%		27	8.2%
62	4.3%		64	8.3%
56	4.3%		57	8.9%
31	4.4%		37	9.5%
28	4.4%			
14	4.4%			
68	4.4%			
42	4.4%			
18	4.4%			
66	4.5%			
47	4.5%			
23	4.6%			
20	4.6%			
9	4.6%			
58	4.6%			
65	4.7%			
26	4.8%			
53	4.8%			
36	4.8%			
1	4.9%			
59	4.9%			
67	4.9%			
71	4.9%			
total	46		total	27

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132** has been served, by first class mail, on March 13, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

EXHIBIT B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	March 13, 2013	M&E Docket:	117744-00023

Mail Stop Inter Partes Reexam
Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on
March 13, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF DAVID T. LIN, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, David T. Lin, Ph.D. do hereby make the following declaration:

I. SUMMARY OF CREDENTIALS AND EXPERIENCE

1. Since January 2005, I have served as a Senior Consultant to Biologics Consulting Group, Inc. ("BCG"), a team of consultants who provide national and international regulatory and product development advice on the development and commercial production of small molecular weight synthetic drug, biotechnological and biological products.

2. While BCG is being paid for my time, I am not an employee of, nor do I have any financial interest in, MonoSol Rx, LLC ("Patentee" and/or "MonoSol").

3. Before joining BCG, I held various positions with the United States Food and Drug Administration ("FDA"). From 1997-2001, I was a Chemistry Reviewer in the Division of Reproductive and Urologic Drug Products, Center for Drug Evaluation and Research ("CDER"). In 2001, I became the Team Leader in the same Division and served in that role until 2003 when I was promoted to the position of acting Deputy Division Director in the Division of New Drug Chemistry III, Office of New Drug Chemistry (currently referred to as Office of New Drug Quality Assessment). In 2004, I was promoted to the position of acting Division Director.

4. As a Chemistry Reviewer at CDER, I was responsible for the comprehensive review of Chemistry, Manufacturing and Controls ("CMC") data for drugs being investigated during Phase 1, 2, and 3 clinical studies. I was also responsible for the review of CMC data in New Drug Applications and provided regulatory input to CMC reviewers responsible for review of Abbreviated New Drug Applications. This included providing scientific and regulatory guidance during development of small molecular weight drugs and biotechnological/biological drugs across a wide variety of dosage forms. I have reviewed CMC data submitted with respect to over 100 Investigational New Drug Applications and New Drug Applications (original and supplemental) as a chemistry reviewer, contributed to decisions regarding the approval of drugs, made presentations before scientific and regulatory conferences and participated in a variety of special FDA projects and committees, including serving as the co-Chair of the CMC Good Review Practices Committee.

5. As Team Leader, acting Deputy Division Director and acting Division Director in the Office of New Drug Chemistry, I was actively involved in directing the content of FDA guidances that pertained to CMC topics. As acting Deputy Division Director and Division Director, I was directly involved in discussions, regarding the content of the 2003 FDA draft guidance on Drug Product-Chemistry, Manufacturing, and Controls Information, with the committee responsible for writing this guidance. I had signatory authority for this draft guidance prior to public issuance by FDA. As acting Deputy Division Director and Division Director, I was involved in regular meetings with the supervisory staff in the Office of Generic Drugs to discuss regulatory and review policy issues that are common to both New Drug Applications and Abbreviated New Drug Applications.

6. I consider myself an expert in the fields of FDA practice and procedure as applicable to the testing requirements for drugs and review of Investigational New Drug Applications (INDs) and New Drug Applications (NDAs).

7. I received my B.A. in Biochemistry from the University of Pennsylvania in 1984, my Ph.D. in Organic Chemistry from the University of Maryland in 1989 and my M.B.A. from the University of Maryland's RH Smith School of Business in 2002. Attached hereto as Exhibit A is my curriculum vitae, including a list of my publications for the past ten years.

8. I have carefully reviewed Chen (WO 00/42992) ("Chen").

II. U.S. STATUTORY AND REGULATORY BACKGROUND FOR TESTING DRUGS FOR POTENCY AND DOSAGE UNITS FOR UNIFORMITY

9. From a US regulatory perspective, for a drug to be approved for commercial marketing and distribution, specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product must be provided in a New Drug Application.[1] In addition, reference to the current U.S. Pharmacopeia (USP) may satisfy these requirements.

10. Section 501(b) of the Food, Drug, and Cosmetic Act (the Act) deems an official drug (i.e., a drug represented as a drug which is recognized in the U.S. Pharmacopeia) to be adulterated if it fails to conform to compendial standards of quality, strength or purity. Compendial tests or assay methods are used when determining such conformance under 501(b); the standards are stated in individual monographs as well as portions of the General Notices section of the USP/NF. Standards and test methods have been established for such characteristics as potency and content uniformity.

11. Section 501(c) of the Act deems a drug that is not recognized in the USP to be adulterated if it fails to meet the strength, purity or quality which it is represented to possess.

[1] 21 CFR 314.50(d)(1)(ii)(a)

The applicable quality standards for a drug not recognized in the USP can be determined from such sources as the labeling of the drug (or drug product), the manufacturer's written specifications, and new drug applications.

12. The current good manufacturing practice (cGMP) regulations include the minimum requirements for the preparation of drug product for administration to humans. One of the requirements is that the strength[2] of the drug (active ingredient) in the drug product must be determined for each batch of drug product manufactured for commercial distribution.[3] Strength is taken to mean content or assay of the drug.

13. Batch uniformity of the drug products is ensured with procedures that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch.[4] FDA also describes in guidance that it is expected the sampling plan for drug product is representative of the batch.[5]

14. Controls include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that the drug product conform to appropriate standards of identity, strength, quality, and purity.[6]

15. Regulatory specifications must be established to ensure that the dosage form will meet acceptable therapeutic and physicochemical standards throughout the shelf-life of the marketed product.[5] These specifications include tests for strength (content or assay) and uniformity of dosage units.

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[2] 21 CFR 210.3(b)(16)

[3] 21 CFR 211.165(a)

[4] 21 CFR 211.110(a)

[5] FDA Guideline for Submitting Documentation for the Manufacture and Controls for Drug Products, February 1987

[6] 21 CFR 211.160(b)

16. Testing to establish uniformity of dosage units is defined in the USP under the USP general chapter <905>.[7]

III. CHEN'S DISCLOSURE IS INSUFFICIENT

17. I have been asked to review Chen and render an opinion as to whether there is sufficient information contained within to allow regulatory FDA approval and commercialization of a drug product that is manufactured as described. After review of the patent in light of FDA practice and procedure, it is my opinion that there is insufficient disclosure to allow FDA to determine that a drug product as described can be manufactured for commercial distribution, manufactured in a consistent manner and meet specifications that will ensure the identity, strength, quality, purity, and potency of the drug product. In particular, Chen lacks any disclosure which would necessarily lead to the manufacture of films with uniformity of content (strength) of drug active required for FDA approval.

18. As would be required for FDA approval Chen does not disclose sufficient information that films containing drug can be produced consistently with respect to uniformity of content of the drug. No information was disclosed that demonstrated uniformity of content in the amounts of drug in individual dosage units. Chen discloses no specific test methods, and hence no test results, that could allow for the determination of the actual amount of drug (active) in individual dosage units.

19. As required for FDA approval, Chen's patent did not disclose sufficient information regarding the manufacturing process and process controls. The information disclosed by Chen would not ensure that films containing drug could be manufactured to meet specifications that ensure consistent strength.

20. Even if the information disclosed in Chen could be utilized to develop a manufacturing process for films containing drug, there is no information regarding the test methods that are necessary to determine the amount of drug in individual dosage units.

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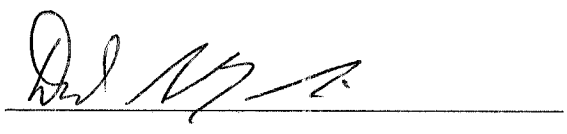
[7] USP General Chapter <905> Uniformity of Dosage Units

21. Therefore, Chen's disclosure is lacking, both explicitly and inherently, the disclosure necessary to provide for the manufacture of drug-containing films with the uniformity of content in amount of drug (active) in individual dosage units to make FDA approvable film products. It is my understanding that an inherent disclosure may not be established by probabilities or possibilities and that the mere fact that a certain thing may result from a given set of circumstances is not sufficient and that to be inherent requires that the missing disclosure is necessarily present.

22. Finally, Chen's patent discloses the release profiles of four active agents from films. See Chen, Figure 5. The release profile data presented in Figure 5 show a high degree of variability at each data point. For example, the release profile for nicotine containing film product show that the amount of nicotine released at the 5 minute and 8 minute time point can be as high as approximately 115-120%. This level of active agent is greater than the 110% level (from an expected amount of 100%) that is considered acceptable to FDA for regulatory approval of a product that purports to be manufactured consistently with acceptable content uniformity. These data indicate that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film.

23. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and. that such statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 13th day of March, 2013



David T. Lin

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **DECLARATION OF DAVID T. LIN, PH.D. UNDER 37 C.F.R. § 1.132** has been served, by first class mail, on March 13, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

EXHIBIT A

DAVID TSOCHUNG LIN

9121 Fall River Lane, Potomac, MD 20854 (301) 299-2853 dlin@bcg-usa.com

EXPERTISE

- 18+ years pharmaceutical regulatory experience.
  - 7+ years regulatory chemistry, manufacturing and controls (CMC) experience at CDER/FDA on small molecular-weight drugs, botanical drugs, peptide drugs, and protein drugs formulated in a broad range of sterile and non-sterile dosage forms.
  - 3+ years research experience at CBER/FDA.
  - 8+ years experience as regulatory CMC consultant.
- Unique combination of biologic/biotechnological and small molecular-weight drug regulatory experience, including device/drug and device/biologics combination products.
- Understanding of FDA regulatory requirements and expectations for drug development and marketing approval.
- Performed primary CMC review and assessment of drug products for treatment of reproductive and urologic disorders and diseases.
- Supervised CMC review activities in 7 CDER medical reviewing divisions including Reproductive/Urologic, Anti-viral, Dermatologic/Dental, Anti-inflammatory/ Analgesic/Ophthalmologic, Anti-infective, Special Pathogen/Immunologic, and Over-the-Counter drug products.
- Understanding of drug substance and drug product analytical method development and validation.
- Understanding of drug substance and drug product stability protocol development and stability data analysis.
- Understanding of current Good Manufacturing Practices (cGMPs)
- Experienced in chemical synthesis, small-scale and pilot-scale fermentation, biologics/ biotechnology, and protein chemistry.
- Experienced working in cross-functional teams (i.e., Pharmacology/toxicology, Clinical, Biostatistics, Biopharmaceutics, and Analytical).
- Ph.D. in Organic Chemistry; M.B.A. degree and training for managers.

EXPERIENCE

BIOLOGICS CONSULTING GROUP, INC. Alexandria, VA
January 2005 – Present
Senior Consultant

- Evaluate and provide advice on client CMC scientific and regulatory strategies for a wide range of therapeutic drug products (biologic and non-biologic) in dosage forms that include tablets, topicals, injectables, transdermals, implants, sprays, and inhalation, at all stages of product development, from pre-IND through post-NDA/BLA approval.
- Review and provide advice on IND and NDA/BLA submissions for suitability relative to FDA expectations for CMC data.
- Perform gap analysis audits for deficiencies relative to FDA expectations.
- Conduct regulatory and scientific due diligence audits for business acquisitions and licensing partnerships. Provide assessment of strengths and deficiencies.
- Represent clients in interactions with FDA.
- Prepare and write submissions to FDA, with focus on CMC sections.
- Represent client as FDA regulatory expert in legal proceedings.
- Advise clients on manufacturing contractor and vendor evaluation and selection.
- Provide management and technical oversight of contract manufacturing organizations (CMOs).
- Involved in business development to increase client base.
- Provide scientific and regulatory training and presentations at pharmaceutical/biopharmaceutical conferences.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, OFFICE OF NEW DRUG CHEMISTRY, DIVISION OF NEW DRUG CHEMISTRY III. Rockville, MD
July 2003 – December 2004
Division Director (acting) *March 2004 – December 2004*
Deputy Division Director (acting) *July 2003 – March 2004*

- Supervised 34 employees in 9 therapeutic product classes, includes 6 Team Leaders, review chemists and administrative staff. Responsible for employee work performance review and career development.
- Planned and set long-range plans and schedules for Division work. Directed and coordinated workload, and assured implementation of Division policies, goals and objectives.
- Evaluated budget and fiscal controls to manage Division functions.
- Made critical decisions and provided expert advice concerning regulatory, scientific and compliance approaches and options consistent with Office policies and objectives.
- Represented FDA in dealing and negotiating with the regulated industry, and professional and industry organizations.
- Participated as invited speaker at regulatory and scientific conferences on behalf of FDA.
- Served as the Chair of the Stability Guidance Technical Committee, Co-chair of the Conjugated Estrogens Working Group and Co-chair of the Good Review Practices Working Group.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS. Rockville, MD
October 2001-July 2003
Lead Chemist (Team Leader)

- Managed a team of 4 review chemists in 2 therapeutic product classes.
- Responsible for secondary review, consistency of CMC reviews and adherence to FDA/ONDC policies and guidances.
- Coordinated reviewers' workload of IND and NDA submissions to ensure that reviews were conducted in timely manner.
- Interacted extensively with the regulated industry to provide regulatory direction during IND drug development and NDA post-approval activities.
- Active in the development of FDA guidances for industry and internal good review practices. Served as the Chair of the Stability Guidance Technical Committee, Co-chair of the Conjugated Estrogens Working Group and Co-chair of the Good Review Practices Working Group.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS. Rockville, MD
April 1997-October 2001
Chemistry Reviewer

- Evaluated the quality of new drug products submitted to the FDA for approval.
- Integral part of a cross-functional review team responsible for evaluating the quality and effectiveness of reproductive and urologic drug products being investigated in clinical studies.
- Major contributor to committees responsible for establishing drug product quality standards and publishing guidances for pharmaceutical companies.
- Provided regulatory guidance to pharmaceutical company representatives during drug development.
- Mentored new reviewers.
- Served as computer focal point to facilitate and troubleshoot computer issues.

FOOD & DRUG ADMINISTRATION, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, LABORATORY OF PARASITIC BIOLOGY AND BIOCHEMISTRY. Bethesda, MD
February 1994-April 1997
National Research Council Fellow

- Investigated the biological role of specific proteins in the sexual differentiation of the malaria parasite. Published three research papers in peer-reviewed journals.
- Presented research data at three separate scientific conferences.
- Supervised the research projects of college students.
- Responsible for the coordination of instrument repairs and the ordering of laboratory supplies.

GENERAL ELECTRIC CO., CORPORATE RESEARCH & DEVELOPMENT, BIOLOGICAL SCIENCES LABORATORY. Schenectady, NY
July 1989-January 1994
Staff Scientist

- Developed recombinant biphenyl-metabolizing microorganisms capable of degrading environmental contaminants. Marketed this technology to the GE business units and government agencies responsible for environmental clean-up.
- Investigated the factors affecting aerobic biodegradation of indigenous PCBs in Hudson River sediment by various bacterial strains.
- Isolated and conducted mechanistic studies of the dioxygenase enzymes involved in biodegradation.
- Investigated the scientific and economic feasibility of biologically synthesizing aromatic monomers for use as a feedstock to produce biodegradable polymers.
- Supervised research projects of summer interns.
- Published research in peer-reviewed journals.
- Recruited at major East Coast universities. Interviewed and screened graduating science Ph.D. students for second round interviews at the Research Center.

UNIVERSITY OF MARYLAND, Dept. of Chemistry/Biochemistry. College Park, MD
May 1985-May 1989
Research Assistant

- Investigated mechanism of action of two bacterial enzymes, mandelate racemase and D-amino acid oxidase.
- Synthesized and tested novel halogenated aromatic hydroxy- and amino- acid analogs as potential irreversible inhibitors.
- Published research in peer-reviewed journals and co-authored one chapter in a biotechnology book. In addition, the research data was presented at two national scientific conferences.
- Served as the computer expert for the laboratory group.

EDUCATION

ROBERT H. SMITH SCHOOL OF BUSINESS. College Park, MD
University of Maryland
Master of Business Administration (MBA), *2002*
Concentration: Finance

UNIVERSITY OF MARYLAND. College Park, MD
Department of Chemistry and Biochemistry
Ph. D. -- Organic Chemistry, *1989*
Research Advisor -- Dr. John W. Kozarich

UNIVERSITY OF PENNSYLVANIA. Philadelphia, PA
Bachelor of Arts with Honors – Biochemistry, *1984*
Dean's List, Phi Lambda Upsilon Chemical Honor Society

TRAINING

- Facilitation Skills, CDER/FDA (Fall 2002)
- Six Sigma Strategy and Methods, Univ. of MD (Summer 2002)
- Group Decision-Making Techniques, CDER/FDA (Feb. 2002)
- Managing Written Communications for Team Leaders, CDER/FDA (Spring 2002)
- Organizational Behavior and Human Resources, Univ. of MD (Fall 1999)
- Management of Human Resources, Univ. of MD (Fall 1999)
- Introduction to Drug Law and Regulation, CDER/FDA (Nov. 1998)
- Basic Statistical Methods, CDER/FDA (Fall 1998)

HONORS/AWARDS

- CDER's Team Excellence Award (Nov 2004)
- FDA's Group Recognition Award (May 2004)
- CDER's Special Recognition Award (Nov 2002)
- CDER's Team Excellence Award (Nov 2002)
- OPS/ONDC Special Recognition Award (Dec 2001)
- CDER's Team Excellence Award (Nov 2000)
- OPS/ONDC Special Recognition Award (Jun 2000)
- CDER's Excellence in Mentoring Award (Nov 1999)

PRESENTATIONS

- Conducting Effective & Compliant Stability Programs for Pharmaceuticals & Biologics, "Stability Studies During Development", "Stability of Biopharmaceuticals", "Development of Specifications for Biopharmaceuticals", and "Extractables, Leachables, and Particulates – Safety Concern for Biotechnology Products", Dubai, UAE (Sep 2012).
- 4th DIA China Annual Meeting, "ICH Guidelines Q1D, Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products", and "Q1E, Evaluation of Stability Data", Shanghai, China (May 2012).
- IPA's Current Trends and Practices in Stability Testing, "Stability Testing Requirements for Biopharmaceutical Products", Montreal, Canada (Oct 2011)
- IPA's Current Trends and Practices in Stability Testing, "Stability Program for Combination Products", Montreal, Canada (Oct 2011)
- 3rd DIA China Annual Meeting, "Thinking About Comparability for Biosimilar Proteins", Beijing, China (May 2011).
- IPA's Current Trends and Practices in Stability Testing, "Stability Challenges for Combination Products", Boston, MA (May 2011).
- IPA's Current Trends and Practices in Stability Testing, "Country Specific Stability Requirements", Boston, MA (May 2011).
- Stability Programs Forum, "Stability Testing for Biotechnology/Biologic Products", Philadelphia, PA (Dec 2010).
- 11th Annual EuroTIDES/EuroPEPTIDES Conference, "Stability Considerations and Testing for Peptide-and Oligo-Based Therapeutics", Barcelona, Spain (Nov 2010).
- International Summit of China Pharmaceutical Industry, "FDA Requirements for Peptide Product Development: Considerations from Small Molecule and Biological Products", Hangzhou, China (Oct 2010).

- 7th Annual Method Validation Conference, "Ensure Method Validation Compliance through a Review of FDA Warning Letters", San Francisco, CA (Jul 2010).
- 6th Annual BioProcess International European Conference, "Extractables, Leachables and Particulates – Safety Concern for Biotechnology Products," Vienna, Austria (May 2010)
- ISPE-CSAC Meeting, "Biotechnological Drug Development and Interactions with CDER," Raleigh, NC (Oct 2009).
- Seminar on China International Bio-medicine Outsourcing Service, "Product Quality Issues with GLPs and GCPs," Hangzhou, China (Sep 2009).
- Informa Stability Testing for Biologics Conference, "Understanding Product Expiry and Shelf-Life," Prague, Czech Republic (Sep 2009).
- Informa Stability Testing for Biologics Conference Workshop, "Stability Testing Performed Over a Product Lifecycle," Prague, Czech Republic (Sep 2009).
- IVT Lab Compliance Conference, "Implement a Comprehensive and Compliant Stability Program," Philadelphia, PA (Aug 2009).
- OKBio ACCELERATE Workshop, "Product Development – Regulatory CMC Considerations," Oklahoma City, OK (Jun 2009).
- IVT Method Validation Conference, "Challenges in Understanding Impurities and Degradants for Biological/Biotechnological Products," San Francisco, CA (Oct 2008).
- IVT Method Validation Conference, "Strategies for Setting Biological Product Specifications," San Francisco, CA (Oct 2008).
- CBI 3rd Annual Stability Programs Conference, "Complex Stability Programs for Biologics," Philadelphia, PA (Jun 2008).
- IVT Lab Compliance Conference, "Stability Testing Fundamentals and Considerations in the Current Regulatory Environment," Baltimore, MD (Apr 2008).
- R&D Direction's 5th Annual Drug Development Summit, "Looking Forward in 2008: Regulatory Priorities and Considerations," Amelia Island, FL (Feb 2008).
- 2007 AAPS Annual Meeting, "Critical Stability Evaluation of Biopharmaceuticals During Clinical Development Stages," San Diego, CA (Nov 2007).
- 2007 DIA Annual Meeting, "The Impact of FDA's Quality by Design Initiative on Biologics Development," Atlanta, GA (Jun 2007).
- Institute for International Research: Formulation and Forced Degradation Strategies for Biomolecules, "Regulatory Requirements for Successful Product Development," San Diego, CA (Mar 2007).
- International Pharmaceutical Academy: Effective Management of Stability Programs, "Stability Design Considerations for Global Regulatory Filings," Toronto, Canada (Feb 2007).
- Cambridge Healthtech Institute's PepTalk: Optimizing Protein and Antibody Therapeutics, "Regulatory Considerations for the Development of Protein Therapeutic Products," San Diego, CA (Jan 2007).
- 2006 AAPS Annual Meeting, "The Impact of FDA Initiatives on the Development of Biological Products," San Antonio, TX (Nov 2006).
- SWE Enterprises: Stability Testing for the FDA Regulated Industry, "In-Use Testing of Biotechnological and Biologic Products," Boston, MA (Oct 2006).
- SWE Enterprises: Stability Testing for the FDA Regulated Industry, "Cost Efficient Design of Stability Studies," Boston, MA (Oct 2006).
- Institute for International Research: Chemistry Manufacturing & Controls, "Clarifying and Understanding ICH Guidance to Help Meet International Requirements for Submissions," Philadelphia, PA (July 2006).
- IVT Stability Testing: Implementing Effective Processes for Stability Program Development, "Cost Efficient Design of Stability Studies," San Diego, CA (June 2006).
- IVT Stability Testing: Implementing Effective Processes for Stability Program Development, "Stability Requirements for Global Regulatory Filings," San Diego, CA (June 2006).

- CBI Stability Programs: New Approaches to Test, Analyze and Document Data for Improved Program Design and Global Compliance, "In Use Testing of Biotechnological and Biological Products," Princeton, NJ (June 2006).
- IBC/TIDES: Oligonucleotide and Peptide Technology and Product Development, "Stability Considerations and Testing for Oligo- and Peptide-Based Therapeutics," Carlsbad, CA (May 2006).
- IBC Biopharm Manufacturing and Distribution Summit: Logistics for Biopharmaceutics, "Stability Studies to Support the Chain of Custody of Biotechnology Products," Reston, VA (Dec 2005).
- 2005 AAPS Annual Meeting: AAPS Short Course on Degradation and Stability in Small Molecule Active Pharmaceutical Ingredients/Stability Testing for Global Filings, "Stability Requirements for Global Regulatory Filings," Nashville, TN (Nov 2005).
- Therapeutic Strategies Against Neurodegenerative Conditions, "The Regulatory Product Development Process," Burlington, MA (Oct 2005).
- International Pharmaceutical Federation (FIP) Workshop: Harmonizing Clinical Trial GMP and Quality Requirements Across the EU and Beyond, "The US Investigational New Drug (IND) System," Noordwijk Zee, The Netherlands (Mar 2005).
- 2004 AAPS Annual Meeting, "Phase 2 and 3 IND CMC Guidance: FDA Perspective," Baltimore, MD (Nov 2004).
- 64th Annual World FIP Congress, "Clinical Trial Application Process – CMC: US FDA Perspective," New Orleans, LA (Sep 2004).
- AAPS Pharmaceutical Technologies 3rd Summer Conference: Optimizing the Global Clinical Trial Process, "IND Applications – FDA Perspective," Cherry Hill, NJ (Aug 2004).
- 2004 DIA Annual Meeting, "FDA Stability Guidance Update," Washington, DC (Jun 2004).
- DIA Meeting on CM&C/Regulatory and Technical Strategies, "Challenges and Opportunities in CMC Requirements for Phase 2-3," Bethesda, MD (Mar 2004).
- 2003 PDA Annual Meeting, "Draft FDA Stability Guidance," Atlanta, GA (Nov 2003).
- 2003 DIA Annual Meeting, "Product Quality of Non-clinical and Clinical Trial Materials," San Antonio, TX (Jun 2003).
- PARCS Meeting, "Managing CMC Requirements during IND," Irvine, CA (Apr 2003).
- PARCS Meeting, "Use of SUPAC Guidances during IND Development," Irvine, CA (Apr 2003).
- DIA Meeting on Global Chemistry, Manufacturing and Controls: Pre IND/CTX and IND/CTX Development Challenges, "FDA Perspective on Stability Testing during IND Development," Philadelphia, PA (Feb 2003).

PUBLICATIONS

- C. Syin, D. Parzy, F. Traincard, I. Boccaccio, M.G. Joshi, D.T. Lin, X.-M. Yang, K. Assemat, C. Doerig, and G. Langeley, "The H89 cAMP-dependent protein kinase inhibitor blocks *Plasmodium falciparum* development in infected erythrocytes," *Eur. J. Biochem. 268*, 4842 (2001).
- J.P. McDaniel, C. Syin, D.T. Lin, M.B. Joshi, S. Li, and N.D. Goldman, "Expression and characterization of a *Plasmodium falciparum* protein containing domains homologous to sarcalumenin and a tyrosine kinase substrate, eps15," *Int. J. Parasitol. 29*, 723 (1999).
- D.T. Lin, N.D. Goldman, and C. Syin, "Stage specific expression of a *Plasmodium falciparum* protein related to the eukaryotic mitogen-activated protein kinase," *Mol. Biochem. Parasitol. 78*, 67 (1995).
- M.R. Harkness, J.B. McDermott, D.A. Abramowicz, J.J. Salvo, W.P. Flanagan, M.L. Stephens, F.J. Mondello, R.J. May, J.H. Lobos, K.M. Carroll, M.J.Brennan, A.A. Bracco, K.M. Fish, G.L. Warner, P.R. Wilson, D.K. Dietrich, D.T. Lin, C.B. Morgan, and W.L. Gately, "*In situ* stimulation of aerobic PCB biodegradation in Hudson River sediments," *Science 259*, 503 (1993).
- D.T. Lin, V.M. Powers, L.J. Reynolds, C.P. Whitman, G.L. Kenyon and J.W. Kozarich, "Evidence for the generation of α-carboxy-α-hydroxy-*p*-xylylene from *p*-(bromomethyl)mandelate by mandelate racemase," *J. Am. Chem. Soc. 110*, 323 (1988).

- M.S. Lakshmikumaran, E. D'Ambrosio, L.A. Laimins, D.T. Lin and A.V. Furano, "Long interspersed repeat DNA(LINE) causes polymorphism at the rat insulin 1 locus," *Mol. Cell. Biol. 5*, 2197 (1985).

BOOK CHAPTER

- N.R. Schmuff and D.T. Lin, "Contents of Module 3 for an Electronic Common Technical Document Investigational New Drug Application," in Preparation and Maintenance of the IND Application in eCTD Format, W.K. Sietsema (ed.), FDAnews, Falls Church, VA, 117-134 (2008).
- N.R. Schmuff and D.T. Lin, "Chemistry, Manufacturing and Controls (CMC)," in Wiley Encyclopedia of Clinical Trials, (2008).
- J.A. Gerlt, G.L. Kenyon, J.W. Kozarich, D.T. Lin, D.C. Neidhart, G.A. Petsko, V.M. Powers, S.C. Ransom and A.Y. Tsou, "Structure-function relationships in mandelate racemase and muconate lactonizing enzyme," in Chemical Aspects of Enzyme Biotechnology, T.O. Baldwin, F.M. Raushel and A.I. Scott (eds.), Plenum, New York, NY, 9-21 (1990).

PROCEEDINGS OF MEETINGS

- D.T. Lin, N.D. Goldman, and C. Syin, "*Plasmodium falciparum* mitogen-activated protein kinase homologue contains an unusually large carboxyl terminal domain which is highly charged and homologous to merozoite surface antigens," Molecular Parasitology Meeting, Woods Hole, MA (1995).
- C. Syin, D. Lin, B. Krzyzanowska, and N.D. Goldman, "*Plasmodium* cGMP-dependent protein kinase," FDA Science Forum on Regulatory Sciences, Washington, D.C. (1994).
- J. H. Lobos, M. J. Brennan, J. T. Jackman and D. T. Lin, "*In situ* stimulation of PCB biodegradation in Hudson River sediment: III. enumeration and characterization of aerobic bacteria," ASM Meeting, New Orleans (1992).
- G.L. Kenyon, D.T. Lin, V.M. Powers, L.J. Reynolds, C.P. Whitman and J.W. Kozarich, "Generation of α-carboxy-α-hydroxy-*p*-xylylene from *p*-bromomethyl-mandelate by mandelate racemase-- further evidence for a carbanion mechanism," *FASEB J. 2*, 1329 (1988).
- D.T. Lin, V.M. Powers, L.J. Reynolds, C.P. Whitman, G.L. Kenyon and J.W. Kozarich, "Formation of *p*-xylylene species in the mandelate racemase catalyzed reaction of *p*-(bromomethyl)mandelate," *Fed. Proc. 46*, 2042 (1987)

Electronic Patent Application Fee Transmittal

Application Number:	95002170
Filing Date:	10-Sep-2012
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Filer:	Stephen J. Brown
Attorney Docket Number:	117744-00023

Filed as Large Entity

inter partes reexam Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Request for Inter Reexamination	1813	1	0	0
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**0**

Electronic Acknowledgement Receipt

EFS ID:	15215642
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Stephen J. Brown
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	13-MAR-2013
Filing Date:	10-SEP-2012
Time Stamp:	23:15:29
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response after non-final action-owner timely	FINAL080REPLYTOOA.pdf	653223 8fc8f0e3f49f5bcf46d57581b8d7765071574da1	no	86

Warnings:	
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2	Response after non-final action-owner timely	Declarations.pdf	9066001 fa617de5bca4c8f01850c9912482145029fb095c	no	26
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30246 0f8873435e13b90bd937cd3b03eb008e2ed9e7c7	no	2
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			Total Files Size (in bytes):	9749470	

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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New International Application Filed with the USPTO as a Receiving Office

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

23869 7590 02/26/2013

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
DIAMOND, ALAN D	
ART UNIT	PAPER NUMBER
3991	
MAIL DATE	DELIVERY MODE
02/26/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

NOTICE RE DEFECTIVE PAPER IN INTER PARTES REEXAMINATION	Control No.	Patent Under Reexamination
	95/002,170	7897080
	Examiner	Art Unit
	Alan Diamond	3991

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

1. ☐ No proof of service is included with the paper filed by ☐ patent owner ☐ requester on _____. 37 CFR 1.248 and 1.903. Proof of service is required within a time period of 30-days or one month from the date of this letter, whichever is longer. Failure to serve the paper may result in the paper being refused consideration. If the failure to comply with this requirement results in a patent owner failure to file a timely and appropriate response to any Office action, the prosecution of the reexamination proceeding will be terminated under 37 CFR 1.957(b) or limited under 37 CFR 1.957(c) (as is appropriate for the case).

2. ☐ The paper filed on _____ by the ☐ patent owner ☐ requester is unsigned. A duplicate paper or ratification, properly signed, is required within a time period of 30-days or one month from the date of this letter, whichever is longer. Failure to comply with this requirement will result in the paper not being considered. If the failure to comply results in a patent owner failure to file a timely and appropriate response to any Office action, the prosecution of the reexamination proceeding will be terminated under 37 CFR 1.957(b) or limited under 37 CFR 1.957(c) (as is appropriate for the case).

3. ☐ The paper filed on _____ by the ☐ patent owner ☐ requester is signed by _____ who is not of record. A ratification or a new power of attorney with a ratification, or a duplicate paper signed by a person of record, is required within a time period of 30-days or one month from the date of this letter, whichever is longer. Failure to comply with this requirement will result in the paper not being considered. If the failure to comply results in a patent owner failure to file a timely and appropriate response to any Office action, the prosecution of the reexamination proceeding will be terminated under 37 CFR 1.957(b) or limited under 37 CFR 1.957(c) (as is appropriate for the case).

4. ☐ The amendment filed by patent owner on _____, does not comply with 37 CFR 1.530. Patent owner is given a time period of 30-days or one month from the date of this letter, whichever is longer, to correct this informality, or the prosecution of the reexamination proceeding will be terminated under 37 CFR 1.957(b) or limited under 37 CFR 1.957(c) (as is appropriate for the case). The amendment will not be entered, although the argument the rein will be considered as it applies to the proceeding without the amendment should the prosecution be limited under 37 CFR 1.957(c).

5. ☐ The amendment filed by patent owner on _____, does not comply with 37 CFR ☐1.20(c)(3) and/or ☐1.20(c)(4), as to excess claim fees. Patent owner is given a time period of 30-days or one month from the date of this letter, whichever is longer, to correct this fee deficiency, or the prosecution of the reexamination proceeding will be terminated under 37 CFR 1.957(b) or limited under 37 CFR 1.957(c) (as is appropriate for the case), to effect the "abandonment" set forth in 37 CFR 1.20(c)(5).

6. ☒ Other: See attached page.

/Alan Diamond/
Patent Reexamination Specialist
Central Reexamination Unit 3991

NOTE: PATENT OWNER EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.956. NO EXTENSION OF TIME IS PERMITTED FOR THIRD PARTY REQUESTER. 35 U.S.C. § 314(b)(2).

All correspondence relating to this *inter partes* reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this Office action.

With respect to item No. 6, the response filed by patent owner on 01/29/2013 does not comply with 37 CFR 1.943, which requires that responses by patent owner shall not exceed 50 pages, excluding amendments, appendices of claims and reference materials such as prior art references. In particular, the total page count is 56 pages, which includes 52 pages of Remarks (i.e., pages 79-130) and pages 1-4 of the Declaration by Gerald Fuller (Fuller Declaration). The Fuller Declaration is directed to Dr. Fuller's opinion and thus, is counted towards the page count. The Declaration of B. Arlie Bogue is not counted towards the 50-page limit since it is directed to experimental results. Patent owner is required to exercise one of the following two options: (A) submit a re-drafted response that does not exceed the page limit set by 37 CFR 1.943; or (B) file a copy of the supplemental response with pages redacted to satisfy the 37 CFR 1.943 page limit requirement. Patent Owner is given a time period of 15-DAYS from the date of this letter to file the response. If no response is received, the improper patent owner submission will NOT be considered. See MPEP 2667(I)(A)(2).

Transmittal of Communication to Third Party Requester *Inter Partes* Reexamination	Control No.	Patent Under Reexamination	
	95/002,170	7897080	
	Examiner	Art Unit	
	Alan Diamond	3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

Danielle L. Herritt
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above-identified reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the *inter partes* reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an *ex parte* reexamination has been merged with the *inter partes* reexamination, no responsive submission by any *ex parte* third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

PTO/SB/08a (03-08)
Approved for use through 07/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	95002170
Filing Date	2012-09-10
First Named Inventor	Robert K. Yang
Art Unit	3991
Examiner Name	Diamond, Alan D.
Attorney Docket Number	1199-26 RCE/CON/REX

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4515162		1985-05-07	Yamamoto et al	
	2	4517173		1985-05-14	Kizawa et al	
	3	4529601		1985-07-16	Broberg et al	
	4	4529748		1985-07-16	Wienecke	
	5	4562020		1985-12-31	Hijiya et al	
	6	4569837		1986-02-11	Suzuki et al	
	7	4593053		1986-06-03	Jevne et al	
	8	4608249		1986-08-26	Otsuka et al	

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	First Named Inventor	Robert K. Yang
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	Attorney Docket Number	1199-26 RCE/CON/REX

	9	4615697		1986-10-07	Robinson	
	10	4623394		1986-11-18	Nakamura et al	
	11	4652060		1987-03-24	Miyake	
	12	4659714		1987-04-21	Watt-Smith	
	13	4675009		1987-06-23	Hymes et al	
	14	4695465		1987-09-22	Kigasawa et al	
	15	4704119		1987-11-03	Shaw et al	
	16	4713239		1987-12-15	Babaian et al	
	17	4713243		1987-12-15	Schiraldi et al	
	18	4722761		1988-02-02	Cartmell et al	
	19	4740365		1988-04-26	Yukimatsu et al	

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	20	5028632		1991-07-02	Fuisz	
	21	4748022		1988-05-31	Busciglio	
	22	4765983		1988-08-23	Takayanagi et al	
	23	4772470		1988-09-20	Inoue et al	
	24	4777046		1988-10-11	Iwakura et al	
	25	4789667		1988-12-06	Makino et al	
	26	4849246		1989-07-18	Schmidt	
	27	4860754		1989-08-29	Sharik et al	
	28	RE33093		1989-10-17	Schiraldi et al	
	29	4876092		1989-10-24	Mizobuchi et al	
	30	4876970		1989-10-31	Bolduc	

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	31	4888354		1989-12-19	Chang et al	
	32	4894232		1990-01-16	Reul et al	
	33	4900552		1990-02-13	Sanvordeker et al	
	34	4900554		1990-02-13	Yanagibashi et al	
	35	4900556		1990-02-13	Wheatley et al	
	36	4910247		1990-03-20	Haldar et al	
	37	4915950		1990-04-10	Miranda et al	
	38	4925670		1990-05-15	Schmidt	
	39	4927634		1990-05-22	Sorrentino et al	
	40	4927636		1990-05-22	Hijiya et al	
	41	4937078		1990-06-26	Mezei et al	

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	42	4940587		1990-07-10	Jenkins et al	
	43	4948580		1990-08-14	Browning	
	44	4958580		1990-09-25	Asaba et al	
	45	4978531		1990-12-18	Yamazaki et al	
	46	4981693		1991-01-01	Higashi et al	
	47	4981875		1991-01-01	Leusner et al	
	48	5023082		1991-06-11	Friedman et al	
	49	5024701		1991-06-18	Desmarais	
	50	6488963		2002-12-03	McGinity et al.	

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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
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	Attorney Docket Number	1199-26 RCE/CON/REX

	1	20050037055		2005-02-17	Yang et al.	

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	0191721	WO	A2	2001-12-06	A.E. Staley Manufacturing Co.		☐
	2	0170194	WO	A1	2001-09-27	Warner-Lambert Company		☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
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	Filing Date	2012-09-10
	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Daniel A. Scola, Jr., Reg. No. 29,855/	Date (YYYY-MM-DD)	2013-01-29
Name/Print	Daniel A. Scola, Jr.	Registration Number	29,855

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	14825739
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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
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Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Madam:

This Information Disclosure Statement is being submitted pursuant to 37 C.F.R. 1.98, and identifies a number of patents and publication that may be considered relevant. The Patent Holder makes no representation as to the relevance of these documents, but wishes to make these references of record in this reexamination. Consideration of the references recited herein is requested.

If any fee is due with this submission, the Commission is authorized to charge any such fee to Deposit Account No. 08-2461. Should the Examiner have any questions regarding this submission, the undersigned would be pleased to address them.

Respectfully submitted,

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CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **INFORMATION DISCLOSURE STATEMENT** has been served, by first class mail, on January 29, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

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(54) Title: FAST DISSOLVING ORALLY CONSUMABLE FILMS CONTAINING AN ION EXCHANGE RESIN AS A TASTE MASKING AGENT

(57) Abstract: Physiologically acceptable films, including edible films, are disclosed. The films include a water soluble film-forming polymer, such as pullulan, and a taste masked pharmaceutically active agent, such as dextromethorphan. The taste masking agent is preferably a sulfonated polymer ion exchange resin comprising polystyrene cross-linked with divinylbenzene, such as AMBERLITE. Methods for producing the films are also disclosed.

FAST DISSOLVING ORALLY CONSUMABLE FILMS CONTAINING AN ION EXCHANGE RESIN AS A TASTE MASKING AGENT

SPECIFICATION

FIELD OF THE INVENTION

This invention relates to fast dissolving orally consumable films containing an agent to mask the taste of a pharmaceutically active agent therein, and more specifically to such films containing an ion exchange resin as the taste masking agent.

BACKGROUND OF THE INVENTION

It has been known to administer pharmaceutically active agents in an edible film vehicle.

For example, WO 99/17753 discloses rapidly dissolving films for delivery of drugs to be adsorbed in the digestive tract.

WO 98/26780 discloses a flat, foil, paper or wafer type presentation for the application and release of active substances in the buccal cavity. The specific active ingredient disclosed in WO 98/26780 is buprenorphine.

WO 98/20862 discloses a film for use in the oral cavity that can contain a cosmetic or pharmaceutical active substance.

WO 98/26763 discloses a flat, foil, paper or wafer like presentation for release of active substances into the buccal cavity. The particular active disclosed is apomorphine.

U.S. Patent Application No. 09/395,104 also discloses the delivery of pharmaceutical agents in a edible film vehicle.

U.S. Patent No. 5,411,945 to Ozaki et al. discloses a pullulan binder and products produced therewith, including edible films (Example B-2). The products can include a variety of ingredients in addition to pullulan, such as other polysaccharides, antibacterial agents, flavor-imparting agents and pharmaceutically active substances (column 4, lines 5-15).

U.S. Patent No. 3,784,390 Hijiya et al. discloses pullulan films and their use in coating and packing materials for foods, pharmaceuticals and other oxygen sensitive materials. All of the examples in this patent teach mixing pullulan in hot water.

It has also been known to combine ion exchange resins with pharmaceutically active agents to provide sustained release formulations.

For example, U.S. Patent No. 6,001,392 to Wen et al. discloses a controlled-release syrup suspension for oral administration containing dextromethorphan adsorbed to a polystyrene sulfonate ion exchange resin. Pharmaceutical films are not disclosed.

U.S. Patent No. 5,980,882 to Eichman discloses a method for improving the stability of a pharmaceutical composition that contains a drug-resin complex, comprising adding a chelating agent in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex. Although Eichman teaches that complexing a drug with an ion exchange resin can mask the taste of the drug. Pharmaceutical films are not disclosed.

The inventors are not aware of any suggestion in the published art that ion exchange resins can act as taste masking agents in a fast dissolving orally consumable film. Accordingly, an object of this invention is to provide fast dissolving orally consumable films containing an ion exchange resin to mask the taste of a pharmaceutically active agent therein.

All references cited herein are incorporated herein by reference in their entireties.

SUMMARY OF THE INVENTION

The invention provides a consumable film adapted to adhere to and dissolve in a mouth of a consumer, wherein the film comprises at least one water soluble polymer, at least one pharmaceutically active agent and at least one taste masking agent.

Also provided is a method for preparing the consumable film of the invention, comprising:

dissolving water-soluble ingredients in water to provide an aqueous solution;

mixing at least one water soluble film former and at least one stabilizing agent to provide a film-forming mixture;

combining the film-forming mixture and the aqueous solution to provide a hydrated polymer gel;

mixing oils to form an oil mixture;

adding the oil mixture to the hydrated polymer gel and mixing to provide a uniform gel;

casting the uniform gel on a substrate; and

drying the cast gel to provide the film.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention provides a physiologically acceptable film that is particularly well adapted to adhere to and dissolve in a mouth of a consumer to deliver a pharmaceutically active agent. Preferred films according to the invention comprise a pharmaceutically active agent, an ion exchange resin, a film-forming agent, and at least one of the following additional ingredients: water, antimicrobial agents, plasticizing agents, flavoring agents, saliva stimulating agents, cooling agents, surfactants, stabilizing agents, emulsifying agents, thickening agents, binding agents, coloring agents, sweeteners, fragrances, triglycerides, preservatives, polyethylene oxides, propylene glycol, and the like.

The expression "physiologically acceptable" as used herein is intended to encompass compounds, which upon administration to a patient, are adequately tolerated without causing undue negative side effects. The expression encompasses edible compounds.

The expression "pharmaceutically active agents" as used herein is intended to encompass agents other than foods, which promote a structural and/or functional change in and/or on bodies to which they have been administered. These agents are not particularly limited; however, they should be physiologically acceptable and compatible with the film. Suitable pharmaceutically active agents include, but are not limited to:

A. antimicrobial agents, such as triclosan, cetyl pyridium chloride, domiphen bromide, quaternary ammonium salts, zinc compounds, sanguinarine, fluorides, alexidine, octonidine, EDTA, and the like;

B. non-steroidal anti-inflammatory drugs, such as aspirin, acetaminophen, ibuprofen, ketoprofen, diflunisal, fenoprofen calcium, naproxen, tolmetin sodium, indomethacin, and the like;

C. anti-tussives, such as benzonatate, caramiphen edisylate, menthol, dextromethorphan hydrobromide, chlophedianol hydrochloride, and the like;

D. decongestants, such as pseudoephedrine hydrochloride, phenylepherine, phenylpropanolamine, pseudoephedrine sulfate, and the like;

E. anti-histamines, such as brompheniramine maleate, chlorpheniramine maleate, carbinoxamine maleate, clemastine fumarate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, diphenylpyraline hydrochloride, azatadine meleate, diphenhydramine citrate, doxylamine succinate, promethazine hydrochloride, pyrilamine maleate, tripelennamine citrate, triprolidine hydrochloride, acrivastine, loratadine, brompheniramine, dexbrompheniramine, and the like;

F. expectorants, such as guaifenesin, ipecac, potassium iodide, terpin hydrate, and the like;

G. anti-diarrheals, such a loperamide, and the like;

H. H_2-antagonists, such as famotidine, ranitidine, and the like;

I. proton pump inhibitors, such as omeprazole, lansoprazole, and the like;

J. general nonselective CNS depressants, such as aliphatic alcohols, barbiturates and the like;

K. general nonselective CNS stimulants such as caffeine, nicotine, strychnine, picrotoxin, pentylenetetrazol and the like;

L. drugs that selectively modify CNS function, such as phenyhydantoin, phenobarbital, primidone, carbamazepine, ethosuximide, methsuximide, phensuximide, trimethadione, diazepam, benzodiazepines, phenacemide, pheneturide, acetazolamide, sulthiame, bromide, and the like;

M. antiparkinsonism drugs such as levodopa, amantadine and the like;

N. narcotic-analgesics such as morphine, heroin, hydromorphone, metopon, oxymorphone, levorphanol, codeine, hydrocodone, xycodone, nalorphine, naloxone, naltrexone and the like;

O. analgesic-antipyretics such as salycilates, phenylbutazone, indomethacin, phenacetin and the like; and

P. psychopharmacological drugs such as chlorpromazine, methotrimeprazine, haloperidol, clozapine, reserpine, imipramine, tranylcypromine, phenelzine, lithium and the like.

The amount of pharmaceutically active agent that can be used in the rapidly dissolving films, according to the present invention, is dependent upon the dose needed to provide an effective amount of the pharmaceutically active agent. Examples of doses for specific pharmaceutically active agents that can be delivered per one strip of rapidly dissolving oral film are reviewed in Table A.

TABLE A

PHARMACEUTICALLY ACTIVE AGENT	PREFERRED DOSE
Chlorpheniramine Maleate	4 mg.
Brompheniramine Maleate	4 mg.
Dexchlorpheniramine	2 mg.
Dexbrompheniramine	2 mg.
Triprolidine Hydrochloride	2.5 mg.
Acrivastine	8 mg.
Azatadine Maleate	1 mg.
Loratidine	10 mg.
Phenylephrine Hydrochloride	10 mg.
Dextromethorphan Hydrobromide	10-30 mg.
Ketoprofen	12.5-25 mg.
Sumatriptan Succinate	35 - 70 mg.
Zolmitriptan	2.5 mg.
Loperamide	2 mg.
Famotidine	10 mg.
Nicotine	2 mg.
Diphenhydramine Hydrochloride	12.5-25 mg.
Pseudoephedrine Hydrochloride	30 mg.

Ion exchange resins preferred for use in the films of the invention are water-insoluble and consist of a pharmacologically inert organic or inorganic matrix containing covalently bound functional groups that are ionic or capable of being ionized under the appropriate conditions of pH. The organic matrix may be synthetic (e.g., polymers or copolymers of acrylic acid, methacrylic acid, sulfonated styrene, sulfonated divinylbenzene), or partially synthetic (e.g., modified cellulose and dextrans). The inorganic matrix can also be, e.g., silica gel modified by the addition of ionic groups. The covalently bound ionic groups may be strongly acidic (e.g., sulfonic acid), weakly acidic (e.g., carboxylic acid), strongly basic (e.g., quaternary ammonium), weakly basic (e.g., primary amine), or a combination of acidic and basic groups. In general, those types of ion exchangers suitable for use in ion exchange chromatography and for such applications as deionization of water are suitable for use in these

controlled release drug preparations. Such ion exchangers are described by H. F. Walton in "Principles of Ion Exchange" (pp. 312-343). The ion exchange resins useful in the present invention have exchange capacities below about 6 milliequivalents per gram (meq/g) and preferably below about 5.5 meq/g.

The resin is crosslinked with a crosslinking agent selected from difunctional compounds capable of crosslinking polystyrenes; these are commonly known in the art. Preferably, the crosslinking agent is a divinyl or polyvinyl compound. Most preferably the crosslinking agent is divinylbenzene. The resin is crosslinked to an extent of about 3 to about 20%, preferably about 4 to about 16%, more preferably about 6 to about 10%, and most preferably about 8% by weight based on the total resin. The resin is crosslinked with the crosslinking agent by means well known in the art.

The size of the ion exchange resins should preferably fall within the range of about 20 to about 200 micrometers. Particle sizes substantially below the lower limit are difficult to handle in all steps of the processing. Particle sizes substantially above the upper limit, e.g., commercially available ion exchange resins having a spherical shape and diameters up to about 1000 micrometers, are gritty in liquid dosage forms and have a greater tendency to fracture when subjected to drying-hydrating cycles.

Representative resins useful in this invention include AMBERLITE IRP-69 (obtained from Rohm and Haas) and Dow XYS-40010.00 (obtained from The Dow Chemical Company). Both are sulfonated polymers composed of polystyrene cross-linked with 8% of divinylbenzene, with an ion exchange capacity of about 4.5 to 5.5 meq/g of dry resin (H+-form). Their essential difference is in physical form. AMBERLITE IRP-69 comprises irregularly-shaped particles with a size range of 47 to 149 micrometers, produced by milling the parent, large-sized spheres of AMBERLITE IRP-120. The Dow XYS-40010.00 product comprises spherical particles with a size

range of 45 to 150 micrometers. Another useful exchange resin, Dow XYS-40013.00, is a polymer composed of polystyrene cross-linked with 8% of divinylbenzene and functionalized with a quaternary ammonium group; its exchange capacity is normally within the range of approximately 3 to 4 meq/g of dry resin.

The most preferred resin is AMBERLITE IRP-69. However, in less preferred embodiments, the taste masking agent need not be an ion exchange resin. In these embodiments, the taste masking agent can be, e.g., magnesium trisilicate. See, e.g., U.S. Patents Nos. 4,650,663 and 4,581,232 to Peters et al. Taste can also be masked by polymers, such as EUDRAGIT E (Rohm and Haas), and/or cellulosics, such as ethylcellulose, and the like.

The film-forming agent used in the films according to the present invention can be selected from the group consisting of pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof. A preferred film former is pullulan, in amounts ranging from about 0.01 to about 99 wt%, preferably about 30 to about 80 wt%, more preferably from about 45 to about 70 wt% of the film and even more preferably from about 60 to about 65 wt% of the film.

Unless specified otherwise, the term "wt%" as used herein with reference to the final product (i.e., the film, as opposed to the formulation used to create it), denotes the percentage of the total dry weight contributed by the subject ingredient. This theoretical value can differ from the experimental

value, because in practice, the film typically retains some of the water and/or ethanol used in preparation.

In embodiments containing relatively high oil content, it is preferable to avoid substantial amounts of humectant in the film (and more preferable to have no humectant in the film), so as to avoid producing an overly moist, self-adhering film. In particular, it is preferred to formulate high oil content films with a plasticizing agent other than glycerin, which is also a humectant, and with a sweetener other than sorbitol, which is a mild humectant.

Saliva stimulating agents can also be added to the films according to the present invention. Useful saliva stimulating agents are those disclosed in U.S. Patent No. 4,820,506. Saliva stimulating agents include food acids such as citric, lactic, malic, succinic, ascorbic, adipic, fumaric and tartaric acids. Preferred food acids are citric, malic and ascorbic acids. The amount of saliva stimulating agents in the film is from about 0.01 to about 12 wt%, preferably about 1 wt% to about 10 wt%, even more preferably about 2.5 wt% to about 6 wt%.

Preferred plasticizing agents include triacetin in amounts ranging from about 0 to about 20 wt%, preferably about 0 to about 2 wt%. Other suitable plasticizing agents include monoacetin and diacetin.

Preferred cooling agents include monomenthyl succinate, in amounts ranging from about 0.001 to about 2.0 wt%, preferably about 0.2 to about 0.4 wt%. A monomenthyl succinate containing cooling agent is available from Mane, Inc. Other suitable cooling agents include WS3, WS23, Ultracool II and the like.

Preferred surfactants include mono and diglycerides of fatty acids and polyoxyethylene sorbitol esters, such as, Atmos 300 and Polysorbate 80. The surfactant can be added in amounts ranging from about 0.5 to about 15 wt%, preferably about 1 to about 5 wt% of the film. Other suitable surfactants

include pluronic acid, sodium lauryl sulfate, and the like.

Preferred stabilizing agents include xanthan gum, locust bean gum and carrageenan, in amounts ranging from about 0 to about 10 wt%, preferably about 0.1 to about 2 wt% of the film. Other suitable stabilizing agents include guar gum and the like.

Preferred emulsifying agents include triethanolamine stearate, quaternary ammonium compounds, acacia, gelatin, lecithin, bentonite, veegum, and the like, in amounts ranging from about 0 to about 5 wt%, preferably about 0.01 to about 0.7 wt% of the film.

Preferred thickening agents include methylcellulose, carboxyl methylcellulose, and the like, in amounts ranging from about 0 to about 20 wt%, preferably about 0.01 to about 5 wt%.

Preferred binding agents include starch, in amounts ranging from about 0 to about 10 wt%, preferably about 0.01 to about 2 wt% of the film.

Suitable sweeteners that can be included are those well known in the art, including both natural and artificial sweeteners. Suitable sweeteners include, e.g.:

A. water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose (dextrose), mannose, galactose, fructose (levulose), sucrose (sugar), maltose, invert sugar (a mixture of fructose and glucose derived from sucrose), partially hydrolyzed starch, corn syrup solids, dihydrochalcones, monellin, steviosides, and glycyrrhizin;

B. water-soluble artificial sweeteners such as the soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2, 2-dioxide, the potassium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide (acesulfame-K), the free acid form of saccharin,

and the like;

C. dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, such as L-aspartyl-L-phenylalanine methyl ester (aspartame) and materials described in U.S. Pat. No. 3,492,131, L- alpha-aspartyl-N-(2,2,4,4--tetramethyl-3-thietanyl)-D-alaninamide hydrate, methyl esters of L-aspartyl-L-phenylglycerin and L-aspartyl-L-2,5,dihydrophenyl-glycine, L-aspartyl-2,5-dihydro- L-phenylalanine, L-aspartyl-L-(1-cyclohexyen)-alanine, and the like;

D. water-soluble sweeteners derived from naturally occurring water-soluble sweeteners, such as a chlorinated derivative of ordinary sugar (sucrose), known, for example, under the product description of sucralose; and

E. protein based sweeteners such as thaumatoccous danielli (Thaumatin I and II).

In general, an effective amount of auxiliary sweetener is utilized to provide the level of sweetness desired for a particular composition, and this amount will vary with the sweetener selected. This amount will normally be 0.01 % to about 10 % by weight of the composition when using an easily extractable sweetener. The water-soluble sweeteners described in category A above, are usually used in amounts of about 0.01 to about 10 wt%, and preferably in amounts of about 2 to about 5 wt%. Some of the sweeteners in category A (e.g., glycyrrhizin) can be used in amounts set forth for categories B-E below due to the sweeteners' known sweetening ability. In contrast, the sweeteners described in categories B-E are generally used in amounts of about 0.01 to about 10 wt%, with about 2 to about 8 wt% being preferred and about 3 to about 6 wt% being most preferred. These amounts may be used to achieve a desired level of sweetness independent from the flavor level achieved from any optional flavor oils used. Of course, sweeteners need not be added to films intended for non-oral administration.

The flavorings that can be used include those known to the skilled artisan, such as natural and artificial flavors. These flavorings may be chosen from synthetic flavor oils and flavoring aromatics, and/or oils, oleo resins and extracts derived from plants, leaves, flowers, fruits and so forth, and combinations thereof. Representative flavor oils include: spearmint oil, cinnamon oil, peppermint oil, clove oil, bay oil, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, and oil of bitter almonds. Also useful are artificial, natural or synthetic fruit flavors such as vanilla, chocolate, coffee, cocoa and citrus oil, including lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. These flavorings can be used individually or in admixture. Commonly used flavors include mints such as peppermint, artificial vanilla, cinnamon derivatives, and various fruit flavors, whether employed individually or in admixture. Flavorings such as aldehydes and esters including cinnamyl acetate, cinnamaldehyde, citral, diethylacetal, dihydrocarvyl acetate, eugenyl formate, p-methylanisole, and so forth may also be used. Generally, any flavoring or food additive, such as those described in Chemicals Used in Food Processing, publication 1274 by the National Academy of Sciences, pages 63-258, may be used. Further examples of aldehyde flavorings include, but are not limited to acetaldehyde (apple); benzaldehyde (cherry, almond); cinnamic aldehyde (cinnamon); citral, i.e., alpha citral (lemon, lime); neral, i.e. beta citral (lemon, lime); decanal (orange, lemon); ethyl vanillin (vanilla, cream); heliotropine, i.e., piperonal (vanilla, cream); vanillin (vanilla, cream); alpha-amyl cinnamaldehyde (spicy fruity flavors); butyraldehyde (butter, cheese); valeraldehyde (butter, cheese); citronellal (modifies, many types); decanal (citrus fruits); aldehyde C-8 (citrus fruits); aldehyde C-9 (citrus fruits); aldehyde C-12 (citrus fruits); 2-ethyl butyraldehyde (berry fruits); hexenal, i.e. trans-2 (berry fruits); tolyl aldehyde (cherry, almond); veratraldehyde (vanilla);

2,6-dimethyl- 5-heptenal, i.e. melonal (melon); 2-6-dimethyloctanal (green fruit); and 2-dodecenal (citrus, mandarin); cherry; grape; mixtures thereof; and the like.

The amount of flavoring employed is normally a matter of preference subject to such factors as flavor type, individual flavor, and strength desired. Thus, the amount may be varied in order to obtain the result desired in the final product. Such variations are within the capabilities of those skilled in the art without the need for undue experimentation. In general, amounts of about 0.1 to about 30 wt% are useable with amounts of about 2 to about 25 wt% being preferred and amounts from about 8 to about 10 wt% are more preferred.

The compositions of this invention can also contain coloring agents or colorants. The coloring agents are used in amounts effective to produce the desired color. The coloring agents useful in the present invention, include pigments such as titanium dioxide, which may be incorporated in amounts of up to about 5 wt%, and preferably less than about 1 wt%. Colorants can also include natural food colors and dyes suitable for food, drug and cosmetic applications. These colorants are known as FD&C dyes and lakes. The materials acceptable for the foregoing spectrum of use are preferably water-soluble, and include FD&C Blue No. 2, which is the disodium salt of 5,5-indigotindisulfonic acid. Similarly, the dye known as Green No. 3 comprises a triphenylmethane dye and is the monosodium salt of 4-[4-N-ethyl-p-sulfobenzylamino) diphenyl-methylene]-[1-N-ethyl-N-p-sulfonium benzyl)-2,5-cyclo-hexadienimine]. A full recitation of all FD&C and D&C dyes and their corresponding chemical structures may be found in the Kirk-Othmer Encyclopedia of Chemical Technology, Volume 5, Pages 857-884, which text is accordingly incorporated herein by reference.

The films can also include a triglyceride. Examples of triglycerides include vegetable oils such as corn oil, sunflower oil, peanut oil, olive oil,

canola oil, soybean oil and mixtures thereof. A preferred triglyceride is olive oil. The triglyceride is added to the film in amounts from about 0.1 wt% to about 12 wt%, preferably in a range from about 0.5 wt% to about 9 wt%, of the film.

The films can include a preservative in amounts from about 0.001 wt% to about 5 wt%, preferably from about 0.01 wt% to about 1 wt% of the film. Preferred preservatives include sodium benzoate and potassium sorbate. Other suitable preservatives include, but are not limited to, salts of edetate (also known as salts of ethylenediaminetetraacetic acid, or EDTA, such as disodium EDTA) and parabens (e.g., methyl, ethyl, propyl or butyl-hydroxybenzoates, etc.) or sorbic acid. The preservatives listed above are exemplary, but each preservative must be evaluated on an empirical basis, in each formulation, to assure the compatibility and efficacy of the preservative. Methods for evaluating the efficacy of preservatives in pharmaceutical formulations are known to those skilled in the art.

The films can also include a polyethylene oxide compound. The molecular weight of the polyethylene oxide compound ranges from about 50,000 to about 6,000,000. A preferred polyethylene oxide compound is N-10 available from Union Carbide Corporation. The polyethylene oxide compound is added in amounts from about 0.1 wt% to about 5 wt%, preferably from about 0.2 wt% to about 4.0 wt% of the film.

The films can also include propylene glycol. The propylene glycol is added in amounts from about 1 wt% to about 20 wt%, preferably from about 5 wt% to about 15 wt% of the film.

Methods for preparing films according to the invention are capable of encapsulating the oil ingredients within the film-forming matrix and maintaining the integrity of the film, even when the film contains oils in amounts of 10 wt% or more.

In certain methods for preparing films according to the invention, the film-forming ingredients are mixed and hydrated with water separately from the water-soluble ingredients, which are mixed in aqueous solution separately from the organic ingredients and surfactants. In these methods, the final formulation is preferably produced by mixing the film-forming phase with the aqueous phase, then mixing in the organic phase, which includes surfactants, such as Polysorbate 80 and Atmos 300. This mass is mixed until emulsified. In other embodiments, the aqueous and film forming phases are combined into a single phase by dissolving the water soluble ingredients in the water and then adding the gums to hydrate. The organic phase is then added to this single aqueous phase.

The resulting formulation is cast on a suitable substrate and dried to form a film. The film is preferably air-dried or dried under warm air and cut to a desired dimension, packaged and stored. The film can contain from about 0.1% to about 10 wt% moisture, preferably from about 3 % to about 8 wt% moisture, even more preferably from about 4 to about 7 wt% moisture.

The film-forming phase can include pullulan and stabilizing agents such as xanthan gum, locust bean gum and carrageenan. These ingredients are mixed and then hydrated in water for about 30 to about 48 hours to form a gel. The water is preferably heated to a temperature of about 25 to about 45°C to promote hydration. The amount of water is about 40 to 80% of the gel. The resulting hydrated gel is then chilled to a temperature of about 20 to about 30°C for about 1 to about 48 hours. The water is preferably deionized.

In preferred embodiments, the aqueous phase includes water heated to a temperature of about 60 to 90°C, preferably 70 to 80°C, and ingredients such as the pharmaceutically active agent, ion exchange resin (or other masking agent), coloring agent, preservative and sweetener. The water is preferably deionized and the amount of water used is about 5 to about 80 wt% of the final gel

mixture.

The pharmaceutically active agent is sorbed to the ion exchange resin (or other masking agent) without separating ion exchanged pharmaceutically active agent from unexchanged agent and counter ion salts.

Adsorption of the pharmaceutically active agent onto the ion exchange resin particles to form the pharmaceutically active agent/resin complex is a well known technique as shown in U.S. Pat. Nos. 2,990,332 and 4,221,778. In general, the pharmaceutically active agent is mixed with an aqueous suspension of the resin, and in less preferred embodiments, the complex is then washed and dried. Adsorption of pharmaceutically active agent onto the resin may be detected by measuring a change in the pH of the reaction medium, or by measuring a change in concentration of sodium or pharmaceutically active agent.

Binding of pharmaceutically active agent to resin can be accomplished according to four general reactions. In the case of a basic pharmaceutically active agent, these are: (a) resin (Na-form) plus pharmaceutically active agent (salt form); (b) resin (Na-form) plus pharmaceutically active agent (as free base); (c) resin (H-form) plus pharmaceutically active agent (salt form); and (d) resin (H-form) plus pharmaceutically active agent (as free base). All of these reactions except (d) have cationic byproducts, by competing with the cationic pharmaceutically active agent for binding sites on the resin, reduce the amount of pharmaceutically active agent bound at equilibrium. For basic pharmaceutically active agents, stoichiometric binding of pharmaceutically active agent to resin is accomplished only through reaction (d).

Four analogous binding reactions can be carried out for binding an acidic pharmaceutically active agent to an anion exchange resin. These are: (a) resin (Cl--form) plus pharmaceutically active agent (salt form); (b) resin (Cl--form) plus pharmaceutically active agent (as free acid); (c) resin

(OH--form) plus pharmaceutically active agent (salt form); and (d) resin (OH--form) plus pharmaceutically active agent (as free acid). All of these reactions except (d) have ionic by-products and the anions generated when the reactions occur compete with the anionic pharmaceutically active agent for binding sites on the resin with the result that reduced levels of pharmaceutically active agent are bound at equilibrium. For acidic pharmaceutically active agents, stoichiometric binding of pharmaceutically active agent to resin is accomplished only through reaction (d). The binding may be performed, for example, as a batch or column process, as is known in the art.

In less preferred embodiments, the adsorption complex, including pharmaceutically active agent and resin, is collected and washed with ethanol and/or water to insure removal of any unadsorbed pharmaceutically active agent. The complexes are usually air-dried in trays at room or elevated temperature.

The ratio of the pharmaceutically active agent adsorbate to ion exchange resin adsorbent in the adsorption complex is about 1:3 to about 3:1, preferably about 1:2 to about 2:1, most preferably about 1:1. The only limit to using ratios in excess of 1:3 is an economic and aesthetic one.

The amount of the pharmaceutically active agent adsorbed to the ion exchange resin is in the range from about 25 to about 75% by weight of the pharmaceutically active agent/resin adsorption complex (hereinafter referred to as the "pharmaceutically active agent/resin complex" or "complex"). More preferably, the amount of the pharmaceutically active agent adsorbed to the ion exchange resin is in the range from about 33 to about 77% by weight of the pharmaceutically active agent/resin complex. Most preferably, the amount of the pharmaceutically active agent adsorbed to the ion exchange resin is in the range from about 40 to about 60% by weight of the pharmaceutically active agent/resin complex.

The amount of pharmaceutically active agent/resin complex in the formulation is adjusted to deliver a predetermined dose of the pharmaceutically active agent over a predetermined period of time.

For example, a preferred antitussive film of the invention is administered at one dose every 12 hours to deliver a pharmaceutically effective amount of dextromethorphan over a period of approximately 12 hours to a patient in need of such administration. A typical adult dose of a film of the invention measuring 1" x 1.25" (2.54 cm x 3.18 cm) weighs about 60 to about 190 mg and contains about 20 to about 130 mg of pharmaceutically active agent/resin complex to deliver about 5 to about 65 mg of pharmaceutically active agent (e.g., dextromethorphan hydrobromide) when the average pharmaceutically active agent:ion exchange resin ratio is about 1:1.

In a particularly preferred embodiment of the invention, pullulan is present in the film in an amount of about 2 to about 6 mg/cm^2, dextromethorphan is present in the film in an amount of about 1.4 to about 3 mg/cm^2, and sulfonated polymer ion exchange resin is present in said film in an amount of about 1.4 to about 2 mg/cm^2.

The antitussive pharmaceutically active agents that are suitable for use in these preparations are acidic, amphoteric or most often basic antitussives. Examples of basic pharmaceutically active agents useful in the present invention include, but are not limited to dextromethorphan, diphenhydramine, caramiphen, carbapentane, ethylmorphine, noscapine and codeine. In addition, the antitussive embodiments of the invention can further comprise additional agents that are therapeutically effective to treat conditions other than coughing. That is, more than one type of pharmaceutically active agent can be included in a film of the invention. For example, in the case of a film containing an antitussive agent, the film can further comprise an antihistamine, sympathomimetic pharmaceutically active agent (nasal decongestant,

bronchodilator), analgesic, antiinflammatory, cough suppressant and/or expectorant. Compounds which are antihistamines, sympathomimetic pharmaceutically active agents (nasal decongestant, bronchodilator), analgesic, antiinflammatory, cough suppressants and/or expectorants are well known to those of skill in the art and need not be discussed in detail herein.

In embodiments, a certain percentage of the films disclosed herein will contain non-coated pharmaceutically active agent/resin complexes. The remaining pharmaceutically active agent/resin complexes are further characterized by the presence of a coating. In the preferred embodiment of the present invention, about 20 to about 80% of the pharmaceutically active agent/resin complexes in the sustained-release compositions are coated, most preferably about 40 to about 60% of the pharmaceutically active agent/resin complexes. The coating is a water-permeable, diffusion barrier coating material. The presence of a coating allows one to selectively modify the dissolution profile as desired of a pharmaceutical composition comprising the pharmaceutically active agent/resin complexes of the present invention.

The coating materials can in general be any of a large number of conventional natural or synthetic film-forming materials used singly, in admixture with each other, and in admixture with plasticizers, pigments, etc. with diffusion barrier properties and with no inherent pharmacological or toxic properties. In general, the major components of the coating should be insoluble in water, and permeable to water and pharmaceutically active agent. However, it might be desirable to incorporate a water-soluble substance, such as methyl cellulose, to alter the permeability of the coating, or to incorporate an acid-insoluble, base-soluble substance to act as an enteric coating. The coating materials may be applied as a suspension in an aqueous fluid or as a solution in organic solvents. Suitable examples of such coating materials are described by R. C. Rowe in Materials used in Pharmaceutical Formulation. (A. T. Florence,

editor), Blackwell Scientific Publications, Oxford, 1-36(1984), incorporated by reference herein. Preferably the water-permeable diffusion barrier is selected from the group consisting of ethyl cellulose, methyl cellulose and mixtures thereof Most preferably, the coating material is SURELEASE, manufactured by Colorcon which is water based ethyl cellulose latex, plasticized with dibutyl sebacate or with vegetable oils. Other non-limiting coating materials included within the scope of the present invention are AQUACOAT, manufactured by FMC Corporation of Philadelphia, which is ethylcellulose pseudolatex; solvent based ethylcellulose; shellac; zein; rosin esters; cellulose acetate; EUDRAGITS, manufactured by Rohm and Haas of Philadelphia, which are acrylic resins; silicone elastomers; poly(vinyl chloride) methyl cellulose; and hydroxypropylmethyl cellulose.

Conventional coating solvents and coating procedures (such as fluid bed coating and spray coating) can be employed to coat the particles. Techniques of fluid bed coating are taught, for example, in U.S. Patents Nos. 3,089,824, 3,117,027, and 3,253,944. The coating is normally applied to the pharmaceutically active agent/resin complex, but alternatively can be applied to the resin before complexing with the pharmaceutically active agent. Non-limiting examples of coating solvents include ethanol, a methylene chloride/acetone mixture, coating emulsions, methyl acetone, tetrahydrofuran, carbonetetrachloride, methyl ethyl ketone, ethylene dichloride, trichloroethylene, hexane, methyl alcohol, isopropyl alcohol, methyl isobutyl ketone, toluene, 2-nitropropane, xylene, isobutyl alcohol, n-butyl acetate.

It is preferred that the coated pharmaceutically active agent/resin complexes are coated in the range from about 40 to about 70% w/w pharmaceutically active agent/resin complex. More preferably, the pharmaceutically active agent/resin complex is coated in the range from about 45 to about 55% w/w pharmaceutically active agent/resin complex. Most

preferably, the pharmaceutically active agent/resin complex is coated about 50% w/w pharmaceutically active agent/resin complex. Variation in the amount of coating and/or the use of coated/uncoated complex mixtures can be employed to selectively modify the dissolution profile as desired.

The average particle sizes of the non-hydrated coated and uncoated pharmaceutically active agent/resin complexes is about 60 to about 200 and about 60 to about 250 micrometers, respectively. More preferably, average particle sizes of the coated pharmaceutically active agent/resin complexes is between about 70 and about 190 micrometers, and most preferably about 70 to about 180 micrometers. More preferably, average particle sizes of the uncoated pharmaceutically active agent/resin complexes is between about 55 and about 160 micrometers, and most preferably about 60 to about 150 micrometers. It is desirable that about 85%, preferably about 95%, and most preferably about 98% of the resin particles have sizes within the ranges set forth above. Adjustments within these ranges can be made to accommodate desired aesthetic qualities of the final formulation product. It is more preferable that the resin dextromethorphan complex have particle sizes within these ranges as well.

In embodiments, it is possible to hydrate the film-forming ingredients and combine all of the ingredients without heating. This method comprises dissolving the water-soluble ingredients in water to form an aqueous mixture; mixing the film-forming ingredients in powder form to form a powder mixture; adding the powder mixture to the aqueous mixture to form a hydrated polymer gel; stirring the hydrated polymer at room temperature for about 30 minutes to about 48 hours; mixing the cooling agent, menthol and any other oils to form an oil mixture; adding the oil mixture to the hydrated polymer gel and mixing until uniform; deaerating the film until air bubbles are removed, casting the uniform mixture on a suitable substrate; and drying the cast mixture to form a

film. This method hydrates the film-forming ingredients without heating the water, which can reduce energy costs in the manufacturing process and undesirable losses of volatile ingredients to evaporation. Further, mixing the oils in two steps minimizes the amount of flavor lost.

While not wishing to be bound by any theories, it is believed that the film-forming ingredients can be hydrated and mixed without heating due to an ionic effect known as the Donnan equilibrium. Hydrating the film-forming agents in the presence of electrolytes in solution effectively lowers the viscosity of the polymer gel being formed, thus increasing the efficiency of the hydrating process. The water-soluble ingredients of the formulation provide the electrolytes, which are dissolved in the hydration solution prior to addition of the film-forming ingredients. High-shear mixing also accelerates hydration, which delumps the powders, providing greater surface area for water contact. In addition, local heating effects, generated in the shear regions, provide energy for hydration without substantially raising the temperature of the mass.

Examples

The invention will be illustrated in more detail with reference to the following Examples, but it should be understood that the present invention is not deemed to be limited thereto.

Example 1

The ingredients listed in Table 1 were combined to provide a comparative example of an antitussive film in accordance with the following procedure:

A. The water was heated to 50°C. The potassium sorbate and sweeteners were dissolved in the water with mixing. The titanium dioxide was then added with further mixing to form Preparation A.

B. The film-forming ingredients (e.g., xanthan gum, locust bean gum, carrageenan and pullulan) were mixed in a separate container to form

Preparation B.

C. Preparation B was slowly added to Preparation A with rapid mixing, followed by overnight mixing at a reduced rate to provide Preparation C.

D. The glycerin and olive oil were combined in a separate container and then the menthol and monoammonium glycyrrhizinate (MAG) were dissolved therein by heating to 45°C to form Preparation D.

E. Preparation D was added to Preparation C with thorough mixing and then the flavor agents were added with continued mixing to provide Preparation E.

F. Dextromethorphan coated with ethyl cellulose was then added to Preparation E with mixing. The pH was adjusted as necessary to 6.0 using 10% citric acid solution to provide Preparation F (Examples 1-3 only).

Preparation F was poured on a mold and cast to form a film of a desired thickness at room temperature. The film was dried under warm air and cut to a desired dimension (dictated by, e.g., dosage and mouthfeel) for taste testing. The film was segmented into 1" x 1.25" (2.54 cm x 3.18 cm) dosage units, each of which had a thickness of 0.009±0.002 in (0.23±0.05 mm) and a weight of 70±3 mg.

A placebo film was also prepared in accordance with the foregoing to facilitate evaluation of, e.g., the taste and appearance of the active film.

Table 1

Material	% w/w in batch	g/batch	%w/w*	mg/dose*	%w/w* active film	% w/w actual batch
Coated Dextromethorphan (55% DM)		103.6291		27.3000	29.5775	9.3899
Xanthan Gum	0.0600	0.6000	0.2432	0.1581	0.1713	0.0544
Locust Bean Gum	0.0700	0.7000	0.2837	0.1844	0.1998	0.0634
Carrageenan	0.3000	3.0000	1.2159	0.7903	0.8563	0.2718
Pullulan	16.0000	160.0000	64.8466	42.1503	45.6666	14.4976
Potassium Sorbate	0.0600	0.6000	0.2432	0.1581	0.1713	0.0544
Acesulfame Potassium Salt	0.5000	5.0000	2.0265	1.3172	1.4271	0.4531
Aspartame NF	1.4000	14.0000	5.6741	3.6882	3.9958	1.2685
Purified Water	75.3264	753.2640				68.2534
Physcool	0.1000	1.0000	0.4053	0.2634	0.2854	0.0906
Menthol	1.0000	10.0000	4.0529	2.6344	2.8542	0.9061
Citric Acid	0.0710	0.7100	0.2878	0.1870	0.2026	0.0643
Cherry Flavor (Givudan)	0.1500	1.5000	0.6079	0.3952	0.4281	0.1359
Peppermint Flavor	0.5000	5.0000	2.0265	1.3172	1.4271	0.4531
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.1000	0.0405	0.0263	0.0285	0.0091
Polysorbate 80 NF	0.3500	3.5000	1.4185	0.9220	0.9990	0.3171
Atmos 300	0.3500	3.5000	1.4185	0.9220	0.9990	0.3171
Glycerine	3.0000	30.0000	12.1587	7.9032	8.5625	2.7183
Olive Oil	0.5000	5.0000	2.0265	1.3172	1.4271	0.4531
FD&C green #3	0.0026	0.0260	0.0105	0.0068	0.0074	0.0024
Titanium Dioxide	0.2500	2.5000	1.0132	0.6586	0.7135	0.2265
Total w/o active		0.0000	100.0000	65.0000		
Total with active	100.0000	1103.6291		92.3000	100.0000	100.0000
* assuming that all water is evaporated						

The active film was gritty and bitter.

Example 2

Comparative films having the ingredients listed in Table 2 were prepared in accordance with the method of Example 1.

Table 2

Material	%w/w in batch	g/batch	%w/w* placebo film	mg/dose*	%w/w* active film	% w/w actual batch
Coated Dextromethorphan (53.5% DM)		106.4239		28.0374	30.1356	9.6187
Xanthan Gum	0.0600	0.6000	0.2432	0.1581	0.1699	0.0542
Locust Bean Gum	0.0700	0.7000	0.2837	0.1844	0.1982	0.0633
Carrageenan	0.3000	3.0000	1.2159	0.7904	0.8495	0.2711
Pullulan	16.0000	160.0000	64.8493	42.1520	45.3065	14.4610
Potassium Sorbate	0.0600	0.6000	0.2432	0.1581	0.1699	0.0542
Acesulfame Potassium Salt	0.5000	5.0000	2.0265	1.3173	1.4158	0.4519
Aspartame NF	1.4000	14.0000	5.6743	3.6883	3.9643	1.2653
Purified Water	75.3274	753.2740				68.0819
Physcool	0.1000	1.0000	0.4053	0.2635	0.2832	0.0904
Menthol	1.0000	10.0000	4.0531	2.6345	2.8317	0.9038
Citric Acid (used to adjust pH to 6.0)	0.0700	0.7000	0.2837	0.1844	0.1982	0.0633
Cherry Flavor (Givudan)	0.1500	1.5000	0.6080	0.3952	0.4247	0.1356
Peppermint Flavor	0.5000	5.0000	2.0265	1.3173	1.4158	0.4519
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.1000	0.0405	0.0263	0.0283	0.0090
Polysorbate 80 NF	0.3500	3.5000	1.4186	0.9221	0.9911	0.3163
Atmos 300	0.3500	3.5000	1.4186	0.9221	0.9911	0.3163
Glycerine	3.0000	30.0000	12.1592	7.9035	8.4950	2.7114
Olive Oil	0.5000	5.0000	2.0265	1.3173	1.4158	0.4519
FD&C Green #3	0.0026	0.0260	0.0105	0.0069	0.0074	0.0024
Titanium Dioxide	0.2500	2.5000	1.0133	0.6586	0.7079	0.2260
Total w/o active		0.0000	100.0000	65.0000		
Total with active	100.0000	1106.4239		93.0374	100.0000	100.0000
* assuming that all water is evaporated						

The active film was gritty and bitter.

Example 3

Comparative films having the ingredients listed in Table 3 were prepared in accordance with the method of Example 1.

Table 3

Material	%w/w in batch	g/batch	%w/w* placebo film	mg/dose*	%w/w* active film	% w/w actual batch
Coated Dextromethorphan (60% DM)		94.7292		25.0000	27.7778	8.6532
Xanthan Gum	0.0600	0.6000	0.2436	0.1583	0.1759	0.0548
Locust Bean Gum	0.0700	0.7000	0.2842	0.1847	0.2053	0.0639
Carrageenan	0.3000	3.0000	1.2180	0.7917	0.8797	0.2740
Pullulan	16.0000	160.0000	64.9625	42.2256	46.9174	14.6155
Potassium Sorbate	0.0600	0.6000	0.2436	0.1583	0.1759	0.0548
Acesulfame Potassium Salt	0.5000	5.0000	2.0301	1.3196	1.4662	0.4567
Aspartame NF	1.4000	14.0000	5.6842	3.6947	4.1053	1.2789
Purified Water	75.3704	753.7040				68.8484
Physcool	0.1000	1.0000	0.4060	0.2639	0.2932	0.0913
Menthol	1.0000	10.0000	4.0602	2.6391	2.9323	0.9135
Citric Acid	0.0270	0.2700	0.1096	0.0713	0.0792	0.0247
Cherry Flavor (Givudan)	0.1500	1.5000	0.6090	0.3959	0.4399	0.1370
Peppermint Flavor	0.5000	5.0000	2.0301	1.3196	1.4662	0.4567
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.1000	0.0406	0.0264	0.0293	0.0091
Polysorbate 80 NF	0.3500	3.5000	1.4211	0.9237	1.0263	0.3197
Atmos 300	0.3500	3.5000	1.4211	0.9237	1.0263	0.3197
Glycerine	3.0000	30.0000	12.1805	7.9173	8.7970	2.7404
Olive Oil	0.5000	5.0000	2.0301	1.3196	1.4662	0.4567
FD&C green #3	0.0026	0.0260	0.0106	0.0069	0.0076	0.0024
Titanium Dioxide	0.2500	2.5000	1.0150	0.6598	0.7331	0.2284
Total w/o active		0.0000	100.0000	65.0000		
Total with active	100.0000	1094.7292		90.0000	100.0000	100.0000
* assuming that all water is evaporated						

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The active film was very thin, blue and gritty. Sensations of bitterness and numbness were minimal, but the flavor was not entirely agreeable.

Example 4

Films of the invention having the ingredients listed in Table 4 were prepared in accordance with the method of Example 1, except that Step F comprised adding uncoated dextromethorphan hydrobromide and AMBERLITE resin to Preparation E as separate ingredients.

Table 4

Material	%w/w in batch	g/batch	%w/w* placebo film	mg/dose*	%w/w* active film	% w/w actual batch
Dextromethorphan		17.0326		15.0000	15.7563	5.0951
Amberlite IRP69		17.2597		15.2000	15.9664	5.1630
Xanthan Gum	0.0600	0.1800	0.2439	0.1585	0.1665	0.0538
Locust Bean Gum	0.0700	0.2100	0.2845	0.1849	0.1943	0.0628
Carrageenan	0.3000	0.9000	1.2194	0.7926	0.8326	0.2692
Pullulan	16.0000	48.0000	65.0338	42.2720	44.4033	14.3587
Potassium Sorbate	0.0600	0.1800	0.2439	0.1585	0.1665	0.0538
Acesulfame Potassium Salt	0.5000	1.5000	2.0323	1.3210	1.3876	0.4487
Aspartame NF	1.4000	4.2000	5.6905	3.6988	3.8853	1.2564
Purified Water	75.3974	226.1922				67.6630
Physcool	0.1000	0.3000	0.4065	0.2642	0.2775	0.0897
Menthol	1.0000	3.0000	4.0646	2.6420	2.7752	0.8974
Citric Acid	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Cherry Flavor (Givudan)	0.1500	0.4500	0.6097	0.3963	0.4163	0.1346
Peppermint Flavor	0.5000	1.5000	2.0323	1.3210	1.3876	0.4487
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0300	0.0406	0.0264	0.0278	0.0090
Polysorbate 80 NF	0.3500	1.0500	1.4226	0.9247	0.9713	0.3141
Atmos 300	0.3500	1.0500	1.4226	0.9247	0.9713	0.3141
Glycerine	3.0000	9.0000	12.1938	7.9260	8.3256	2.6923
Olive Oil	0.5000	1.5000	2.0323	1.3210	1.3876	0.4487
FD&C green #3	0.0026	0.0078	0.0106	0.0069	0.0072	0.0023
Titanium Dioxide	0.2500	0.7500	1.0162	0.6605	0.6938	0.2244
Total w/o active		300.0000	100.0000	65.0000		
Total with active	100.0000	334.2922		95.2000	100.0000	100.0000
* assuming that all water is evaporated						

The active film had a pleasing appearance and taste.

Example 5

The ingredients listed in Table 5 were combined to provide an example of an antitussive film of the invention in accordance with the following procedure:

A. The water was heated to 75°C. Uncoated dextromethorphan hydrobromide was dissolved with mixing in the water, while maintaining the temperature at 75°C. AMBERLITE resin was then mixed into the water with heating for 4 to 5 hours at 70-80°C. Heating was stopped, water lost to evaporation was replaced, and the potassium sorbate and sweeteners were then added to the composition with mixing to form Preparation A.

B. The film-forming ingredients (e.g., xanthan gum, locust bean gum, carrageenan and pullulan) were mixed in a separate container to form Preparation B.

C. Preparation B was slowly added to Preparation A with rapid mixing, followed by overnight mixing at a reduced rate to provide Preparation C.

D. The menthol was dissolved with mixing in the alcohol in a separate container. The Physcool was then dissolved with mixing therein. The MAG, Polysorbate 80, Atmos 300 and flavors were then added to the mixture and mixed to enhanced uniformity to form Preparation D.

E. Preparation D, glycerine and mannitol were added to Preparation C with thorough mixing to provide Preparation E.

Preparation E was poured on a mold and cast to form a film of a desired thickness at room temperature. The film was dried under warm air and cut to a desired dimension (dictated by, e.g., dosage and mouthfeel) for taste testing. The film was segmented into 1.5 in^2 (9.7 cm^2) dosage units, each of which had a thickness of 0.009±0.002 in (0.23±0.05 mm) and a weight of 70±3 mg.

A placebo film was also prepared in accordance with the foregoing to facilitate evaluation of, e.g., the taste and appearance of the active film.

Table 5

Material	%w/w in batch	g/batch	mg/dose*	%w/w* film	% w/w actual batch
Dextromethorphan HBr		11.4615	15.0000	21.4286	9.2666
Amberlite IRP69		12.2256	16.0000	22.8571	9.8843
Xanthan Gum	0.0600	0.0600	0.0944	0.1348	0.0485
Locust Bean Gum	0.0700	0.0700	0.1101	0.1573	0.0566
Carrageenan	0.3000	0.3000	0.4718	0.6740	0.2425
Pullulan	16.0000	16.0000	25.1613	35.9447	12.9359
Potassium Sorbate	0.0600	0.0600	0.0944	0.1348	0.0485
Acesulfame Potassium Salt	0.5000	0.5000	0.7863	1.1233	0.4042
Aspartame NF	1.4000	1.4000	2.2016	3.1452	1.1319
Purified Water	70.2000	70.2000			56.7561
Alcohol USP	5.0000	5.0000			4.0425
Physcool	0.1000	0.1000	0.1573	0.2247	0.0808
Menthol	1.5000	1.5000	2.3589	3.3698	1.2127
Peppermint Flavor	0.1000	0.1000	0.1573	0.2247	0.0808
Raspberry Flavor (Givudan)	0.5000	0.5000	0.7863	1.1233	0.4042
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0100	0.0157	0.0225	0.0081
Polysorbate 80 NF	0.3500	0.3500	0.5504	0.7863	0.2830
Atmos 300	0.3500	0.3500	0.5504	0.7863	0.2830
Glycerine	1.5000	1.5000	2.3589	3.3698	1.2127
Mannitol USP	2.0000	2.0000	3.1452	4.4931	1.6170
Total w/o active		100.0000	39.0000		

The active film had a pleasing appearance and taste.

Example 6

Films of the invention having the ingredients listed in Table 6 were prepared in accordance with the method of Example 5.

Table 6

Material	%w/w in batch	g/batch	mg/dose*	%w/w*	%w/w
Dextromethorphan HBr		11.6538	15.0000	21.4286	9.3919
Amberlite IRP69		12.4308	16.0000	22.8571	10.0180
Xanthan Gum	0.0600	0.0600	0.0925	0.1321	0.0484
Locust Bean Gum	0.0700	0.0700	0.1079	0.1542	0.0564
Carrageenan	0.3000	0.3000	0.4625	0.6606	0.2418
Pullulan	16.0000	16.0000	24.6640	35.2343	12.8944
Potassium Sorbate	0.0600	0.0600	0.0925	0.1321	0.0484
Acesulfame Potassium Salt	0.5000	0.5000	0.7708	1.1011	0.4030
Aspartame NF	1.4000	1.4000	2.1581	3.0830	1.1283
Purified Water	69.7000	69.7000			56.1713
Alcohol USP	5.0000	5.0000			4.0295
Physcool	0.1000	0.1000	0.1542	0.2202	0.0806
Menthol	2.0000	2.0000	3.0830	4.4043	1.6118
Peppermint Flavor	0.1000	0.1000	0.1542	0.2202	0.0806
Raspberry Flavor (Givudan)	0.5000	0.5000	0.7708	1.1011	0.4030
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0100	0.0154	0.0220	0.0081
Polysorbate 80 NF	0.3500	0.3500	0.5395	0.7708	0.2821
Atmos 300	0.3500	0.3500	0.5395	0.7708	0.2821
Glycerine	1.5000	1.5000	2.3123	3.3032	1.2089
Mannitol USP	2.0000	2.0000	3.0830	4.4043	1.6118
Total w/o active		0.0000	39.0000		
Total with active	100.0000	124.0846	70.0000	100.0000	100.0000
* assuming that all water and alcohol is evaporated					

The active film had a pleasing appearance and taste.

Example 7

A film of the invention having the ingredients listed in Table 7 were

prepared in accordance with the method of Example 5. The film was segmented into 1" x 1.25" (2.54 cm x 3.18 cm) dosage units, each of which had a thickness of 0.009±0.002 in (0.23±0.05 mm) and a weight of 63.6±3 mg.

Table 7

Material	%w/w in batch	kg/batch	mg/dose*	%w/w*	%w/w
Dextromethorphan HBr		1.3567	15.0000	23.5981	9.3918
Amberlite IRP69		1.4472	16.0000	25.1713	10.0180
Xanthan Gum	0.0600	0.0070	0.0772	0.1215	0.0484
Locust Bean Gum	0.0700	0.0081	0.0901	0.1417	0.0564
Carrageenan	0.3000	0.0349	0.3661	0.6075	0.2418
Pullulan	16.0000	1.8627	20.5941	32.3988	12.8944
Potassium Sorbate	0.0600	0.0070	0.0772	0.1215	0.0484
Acesulfame Potassium Salt	0.5000	0.0582	0.6436	1.0125	0.4030
Aspartame NF	1.4000	0.1630	1.8020	2.8349	1.1283
Purified Water	69.7000	8.1145			56.1714
Alcohol USP	5.0000	0.5821			4.0295
Physcool	0.1000	0.0116	0.1287	0.2025	0.0806
Menthol	2.0000	0.2328	2.5743	4.0498	1.6118
Peppermint Flavor	0.1000	0.0116	0.1287	0.2025	0.0806
Raspberry Flavor (Givudan)	0.5000	0.0582	0.6436	1.0125	0.4030
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0012	0.0129	0.0202	0.0081
Polysorbate 80 NF	0.3500	0.0407	0.4505	0.7087	0.2821
Atmos 300	0.3500	0.0407	0.4505	0.7087	0.2821
Glycerine	1.5000	0.1746	1.9307	3.0374	1.2089
Mannitol USP	2.0000	0.2328	2.5743	4.0498	1.6118
Total w/o active + resin		11.6420	32.5644		
Total with active + resin	100.0000	14.4459	63.5644	100.0000	100.0000
* assuming that all water and alcohol is evaporated					

The active film had a pleasing appearance and taste.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

CLAIMS

WHAT IS CLAIMED IS:

1. A consumable film adapted to adhere to and dissolve in a mouth of a consumer, wherein said film comprises at least one water soluble polymer, at least one pharmaceutically active agent and at least one taste masking agent.

2. The consumable film according to claim 1, wherein said at least one water soluble polymer is a member selected from the group consisting of pullulan, hydroxyproplymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof.

3. The consumable film according to claim 2, wherein said at least one water soluble polymer is pullulan.

4. The consumable film according to claim 1, wherein said at least one pharmaceutically active agent is a member selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory agents, antitussives, decongestants, anti-histamines, expectorants, anti-diaherrals, H_2-antagonists, proton pump inhibitors, central nervous system agents, analgesics and mixtures thereof.

5. The consumable film according to claim 4, wherein the antimicrobial agent is a member selected from the group consisting of triclosan, cetyl pyridium chloride, domiphen bromide, quaternary ammonium salts, zinc compounds, sanguinarine, fluorides, alexidine, octonidine, EDTA and mixtures thereof.

6. The consumable film according to claim 4, wherein the non-steroidal anti-inflammatory agent is a member selected from the group consisting of aspirin, acetaminophen, ibuprofen, diflunisal, fenoprofen calcium, naproxen, tolmetin sodium, indomethacin, and mixtures thereof.

7. The consumable film according to claim 4, wherein the antitussive is a member selected from the group consisting of benzonatate, caramiphen edisylate, dextromethorphan, chlophedianol, diphenhydramine, salts thereof and mixtures thereof.

8. The consumable film according to claim 4, wherein the decongestant is selected from the group consisting of pseudoephedrine, phenylepherine, phenylpropanolamine, salts thereof and mixtures thereof.

9. The consumable film according to claim 4, wherein the anti-histamine is selected from the group consisting of brompheniramine maleate, chlorpheniramine maleate, carbinoxamine maleate, clemastine fumarate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, diphenhydramine citrate, diphenylpyraline hydrochloride, doxylamine succinate, promethazine hydrochloride, pyrilamine maleate, tripelennamine citrate, triprolidine hydrochloride and mixtures thereof.

10. The consumable film according to claim 4, wherein the expectorant is selected from the group consisting of guaifenesin, ipecac, potassium iodide, terpin hydrate and mixtures thereof.

11. The consumable film according to claim 4, wherein the anti-diarrheal is loperamide.

12. The consumable film according to claim 4, wherein the H_2-antagonist is selected from the group consisting of famotidine, ranitidine and mixtures thereof.

13. The consumable film according to claim 4, wherein the proton pump inhibitor is selected from the group consisting of omeprazole,

lansoprazole, and mixtures thereof.

14. The consumable film according to claim 1, wherein the at least one taste masking agent is an ion exchange resin.

15. The consumable film according to claim 14, wherein the ion exchange resin is a sulfonated polymer comprising polystyrene cross-linked with divinylbenzene.

16. The consumable film according to claim 14, wherein the ion exchange resin is a sulfonated polymer comprising polystyrene cross-linked with 8% of divinylbenzene, with an ion exchange capacity of about 4.5 to 5.5 meq/g of dry resin (H^+-form).

17. The consumable film according to claim 16, wherein the ion exchange resin has irregularly-shaped particles ranging in size from about 47 to about 149 micrometers.

18. The consumable film according to claim 16, wherein the ion exchange resin has spherical particles ranging in size from about 45 to about 150 micrometers.

19. The consumable film according to claim 14, wherein the ion exchange resin is a polymer composed of polystyrene cross-linked with 8% of divinylbenzene and functionalized with a quaternary ammonium group, and wherein an exchange capacity of said ion exchange resin is normally within a range of about 3 to about 4 meq/g of dry ion exchange resin.

20. The consumable film according to claim 1, wherein the at least one taste masking agent is magnesium trisilicate.

21. The consumable film according to claim 1, wherein said at least one water soluble polymer is pullulan, said at least one pharmaceutically active agent is dextromethorphan, and said at least one taste masking agent is a sulfonated polymer ion exchange resin comprising polystyrene cross-linked with divinylbenzene.

22. The consumable film according to claim 21, wherein said pullulan is present in an amount of about 40 to about 80 wt% of said film, said dextromethorphan is present in an amount of about 5 to about 40 wt% of said film, said sulfonated polymer ion exchange resin is present in an amount of about 5 to about 40 wt% of said film, and a ratio of said dextromethorphan to said sulfonated polymer ion exchange resin is 1:3 to 3:1.

23. The consumable film according to claim 22, wherein said pullulan is present in said film in an amount of about 2 to about 6 mg/cm^2, said dextromethorphan is present in said film in an amount of about 1.4 to about 2 mg/cm^2, and said sulfonated polymer ion exchange resin is present in said film in an amount of about 1.4 to about 2 mg/cm^2.

24. The consumable film according to claim 22, further comprising:

about 0.01 to about 5 wt% of at least one stabilizing agent;

about 0.001 to about 0.1 wt% of at least one of at least one coloring agent;

about 0.1 to about 70 wt% of water;

about 0.1 to about 15 wt% of at least one sweetening agent;

about 0.1 to about 15 wt% of at least one flavoring agent;

about 0.1 to about 4 wt% of at least one cooling agent;

about 0.1 to about 5 wt% of at least one surfactant;

about 0.1 to about 12 wt% of a triglyceride;

about 0.001 to about 5 wt% of a preservative;

about 0.1 to about 5 wt% of a polyethylene oxide compound; and

about 1 to about 20 wt% of propylene glycol.

25. A method for preparing the consumable film of claim 1, said method comprising:

dissolving water-soluble ingredients in water to provide an aqueous solution;

mixing at least one water soluble film former and at least one stabilizing agent to provide a film-forming mixture;

combining said film-forming mixture and said aqueous solution to provide a hydrated polymer gel;

mixing oils to form an oil mixture;

adding said oil mixture to said hydrated polymer gel and mixing to provide a uniform gel;

casting the uniform gel on a substrate; and

drying the cast gel to provide said film.

26. The method of claim 25, wherein said at least one pharmaceutically active agent and said at least one taste masking agent are incorporated into said aqueous solution or into said uniform gel.

27. The method of claim 25, wherein said at least one taste masking agent is an ion exchange resin, and said at least one pharmaceutically active agent is sorbed to said ion exchange resin without separating ion exchanged pharmaceutically active agent from unexchanged agent and counter ion salts.

INTERNATIONAL SEARCH REPORT

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 0 225 615 A (CIBA-GEIGY) 16 June 1987 (1987-06-16) claims 1-4,10 page 6, paragraph 2 page 10; example 6	1,2,4,7, 14-19 21-27
X	EP 0 438 147 A (SCLAVO) 24 July 1991 (1991-07-24) claims 1-5,13	1,2, 14-19
P,X Y,P	WO 00 42992 A (LAVIPHARM) 27 July 2000 (2000-07-27) claims 1,11,12,15,17,21,23,40 page 14, line 12 - line 21 page 18; table 1	1-4 21-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 225615 A	16-06-1987	US 4788055 A	29-11-1988
		AU 597316 B	31-05-1990
		AU 6618186 A	11-06-1987
		DK 589086 A,B,	10-06-1987
		FI 864975 A,B,	10-06-1987
		IE 320986 L	09-06-1987
		JP 62138428 A	22-06-1987
		NO 864918 A	10-06-1987
		PT 83877 A,B	01-01-1987
		ZA 8609255 A	29-07-1987
EP 438147 A	24-07-1991	IT 1238072 B	03-07-1993
		CA 2034519 A	20-07-1991
		JP 4210924 A	03-08-1992
		MX 24039 A	28-02-1994
		US 5441933 A	15-08-1995
WO 0042992 A	27-07-2000	AU 2222600 A	07-08-2000

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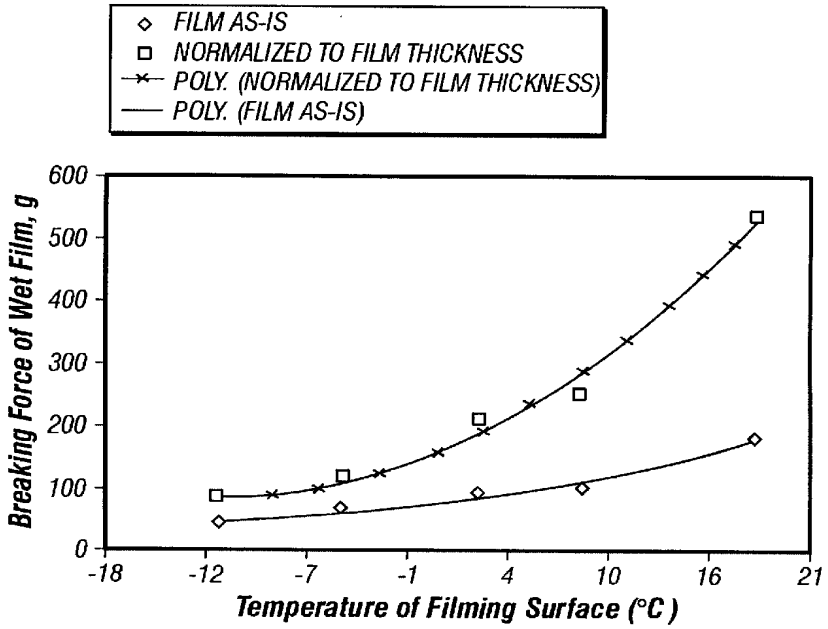
(54) Title: MODIFIED STARCH AS A REPLACEMENT FOR GELATIN IN SOFT GEL FILMS AND CAPSULES



(57) Abstract: Film-forming compositions are disclosed that can comprise, on a dry solid basis, 25 to 75 percent by weight of certain starch derivatives having a DE less than about 1,25 to 75 % plasticizer, and 0.1 to 15 % hydrocolloid gum. The starch derivatives can be chemically modified starches which range in molecular weight from 100,000 to 2,000,000. These starch-based systems can completely replace gelatin in edible film-forming applications such as soft and hard gel capsules.

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MODIFIED STARCH AS A REPLACEMENT FOR GELATIN IN SOFT GEL FILMS AND CAPSULES

BACKGROUND OF THE INVENTION

This invention relates to starch compositions useful in forming flexible films. More particularly, it relates to film-forming compositions containing certain modified starches.

Gelatin is a protein that forms thermo-reversible films. Gel masses composed of gelatin and a plasticizer such as glycerin are formulated to be liquid above room temperature, form a film when cast on a cooled surface, and re-melt when exposed to higher temperatures again. This ability to re-tackify enables encapsulation of liquid materials in gelatin soft capsules. Films formed from plasticized gelatin set very quickly and have high wet film strength. They are also very elastic with good clarity. Plasticized gelatin also has a relatively low viscosity, even when used at high solids concentrations. In addition, when gelatin is in the presence of water at room temperature, it swells but does not go into solution until heat is applied.

In the manufacture of soft gel films and capsules, the soft gel composition must possess the properties of good wet and dry film strength, insolubility in cold water, oil, and alcohol, solubility in hot water, temperature and pressure sealability, film clarity, film flexibility, edibility, inertness to drugs or other materials to be encapsulated, and rapid setting from a hot liquid to form a gel. In the manufacture of photographic elements, the soft gel films must possess the qualities of clarity, strength, setting power, flexibility, and non-interaction with other chemicals in the photographic film.

Although gelatin is useful in soft gel applications because of its rapid gelling ability, excellent film forming properties, and ability to impart oxygen impermeability, it has the disadvantages of high cost, limited availability, non-kosher status for food products and, at times, batch property variations. Because of these shortcomings, those industries where the need for gelatin is greatest have long sought means for replacing gelatin.

A useful gelatin replacer must be compatible with common plasticizers and fill materials used in the industry, and must provide properties equivalent to those of the gelatin which it is replacing for a particular application, e.g., film or binding strength in the pharmaceutical industry, phototransmissibility and resistance to abrasion in the photographic industry, and binding strength in the adhesive industry.

SUMMARY OF THE INVENTION

One aspect of the present invention is a film-forming composition that comprises starch material selected from the group consisting of modified starch and waxy starch; gum; and plasticizer. The modified starch or waxy starch has a dextrose equivalent (DE) of less than about 1, and preferably has no measurable DE. This composition can be, but is not required to be, 100% gelatin-free. Thus, the composition can be used as a gelatin replacement, or as an extender in gelatin formulations.

The composition typically will be prepared with water, and have a solids concentration of about 30-70% by weight. The solids in the composition preferably comprise 25-75% starch material, 25-75% plasticizer, and 0.1-15% gum. In certain preferred embodiments of the invention, the weight ratio of gum to starch is from about 0.1:1 to about 1:1, and the weight ratio of starch and gum to plasticizer is from about 1:0.8 to about 1:3.

The starch material preferably comprises starch which has been chemically modified with a monoreactive moiety to a degree of substitution of least about 0.015. It is also preferred that the starch material has an average molecular weight between about 100,000-2,000,000. In a particularly preferred embodiment, the starch material is selected from the group consisting of ether and ester derivatives of starch, such as hydroxypropyl, hydroxyethyl, succinate, and octenyl succinate starch. One specific embodiment of the invention comprises hydroxypropylated potato starch having a degree of substitution of about 0.015-0.30 and a molecular weight of about 100,000-2,000,000.

The gum preferably is selected from the group consisting of carrageenan, locust bean, xanthan, gellan, agar, alginates, guar, gum arabic, and pectin. A combination of kappa carrageenan and iota carrageenan, most preferably in a weight ratio of about 1:1, is especially preferred. The plasticizer preferably comprises at least one polyol, such as glycerol, sorbitol, maltitol, or a mixture of one or more of these. The composition of the present invention can optionally also comprise at least one monovalent or divalent cation, such as sodium, potassium, and calcium salts, or mixtures thereof.

Another aspect of the invention is an edible film that comprises the above-described starch-based composition, usually with much of the water removed. Yet another aspect of the invention is a soft gel capsule that comprises a sealed capsule wall and a first substance that is encapsulated by the sealed capsule wall. The capsule wall comprises the above-described starch-based composition. In one embodiment of the invention, the film or the capsule wall consists essentially of the combination of starch material, gum, and plasticizer.

The first substance encapsulated by the capsule wall can be any of a variety of materials which have been encapsulated by gelatin in the past. Many such substances are edible, including drugs, vitamins, nutritional supplements, and pre-measured food ingredients such as flavorings. It can also comprise, for example, photographic or dye solutions.

Another aspect of the invention is a method of encapsulating a first substance. This method comprises the steps of: providing a first substance and an edible film as described above; and encapsulating the first substance in the film. Preferably, the film used in this method has been formed on a surface having a temperature of at least about 38°C (100°F).

One object of this invention to provide an economical means for replacing gelatin in compositions utilized in the production of soft gel for food, pharmaceutical, and industrial applications. It is a further object of this invention to provide starch-based materials which are compatible with the existing application equipment used for manufacture of the various products which are primarily comprised of gelatin films.

The starch-based systems of the present invention, when incorporated as a replacement for gelatin in aqueous solutions, display properties superior to those of their parent base starch. More precisely, modified starches that have been chemically modified with monoreactive moieties to a degree of substitution of at least 0.015 DS, and degraded to molecular weights between 100,000 and 2,000,000, or, alternatively, waxy starches, when combined with gum and plasticizing agents, are a highly functional replacement for gelatin in soft gel film forming applications. The presence of gum increases the rate of film formation and enhances film strength.

In compositions of the present invention, the starch and gum preferably are mixed with plasticizers at ratios ranging from about 1 part starch and gum to about 0.8-3 parts plasticizer. The total solids in the composition preferably range from about 30 to 70% weight. Edible films are prepared by blending together the starch, gum, plasticizer, and water, and heating the mixture to a temperature and for a time sufficient to gelatinize the starch fully, (e.g., 80-100 °C for 10-60 min). A vacuum can be used either during or after cooking to remove entrained air and improve film properties. Additional materials may be added to the mixture of starch and plasticizer in order to impart improved functionality. Furthermore, properties of this system can be modified by the inclusion of various mono and divalent cations, including but not limited to sodium, potassium, and calcium. The mixture is then sheeted, while hot, to form a thin film. This film can be formed into soft gel capsules, encapsulating pharmaceutical, nutritional, photographic, or other materials, using well-known techniques.

The modified starch-based compositions of the present invention provide an acceptable balance of critical variables including mass viscosity and pot life, film rate, wet film strength, dry film strength and flexibility, and thermo-reversibility.

In one embodiment of the invention, wet film strength is significantly improved by increasing the temperature of the surface on which the film is formed. It is preferred in the present invention to use film-forming surface temperatures of about 38°C (100°F) or greater. Commercial capsule filming drum temperatures are often set around 10°C (50°F) for gelatin filming, but can easily be adjusted to 38-43°C (100-110°F). Breaking strengths can be increased by as much as 500% by increasing surface temperature from 12-66°C (53°F to 150°F). Films cast at 41°C (105°F) can have as much as twice the breaking strength films cast on 12°C (53°F) surfaces.

In one particularly preferred embodiment, the gum component of the composition consists essentially of 50% kappa carrageenan and 50% iota carrageenan. This combination can increase film strength by as much as 50% over films formed with 100% kappa carrageenan as the gum component, increase film elasticity, reduce the viscosity of the hot mass, lower the minimum temperature at which the gelled mass can be handled in liquid form, and lower the gel-setting temperature of the mass. This composition also broadens the temperature range over which the mass gels, which can improve the ease of film sealing.

The present invention has a number of benefits. One advantage of the invention is that it is a simple, cost-effective, dependable, intrinsically safe, Kosher, and efficient means for replacing the gelatin used in soft gel capsule compositions.

Another advantage of the invention is that the preparation of the starch-based compositions can be carried out by ordinary means with conventional manufacturing apparatus. The resulting compositions can be utilized in any commercial process requiring gelatin and to which conventional coating and drying methods are adaptable. Examples of end-product uses for the compositions of the present invention include encapsulated bath beads, paint balls, and pharmaceuticals. Therefore, the present invention provides a novel, efficient means for replacing gelatin in these and other applications.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the effect of the temperature of the surface on which a film is formed on the strength of that film.

Figure 2 is a graph showing the effect of temperature on flow and gelation for compositions containing different types of carrageenan.

Figure 3 is a graph showing the effect of mass solids percentage on the flowability of compositions containing different types of carrageenan.

DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS

Examples of modified starches that can be used in the present invention include non-retrograding starches derived by chemical modification of starch from any plant source, including corn, waxy maize, potato, sweet potato, wheat, rice, sago, tapioca, sorghum, high amylose corn, and the like. The particular starch chosen will depend on its performance, availability, and cost. The starch should have a DE less than about 1, and preferably has no measurable DE (using the Lane-Eynon method). Among the useful modified starches are the common ether and ester derivatives of starch, including but not limited to hydroxypropyl, hydroxyethyl, succinate, and octenyl succinate starch derivatives. Also included among the modified starches suitable for use in the practice of this invention are the thermally converted, fluidity or thin boiling type products derived from the aforementioned types of chemically modified starches. Such materials may be of lower molecular weight, prepared by heating the modified starch alone or by subjecting the starch to a hydrolytic acid and/or heat treatment, or by any other known method designed for the thermal conversion of the starch, such as enzymic heat treatment.

Preferred modified starches are the hydroxypropyl derivatives of potato starch having a degree of substitution from 0.015-0.30 ds and a molecular weight of from 100,000 to 2,000,000. In the case of waxy starches of corn, potato, etc., the branches of the amylopectin replace the function of the ether or ester substituents; these starches are functional in the present invention without additional chemical modification, although their properties are not impaired by additional modification, and are enhanced by molecular weight reduction.

Suitable plasticizers include, but are not limited to, glycerol, sorbitol, and maltitol. Suitable hydrocolloid gums include carrageenan, locust bean gum, xanthan gum, gellan gum, agar, alginates, guar gum, gum arabic, and pectin.

The properties of the composition can be enhanced by the addition of certain cations, including but not limited to sodium, potassium, and calcium. The presence of these cations, in combination with certain gums, generally enhances viscoelastic properties and gel strength.

A variety of optional ingredients may be incorporated into the starch compositions of this invention, before, during, or after cooking the starch. Among the suitable additives which may be utilized are preservatives, colorants, flavoring agents, hardeners, antifoggers, sensitizers, and spreading agents. The inclusion of such additives has no adverse effect upon the properties exhibited by the novel starch-based compositions of the present invention.

A composition of the present invention is formed by combining the dry solids (i.e., the modified starch or waxy starch, gum, and plasticizer, plus any other additives), slurrying in water, and heating at a temperature and for a time sufficient to gelatinize the starch. Optionally, this can take place under a vacuum. Films can be formed from these starch-based compositions by any conventional method designed to solubilize and deposit a continuous coating or layer of the solution onto a substrate or mold of any form. Among the suitable coating techniques are spraying, dipping, air knife, trailing blade, reverse and direct roll coaters, etc. A film, such as an overcoating or capsule shell, may then be formed by drying the coated solution to a desired moisture content, using any means suitable for the particular purpose. Suitable conventional means include warm or cold air impingement, low humidity chamber or oven drying, etc. For example, in the pharmaceutical industry, soft gel capsules are prepared by casting a film of the gelatin solution and then continuously passing two ribbons of the film between two opposing rollers, each of which is equipped with an internal vacuum that draws in the film through half capsule wells engraved in its surface. The capsule contents are deposited between the shell halves as they are formed and sealed. The process is continuous, ending with the filled capsules being automatically conveyed to and through a drying unit that partially dries the capsule. Drying is completed in warm air tunnels.

The films of the present invention can be re-melted, and two or more of these re-melted films can be joined to form a seal.

The invention is particularly efficacious in the soft gel capsule manufacturing process that calls for film-forming materials, but it is not limited thereto. The characteristics exhibited by the present, novel starch formulations, particularly their ability to serve as a total replacement for gelatin, permit them to be used in a wide range of applications.

Although the emphasis has been placed on describing this invention in connection with film-forming gelatin-free compositions, compositions of the present invention can also be utilized as extenders in gelatin compositions such as creams, emulsions, binders, adhesives, etc.

Further compositions of the present invention can be used in the replacement of gelatin in hard shell capsule manufacturing.

EXAMPLES

The invention will be further illustrated by, but is not intended to be limited to, the following examples.

Compositions were prepared containing the component amounts given in Examples 1-7 on a dry solids basis. Starch molecular weights were measured by gel permeation chromatography and weight averaged. In Examples 1-7, the starch, plasticizer, and gum, if used, were mixed with sufficient deionized water (except where indicated) to give a total slurry mass of 35 g. The components were mixed together in the cup of a Rapid Visco Analyzer (Model RVA-4D, Foss Food Technology, Eden Prairie, MN) (hereafter referred to as "RVA"), and heated, using 160 rpm stirring, to 98°C over 4.5 minutes. The mixture was held at 98°C, with continued stirring, for 6.5 minutes, then transferred to a chilled surface and drawn into a film of 0.5 mm thickness for film testing. A second paste of the same composition was cooked in the same way and then transferred into a pre-heated glass jar, tightly capped, and placed into an oven for pot life evaluations.

In particular, in Examples 1-7, the film samples were prepared by casting a layer of the test solution at about 82°C (180°F) onto a Teflon-coated piece of glass (approximately 22.9 x 33 cm (9 in x 13 in)). The bottom of the glass was in contact with circulating cold water so that the surface temperature of the glass was 52°C. The film was formed by pouring the hot paste onto the Teflon surface and then quickly drawing the paste across the glass using a Bird Applicator or similar device, the gap width of which could be adjusted to control film thickness. Wet film thicknesses were typically 0.5-0.8 mm. The films were cast, dried, and aged in a room controlled to 21°C (70°F) and 25-30% relative humidity.

The viscosity of the starch mixture was measured by the RVA instrument, which records viscosity throughout the cook.

Pot life was evaluated by transferring the hot paste into preheated glass jars with screw lids, and placing these in a 82°C (180°F) oven. The fluidity of the mass was evaluated after 2 hours by tipping the jars upside down and assigning a flow rating of 0-5. A mass that flowed with the ease of water was given a rating of 5; a mass which did not flow at all was given a rating of 0. The oven temperature was then lowered by 10°C and the samples allowed to equilibrate for 2 hours, and then their flow properties re-assessed. The oven was lowered in 5.6°C (10 °F) increments until all samples had a flow rating of zero – that is, they had all gelled.

Thermo-reversibility was assessed by reheating the pot life samples, described above, in 5.6°C (10 °F) increments, allowing them to equilibrate at each temperature, and then assigning a flow rating using the same criteria as for pot life.

The films were evaluated for rate of filming using a Gardco Electronic Multicycle Circular Drying Time Recorder, and following test method procedure ASTM D 5895. The recorder was placed above the wet film, and a stylus was lowered onto the surface of the film and allowed to rotate for a defined time of 10 minutes. Three points were determined from this test: tack free, dry hard, and dry through. Tack free is defined as the point in the path made by the stylus on the film where the continuous track ends and a discontinuous track or tear begins. Dry hard is the point in the path where the stylus no longer tears the film, and only leaves a visible trace. Dry through is reached when the stylus no longer leaves any visible track on the film.

The tensile strength of the wet film was measured using a Stable Microsystems TA-XT2 Texture Analyzer. To do this, 1.3 cm x 20.3 cm (0.5 in x 8 in) strips were cut from the wet film 5 minutes after it was cast and these were loaded onto the Texture Analyzer. The tensile test was started 15 minutes after the film was cast.

Film appearance (color and clarity) was evaluated on the basis of visual observation.

Example 1

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g kappa carrageenan

9.7 g Sorbitol Special (obtained from SPI Polyols, New Castle, Delaware)

Example 2

8.4 g potato starch, substituted with 0.5% hydroxypropyl groups and of 600,000 molecular weight

11.8 g Sorbitol Special

Example 3

8.4 g potato starch, substituted with 3.0% hydroxypropyl groups and of 600,000 molecular weight

11.8 g Sorbitol Special

0.5 mm thickness.

Example 4

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g gellan

9.7 g sorbitol

0.5 mm thickness.

Example 5

5.2 g waxy corn starch of 800,000 molecular weight

0.75 g kappa carrageenan

9.7 g sorbitol

Example 6

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g kappa carrageenan

9.7 g glycerine

Example 7

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g kappa carrageenan

9.7 g Sorbitol Special

Sufficient 1% NaCl to bring to 35 g total mass.

The physical properties of the hot starch/plasticizer pastes for Examples 1-7, and the resulting films, are listed below in Table 1.

Table 1

Example number	Peak viscosity during cook, cps	Hot paste final visc, cps, 98°C	Time until tack free, sec	Time until dry hard, sec	Wet film tensile strength, g force	Pot life rating @ 82°C (180°F)	Minimum flowable temp, °C	Re-softening temp, °C
1	18000	1700	<5	<10	75	3.5	71	66
2	14000	2500	65	100	*			
3	13000	1150	4020	5700	*			
4		2300	<5	<10	108	0.5	>82	>82
5	13000	2400	<5	<10	65	3.0	77	66
6	16000	1500	<5	<10	50	4.0	71	66
7	11000	1300	<5	<10	75	3.5	77	66

* Too weak to test

Example 8

A formulation was prepared having the following composition (on an as-is basis):

16% starch which had been acid-thinned to approximately 600,000 mol wt and substituted with about 4 wt % hydroxypropyl groups (approx. 10% moisture).

2.3% kappa carrageenan (approx. 9% moisture)

26% Sorbitol Special (24% moisture)

6.7% glycerine (1% moisture)

49% added water

When the moisture in the components is taken into account, the total solids of the composition was 44%. The starch to carrageenan ratio was 6.75/1, and the ratio of plasticizer to thickener (starch plus carrageenan) was 1.6/1. The plasticizer was composed of 75% Sorbitol Special and 25% glycerine. The components were mixed together and then heated to 98°C for 15 minutes (or to 92°C for 30 minutes), then poured hot onto a surface and drawn down into a film.

To control the temperature of the surface onto which films were cast, a stream of water was passed underneath and in contact with that surface. In this experiment, the water stream heated water, rather than chilled water as in the previous examples. The surface temperature was controlled by adjusting the thermostat in the water reservoir – a conventional re-circulating water bath.

To determine "minimum flow temperature" and "gel temperature", masses were cooked in an RVA, then transferred to preheated glass vials and placed in a 82°C (180°F) oven. After 2 hours equilibration, the vials were tipped and the flow of the mass observed, and a ranking assigned and recorded. The oven temperature was then reduced by 5.6°C (10°F) and the samples allowed to equilibrate for an additional 2 hours. The "minimum flow temperature" was defined as the lowest temperature at which the mass would easily flow in the vial. It was viscous but "pourable". The "gel temperature" was the highest temperature at which the mass did not flow at all. Since the samples were evaluated in 5.6°C (10°F) increments, the temperature assignments are approximate.

The kappa carrageenan used for this experiment was SKW Satiagel RPT 8/60 Kappa Carrageenan. The iota carrageenan used was FMC SD 389 PF Iota Carrageenan.

During conventional production of gelatin soft-gel capsules, the hot gelatin mass is cast onto a cooled drum (10-13°C; 50-55°F). In this experiment, the surface onto which the mass was cast was heated by the circulating water stream, in order to slow the rate of cooling of the

composition. Figure 1 shows the variation in wet strength of the films formed as the surface temperature varied.

Increasing the temperature of the filming surface dramatically increased wet film strength. (Wet film strength is the important strength parameter since the film must have sufficient integrity within 1-4 minutes of casting to survive an open draw and other rigors of capsule production.) At higher temperatures, the film thicknesses were lower (probably due to flow on the heated surface). When the film strengths were normalized to film thickness (g force per mm thickness), the temperature effect was especially dramatic – increasing 5 fold as the surface temperature increased from 12-66°C (53°F to 150°F). The "as-is" film strength, uncorrected for film thickness, increased 4 fold.

Film rates were not quantified, but all conditions generated films which could be lifted and handled in under a minute.

Without being bound by theory, it is possible that the higher film strength observed when the surface temperature was higher is due to larger, greater numbers and/or more perfect helices. When the films cool slowly, they have time and mobility near the gelation temperature to form larger and/or more perfect helices. A higher percentage of the carrageenan may be involved in helices compared to material that is quench-cooled.

Example 9

Experiments were performed using compositions like that of Example 8, but in which the carrageenan content was reduced by 25% and the total mass solids percentage was increased. These compositions had a mass viscosity and wet film strength similar to that exhibited by the formulation of Example 8. The composition and properties of the two soft gels are compared in Table 2 below. The two gel masses have similar viscosity/temperature profiles, and gel at similar temperatures. (As mentioned above, a flow rating of 5 is similar to water. A rating of zero indicates that the sample is gelled and there is no flow. A rating of at least 3 is preferred for handing on commercial equipment.)

Table 2

mass solids, %	% carrageenan	% starch	Flow rating 82°C	Flow rating 77°C	Flow rating 72°C	Flow rating 66°C	Breaking strength, g 12°C filming	Breaking strength, g 41°C filming
44	4.1	37	4.5	4.0	2.0	0.0	57	180
48	5.2	42	4.0	3.0	2.0	0.0	---	78

A 25% reduction in carrageenan makes the composition significantly less costly. Increased mass solids percentage reduces shrinkage and drying costs.

Example 10

Starch-based compositions were prepared containing the same ingredients as in Example 8, except iota carrageenan was used as a complete replacement for kappa carrageenan. However, films formed from such compositions had a slow film formation rate. In addition, the films formed were soft, weak, and very elastic.

Tests were then performed using a composition like that of Example 8, except that it included a combination of kappa and iota carrageenan, rather than only kappa carrageenan. This change resulted in stronger films (higher yield stress) than either of the two types of carrageenan alone. The strongest films comprised a 50/50 (weight) combination of the two. As much as 50% increase in film strength was measured with the 50/50 blend of kappa/iota compared with the kappa-only films.

The temperature at which the kappa-only gel mass became a rigid gel was high - about 160°F for the composition of Example 8 at 44% solids. The mass viscosity builds rapidly as its temperature is dropped below 82°C (180°F). This could be a problem in manufacturing operations, because the hot mass could set up in a location in manufacturing equipment that is inadvertently underheated. Further, even higher temperatures (88°C plus) are needed to re-soften the kappa-only gel for capsule sealing. Moreover, kappa carrageenan has a very sharp liquid-gel transition, whereas iota's transition is rather broad.

Because the strength of films formed from kappa/iota blends were not a mathematical combination of the two individual carrageenans, and a 50/50 combination of the two gave the strongest films, a mixed gel structure was strongly implied. Carrageenan gels by coiling portions of its carbohydrate backbone into helixes with portions of another carrageenan molecule. If the gel is composed of helixes containing one strand of kappa carrageenan and one strand of iota carrageenan, predicting the softening temperature is not straightforward.

We therefore prepared gel masses composed of either kappa carrageenan, or a 50/50 blend of kappa and iota. All other aspects of the formula were held constant (see Example 8 for the formulation details). A series of gel masses with varying total solids were prepared for each carrageenan composition. The effects on gel temperature are illustrated in Table 3 below. ("Minimum flow" and "gel temperature" are as defined above.)

Table 3

Effect of carrageenan on mass flow properties and gel temperature

% ds	approx min. flow temp, deg C		approx gel temp, deg C	
	kappa	kappa/iota	kappa	kappa/iota
42	71	66	66	60
44	74	71	71	66
45	77	71	71	66
46	82	77	71	66
47	85	77	71	66

It can be seen that replacing half of the kappa carrageenan with iota decreased the temperature at which the mass will flow, and decreased its gel temperature, by about 5.6°C (10°F) for each of the solids levels tested.

At 82°C (180°F) the two formulations had similar flow properties, but the kappa-only samples thickened rapidly with drop in temperature. Figure 2 illustrates the effect. Lower gel temperature, and more gradual gelation, should make the films made from kappa/iota mixtures easier to handle and easier to seal.

Table 3 above illustrates the importance of solids control during handling of these formulations. Figure 3 illustrates the rapid decrease in mass flowability at 77°C (170°F) as mass solids increases. The effect is especially pronounced for the kappa-only formulation. Blending iota carrageenan with kappa allows for higher solids while maintaining manageable viscosity.

Example 11

Two films that comprised the same ingredients as Example 10 were dipped in mineral oil and then were re-melted and sealed together. During capsule production, gelatin films are typically coated with oil before they are sealed. Without being bound by theory, it is believed that in the absence of the oil coating, evaporative cooling makes it difficult to seal the films (the rapid evaporation cools the films below their gel point by the time the two surfaces came together). The mineral oil appeared to suppress evaporation and the starch-based films could be readily sealed. Both films made with kappa carrageenan and with kappa/iota blends sealed readily using this technique.

The preceding description of specific embodiments of the present invention is not intended to be a complete list of every possible embodiment of the invention. Persons skilled

in this field will recognize that modifications can be made to the specific embodiments described here that would be within the scope of the present invention.

WHAT IS CLAIMED IS:

1. A film-forming composition, comprising:
starch material having a dextrose equivalent less than about 1 and selected from the group consisting of modified starch and waxy starch;
gum; and
plasticizer.

2. The composition of claim 1, wherein the composition is gelatin-free.

3. The composition of claim 1, further comprising water.

4. The composition of claim 3, wherein the composition comprises 30-70% by weight dry solids.

5. The composition of claim 4, wherein the dry solids in the composition comprise 25-75% starch material, 25-75% plasticizer, and 0.1-15% gum.

6. The composition of claim 1, wherein the weight ratio of gum to starch is from about 0.1:1 to about 1:1.

7. The composition of claim 1, wherein the weight ratio of starch and gum to plasticizer is from about 1:0.8 to about 1:3.

8. The composition of claim 1, wherein the starch material comprises starch which has been chemically modified with a monoreactive moiety to a degree of substitution of least about 0.015.

9. The composition of claim 8, wherein the starch material has an average molecular weight of about 100,000-2,000,000.

10. The composition of claim 9, wherein the starch material is selected from the group consisting of ether and ester derivatives of starch.

11. The composition of claim 10, wherein the starch material is selected from the group consisting of hydroxypropyl, hydroxyethyl, succinate, and octenyl succinate starch.

12. The composition of claim 1, wherein the starch material comprises hydroxypropylated potato starch having a degree of substitution of about 0.015-0.30 and a molecular weight of about 100,000-2,000,000.

13. The composition of claim 1, wherein the gum is selected from the group consisting of carrageenan, locust bean, xanthan, gellan, agar, alginates, guar, gum arabic, and pectin.

14. The composition of claim 13, wherein the gum comprises a combination of kappa carrageenan and iota carrageenan.

15. The composition of claim 14, wherein the weight ratio of kappa carrageenan to iota carrageenan is about 1:1.

16. The composition of claim 1, wherein the plasticizer comprises at least one polyol.

17. The composition of claim 16, wherein the plasticizer is selected from the group consisting of glycerol, sorbitol, maltitol, and mixtures thereof.

18. The composition of claim 1, further comprising at least one monovalent or divalent cation.

19. The composition of claim 18, wherein the cation is selected from the group consisting of sodium, potassium, and calcium, and mixtures thereof.

20. The composition of claim 1, wherein:
the starch material is selected from the group consisting of (a) ether and ester derivatives of starch having a molecular weight of about 100,000-2,000,000 and a degree of substitution of about 0.015-0.30;
the gum comprises a combination of kappa carrageenan and iota carrageenan; and
the plasticizer comprises at least one polyol.

21. An edible film comprising the composition of any of claims 1-20.

22. A soft gel capsule comprising a sealed capsule wall and a first substance that is encapsulated by the sealed capsule wall;
wherein the capsule wall comprises a composition according to any of claims 1-20.

23. The capsule of claim 22, wherein the capsule wall consists essentially of a composition according to any of claims 1-20.

24. The capsule of claim 22, wherein the first substance is edible.

25. The capsule of claim 21, wherein the first substance is selected from the group consisting of drugs, vitamins, nutritional supplements, and pre-measured food additives.

26. A method of encapsulating a first substance, comprising the steps of:
providing a first substance and an edible film that comprises a composition according to any of claims 1-20; and
encapsulating the first substance in the film.

27. The method of claim 26, wherein the first substance is selected from the group consisting of drugs, vitamins, nutritional supplements, and pre-measured food additives.

28. The method of claim 26, wherein the film is formed at a temperature of at least about 38°C.

1/2

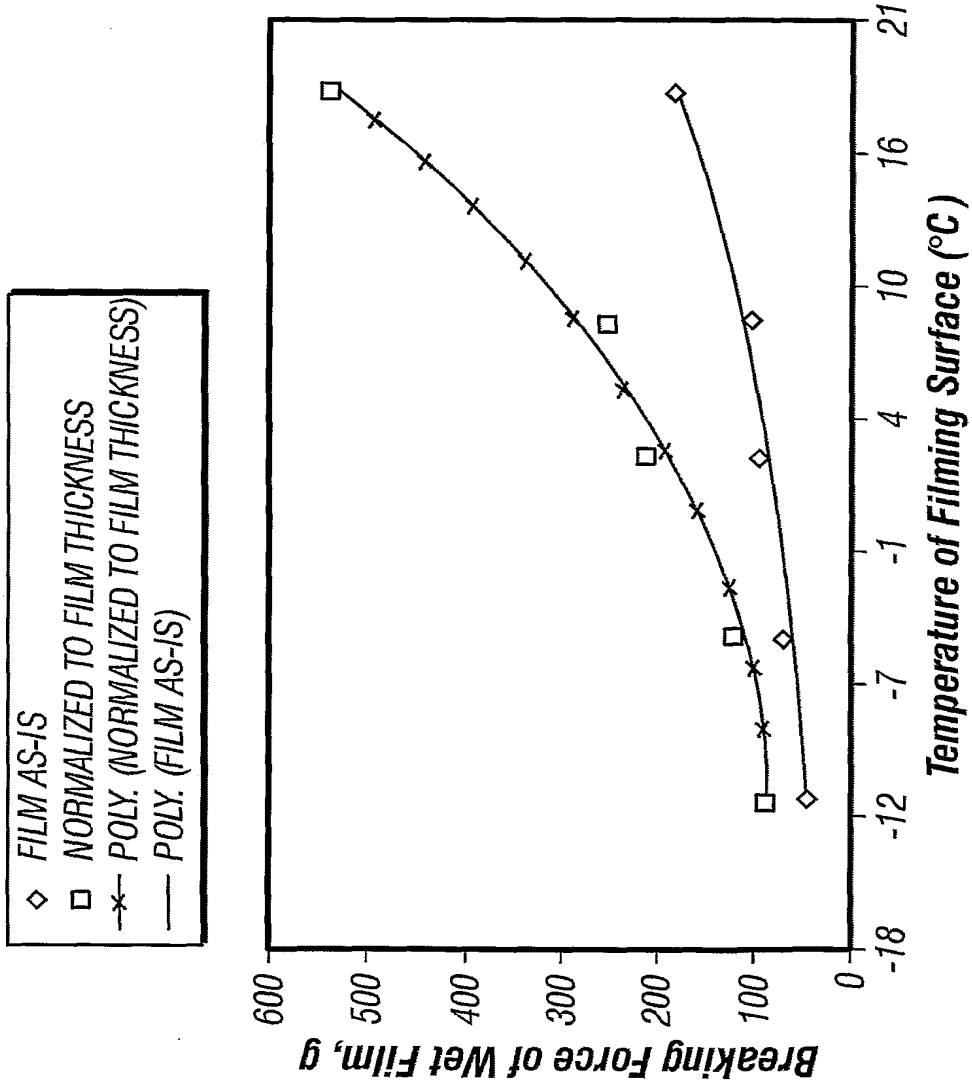

FIG. 1

2/2

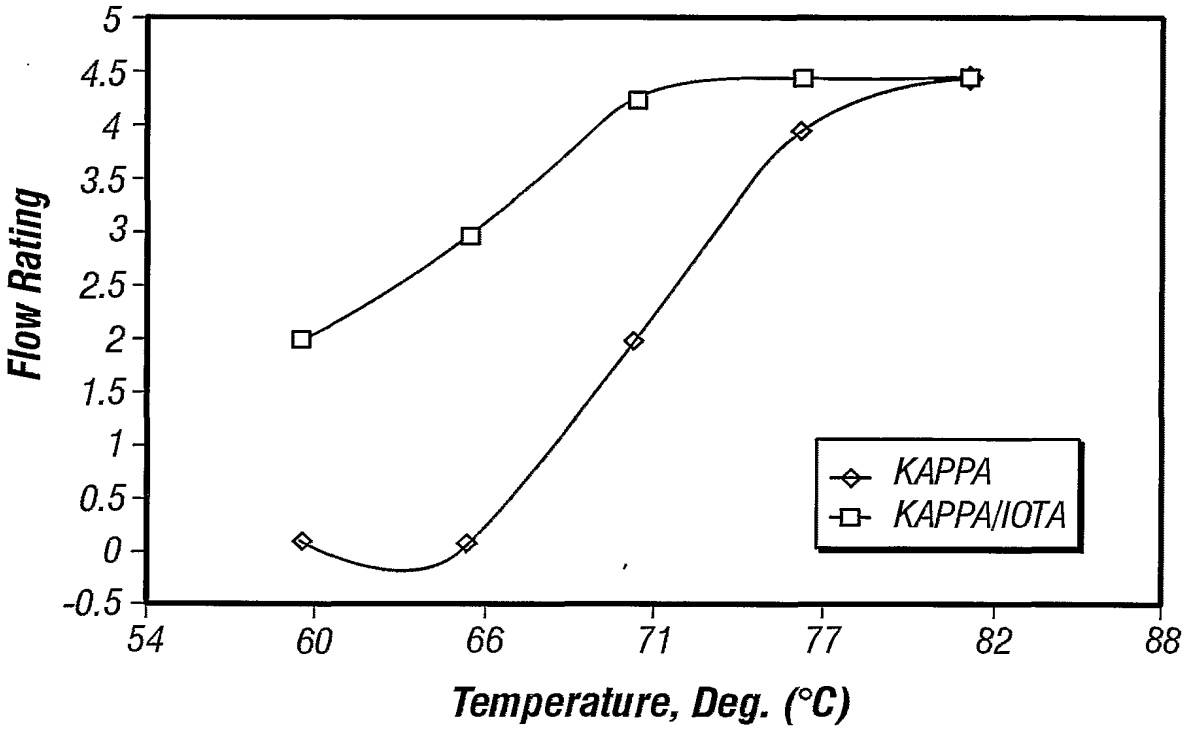

FIG. 2

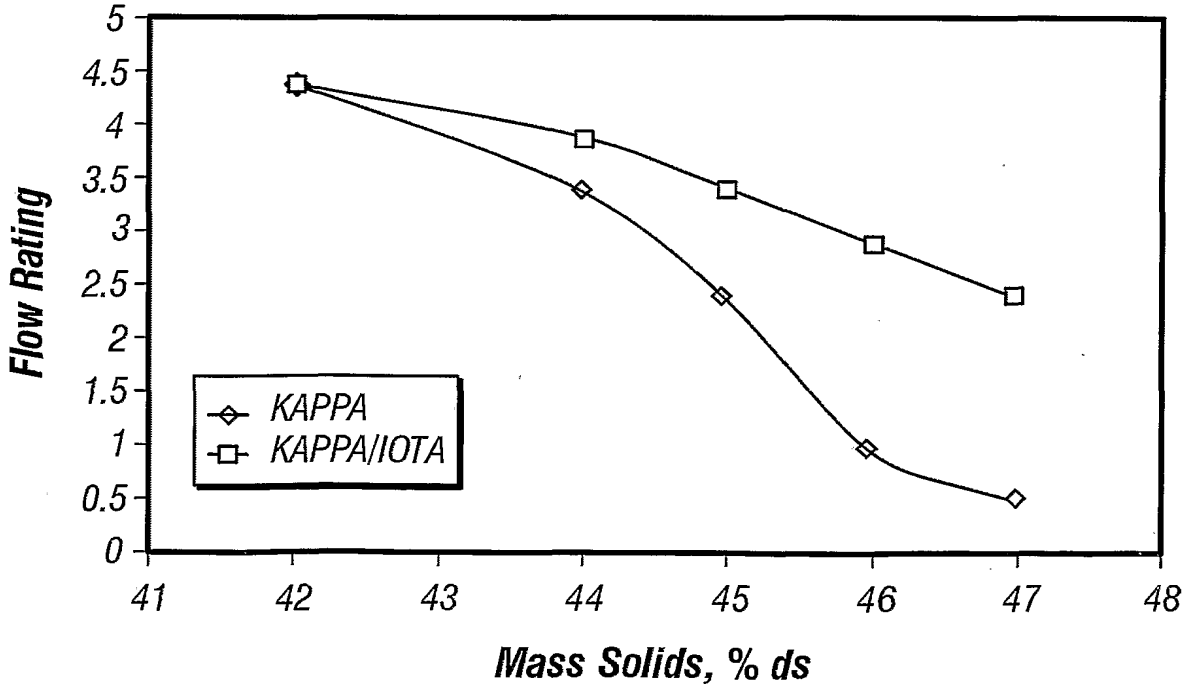

FIG. 3

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09/584,413 1 June 2000 (01.06.2000) US

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(74) Agent: GOODMAN, Kenneth, D.; Williams, Morgan & Amerson, P.C., Suite 250, 7676 Hillmont, Houston, TX 77040 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

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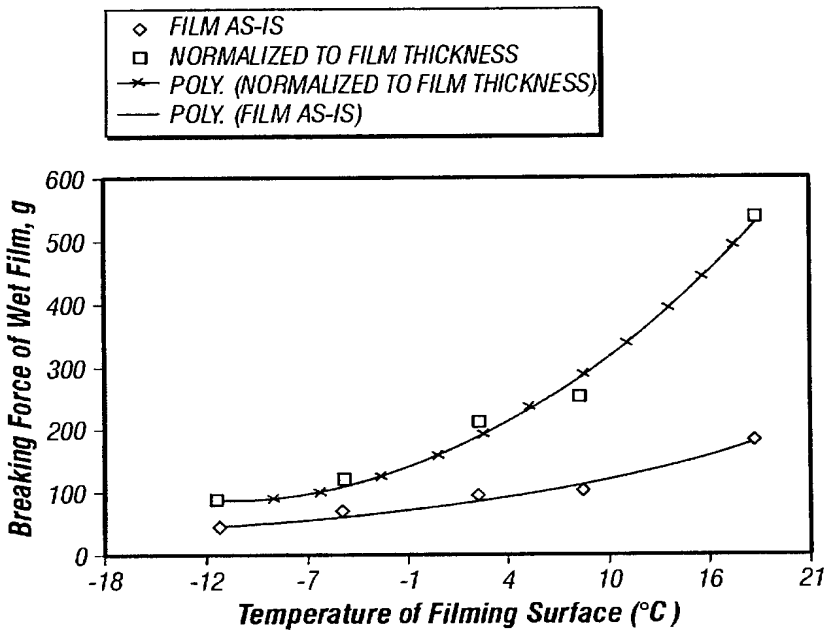
(88) Date of publication of the international search report:
30 May 2002

[Continued on next page]

(54) Title: MODIFIED STARCH AS A REPLACEMENT FOR GELATIN IN SOFT GEL FILMS AND CAPSULES



(57) Abstract: Film-forming compositions are disclosed that can comprise, on a dry solid basis, 25 to 75 percent by weight of certain starch derivatives having a DE less than about 1,25 to 75 % plasticizer, and 0.1 to 15 % hydrocolloid gum. The starch derivatives can be chemically modified starches which range in molecular weight from 100,000 to 2,000,000. These starch-based systems can completely replace gelatin in edible film-forming applications such as soft and hard gel capsules.

WO 01/91721 A3

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

Inter tional Application No
PCT/US 01/14888

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08L3/00 C08J5/18 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C08L C08J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 451 673 A (MARSHALL L. FISHMAN ET AL.) 19 September 1995 (1995-09-19) column 4, line 10 - line 68	1-7,9, 13, 16-19,21
X	FR 2 783 832 A (WARNER LAMBERT COMPANY) 31 March 2000 (2000-03-31) page 2, paragraph 4 -page 3, paragraph 7	1-28
X	WO 00 10538 A (BANNER PHARMACAPS INC) 2 March 2000 (2000-03-02) page 5, line 29 -page 6, line 1 page 7, line 1 -page 9, line 11	1-28

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
23 November 2001	05/12/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lensen, H

1

INTERNATIONAL SEARCH REPORT

Inter ional Application No
PC1/US 01/14888

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 17, no. 266 (C-1062), 25 May 1993 (1993-05-25) & JP 05 004914 A (ASAHI CHEM IND CO LTD), 14 January 1993 (1993-01-14) abstract & DATABASE WPI Week 199307 Derwent Publications Ltd., London, GB; AN 1993-055171 abstract	1-18
P,X	WO 01 03677 A (R.P.SCHERER TECHNOLOGIES) 18 January 2001 (2001-01-18) page 16, line 4 - line 14 page 10, line 18 -page 11, line 15	1-28
A	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 07, 29 September 2000 (2000-09-29) & JP 2000 116339 A (ITOO KAIGAI JIGYO KK), 25 April 2000 (2000-04-25) abstract & DATABASE WPI Week 200032 Derwent Publications Ltd., London, GB; AN 2000-369392 abstract	
A	US 4 009 291 A (WILLIAM A. MITCHELL ET AL.) 22 February 1977 (1977-02-22)	
E	EP 1 103 254 A (PETER GREITHER) 30 May 2001 (2001-05-30) page 3, line 21 - line 46 page 6, line 1 - line 20	1-28

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/14888

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5451673 A	19-09-1995	AU 685805 B2	29-01-1998
		AU 6711094 A	21-11-1994
		CA 2160559 A1	10-11-1994
		EP 0699211 A1	06-03-1996
		NZ 265837 A	22-09-1997
		WO 9425493 A1	10-11-1994
		US 5646206 A	08-07-1997
FR 2783832 A	31-03-2000	FR 2783832 A1	31-03-2000
		AU 5347299 A	17-04-2000
		CN 1321177 T	07-11-2001
		EP 1117736 A1	25-07-2001
		WO 0018835 A1	06-04-2000
WO 0010538 A	02-03-2000	US 6214376 B1	10-04-2001
		AU 5901999 A	14-03-2000
		EP 1105108 A1	13-06-2001
		WO 0010538 A1	02-03-2000
JP 05004914 A	14-01-1993	NONE	
WO 0103677 A	18-01-2001	AU 735699 B2	12-07-2001
		AU 6071500 A	30-01-2001
		EP 1105107 A1	13-06-2001
		WO 0103677 A1	18-01-2001
JP 2000116339 A	25-04-2000	NONE	
US 4009291 A	22-02-1977	CA 1038106 A1	12-09-1978
EP 1103254 A	30-05-2001	EP 1103254 A1	30-05-2001
		AU 1262801 A	04-06-2001
		WO 0137817 A1	31-05-2001

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Approved for use through 07/31/2008. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	95002170
Filing Date	2013-09-10
First Named Inventor	Robert K. Yang
Art Unit	3991
Examiner Name	Diamond, Alan D.
Attorney Docket Number	1199-26 RCE/CON/REX

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5044761		1991-09-03	Yuhki et al	
	2	5047244		1991-09-10	Sanvordeker et al	
	3	5064717		1991-11-12	Suzuki et al	
	4	5089307		1992-02-18	Ninomiya et al	
	5	5158825		1992-10-27	Altwirth	
	6	5166233		1992-11-24	Kuroya et al	
	7	5186938		1993-02-16	Sablotsky et al	
	8	5229164		1993-07-20	Pins et al	

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	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	9	5234957		1993-08-10	Mantelle	
	10	5271940		1993-12-21	Cleary et al	
	11	5272191		1993-12-21	Ibrahim et al	
	12	5346701		1994-09-13	Heiber et al	
	13	6660292		2003-12-09	Zerbe et al.	
	14	5411945		1995-05-02	Ozaki et al	
	15	5413792		1995-05-09	Ninomiya et al	
	16	5433960		1995-07-18	Meyers	
	17	5455043		1995-10-03	Fischel-Ghodsian	
	18	5462749		1995-10-31	Rencher	
	19	5472704		1995-12-05	Santus et al	

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	Application Number	95002170
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	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	20	5518902		1996-05-21	Ozaki et al	
	21	5567431		1996-10-22	Vert et al	
	22	5620757		1997-04-15	Ninomiya et al	
	23	6284264		2001-09-04	Zerbe et al.	
	24	5700478		1997-12-23	Biegajski et al	
	25	5700479		1997-12-23	Lundgren	
	26	5733575		1998-03-31	Mehra et al	
	27	5766620		1998-06-16	Heiber et al	
	28	5881476		1999-03-16	Strobush et al	
	29	5948430		1999-09-07	Zerbe et al	
	30	6153210		2000-11-28	Roberts et al	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	95002170
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	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	31	6177096		2001-01-23	Zerbe et al	
	32	6231957		2001-05-15	Zerbe et al	

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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20010046511	A1	2001-11-29	Zerbe et al.	
	2	20050118217		2005-06-02	Barnhart et al.	

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	1	2432925	DE	C3	1976-01-22	Schering AG		☐
	2	2449865	DE	B2	1976-04-29	Schering AG Berlin and Bergkamen		☐
	3	3630603	DE	C2	1988-03-10	Desitin Arzneimittel GmbH		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	95002170
	Filing Date	2013-09-10
	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	4	0200508	EP	B1	1986-12-10	Nitto Denko Corporation		☐
	5	0219762	EP	A1	1987-04-29	Desitin Arzneimittel GmbH		☐
	6	0241178	EP	B1	1987-10-14	Rohto Pharmaceutical Co., Ltd.		☐
	7	0250187	EP	B1	1987-12-23	Johnson & Johnson Consumer Products, Inc.		☐
	8	0259749	EP	B1	1988-03-16	Desitin Arzneimittel GmbH		☐
	9	0273069	EP	B1	1988-07-06	Uni Colloid Kabushiki Kaisha		☐
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	13	1110546	EP	A1	2001-06-27	Johnson & Johnson Consumer Companies, Inc.		☐
	14	9105540	WO		1991-05-02	Desitin Arzneimittel GMBH		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	95002170
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	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	15	9215289	WO		1992-09-17	Noven Pharmaceuticals, Inc.		☐
	16	9505416	WO		1995-02-23	Cygnus Therapeutic Systems		☐
	17	9518046	WO		1995-07-06	Frank, Richard, D.		☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
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	Application Number	95002170
	Filing Date	2013-09-10
	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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Signature	/Daniel A. Scola, Jr., Reg. No. 29,855/	Date (YYYY-MM-DD)	2013-01-29
Name/Print	Daniel A. Scola, Jr.	Registration Number	29,855

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EFS ID:	14825752
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Stephen J. Brown
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	29-JAN-2013
Filing Date:	10-SEP-2012
Time Stamp:	23:36:16
Application Type:	inter partes reexam

Payment information:

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS_Statement.pdf	12791 59b32973e93bf159453436a901e1f2f8c14fb4f8	no	2

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2	Foreign Reference	DE2432925.pdf	392210 785a64274de8ed518b718c32f2327851641 04446	no	5
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3	Foreign Reference	DE2449865.pdf	270911 a7807c93ccf0f1be4d0b4a61f1c71b0962d2 ba2e	no	4
Warnings:					
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4	Foreign Reference	DE3630603.pdf	410916 43d270c72689866bb57b20e58e53a7c3c07 06535	no	5
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6	Foreign Reference	EP0219762.pdf	688103 f3f4a8e06a9df2addfa149809ee6fce0ff90b8 cb	no	7
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9	Foreign Reference	EP0259749.pdf	581730 f99b5309a79fc5c86c583c4b8632bec86304 0c46	no	8
Warnings:					
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10	Foreign Reference	EP0273069.pdf	947238 b9299eb58d2fb66b5794d86f534654eb161 610b0	no	14
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11	Foreign Reference	EP0381194.pdf	666680 50e92ac9be4945c43d00bb17b54e0f600872a8c6	no	9
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13	Foreign Reference	EP0514691.pdf	405124 cff1313a7ef94cca28f38ca403cf864c293d42c4	no	7
Warnings:					
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14	Foreign Reference	EP1110546.pdf	260125 ff9bdaee40d29a40dca8ddb93206165f3fe07a2b	no	15
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16	Foreign Reference	WO1992015289.pdf	2707694 147be495a68b814a12fd449142952758c5ab897f	no	62
Warnings:					
Information:					
17	Foreign Reference	WO1995005416.pdf	3478794 33db7779286b087629fea18945c8a4c92863aa8a	no	83
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
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Central Reexamination Unit
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U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Madam:

This Information Disclosure Statement is being submitted pursuant to 37 C.F.R. 1.98, and identifies a number of patents and publication that may be considered relevant. The Patent Holder makes no representation as to the relevance of these documents, but wishes to make these references of record in this reexamination. Consideration of the references recited herein is requested.

If any fee is due with this submission, the Commission is authorized to charge any such fee to Deposit Account No. 08-2461. Should the Examiner have any questions regarding this submission, the undersigned would be pleased to address them.

Respectfully submitted,

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CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **INFORMATION DISCLOSURE STATEMENT** has been served, by first class mail, on January 29, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

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(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

(12) **Patentschrift**

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(51) Int. Cl. 4:
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DE-PS	14 17 385
DE-AS	20 12 775
DE-AS	17 67 536
DE-AS	10 88 706
DE-OS	20 06 696
DE-OS	20 01 724
DE-OS	19 31 080
DE-OS	18 00 580
DE-OS	17 20 118
DE-OS	14 70 780
AT	2 79 035
US	38 03 300

In Betracht gezogenes älteres Patent:
DE-PS 24 59 391;
DE-Z.: Fiedler: Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, Aulendorf 1971, S. 24,110,111, 308,376-378,608,609;
Römpp chem. Wörterbuch, Stuttgart 1969, S. 54,682,872;

(54) Folienförmige Arzneimittel

DE 2432925 C3

BUNDESDRUCKEREI 10. 85 508 247/450 50

DE 2432925 C3

Patentansprüche:

1. Folienförmige Arzneimittel mit gleichmäßiger Wirkstoffverteilung mit bis zu 60% Wirkstoffen, bezogen auf getrocknete Arzneimittel, auf Basis filmbildender wasserlöslicher Hydroxyalkyläther der Cellulose, Methylcellulose oder Äthylcellulose, erhalten durch Ausziehen einer Lösung oder Suspension von 48—84 Gewichtsprozent Lösungs- bzw. Suspensionsmittel, 6—20 Gewichtsprozent Folienbildner, 0—30 Gewichtsprozent Füllstoffen und 0,01—2 Gewichtsprozent Polyoxyäthylenpolyoxypropylenpolymeres, Polyoxyäthylenstearate, alkyl- bzw. acylsubstituierte Polyadditionsprodukte des Äthylenoxids als Trennmittel, wobei die Gewichtsprozente auf die Lösung bzw. Suspension bezogen sind, sowie den Wirkstoff und Trocknen und gegebenenfalls Teilen der Folie in Abschnitte.

2. Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß sie als Füllstoffe Cellulose, Zucker, Stärken, Mannit, Calciumcarbonat, Calciumphosphat oder Talkum enthalten.

Die Erfindung betrifft den in den Ansprüchen gekennzeichneten Gegenstand.

Aus der belgischen Patentschrift Nr. 6 37 363 sind Papierfolien bekannt, die mit Wirkstoff beschichtet zur oralen Anwendung geeignet sind. Die Folien bestehen aus in Wasser unlöslichen Cellulosefasern und einem wasserlöslichen Bindemittel. Als wasserlösliche Bindemittel wird vorzugsweise Carboxymethylcellulose-Natrium verwendet. Nach den Beispielen der belgischen Patentschrift wird der Wirkstoff durch Auftropfen des gelösten Wirkstoffes, durch Aufstreuen des festen Wirkstoffes oder durch Durchziehen der Folie durch die Wirkstofflösung auf die Papierfolie gebracht. Das diskontinuierliche Verfahren der gesonderten Herstellung der Folie und Aufbringung des Wirkstoffes hat den Nachteil, daß die Dosierungsgenauigkeit nicht sehr gut ist, was bei den heute niedrig dosierten Wirkstoffen jedoch von großer Wichtigkeit ist. Ungenauigkeiten entstehen aber nicht nur bei dem Aufbringen des Wirkstoffes, sondern auch bei der Herstellung und Vorbehandlung des Trägers und durch Veränderungen bei der Lagerung des Trägermaterials. So hat es sich zum Beispiel gezeigt, daß nach der Rezeptur der belgischen Patentschrift bei Verwendung von Folienziehmaschinen keine gleichmäßige Folienschicht entsteht und daß die Folie bei der Trocknung schrumpft.

Aus den deutschen Offenlegungsschriften DE-OS 18 00 580 und DE-OS 19 31 080 sind Arzneimittelzubereitungen in flüssiger und salbenartiger Form bekannt, die erst nach der Applikation auf der Haut einen festen Film bilden.

Die deutsche Offenlegungsschrift DE-OS 20 06 696 bezieht sich auf ein medizinisches Pflaster oder einen Haftverband mit verschiedenen Ausnehmungen oder Hohlräumen, die mit einer Tablette, mit Puder, Salbe, Creme oder ähnlichen Substanzen gefüllt sind und zur Verabreichung von empfängnisverhütenden Substanzen mit Systemwirkung auf dem Wege durch die Haut geeignet sind. Das Pflaster kann auch aus einem Träger- und einem Klebeteil bestehen, wobei die empfängnisverhütenden Stoffe durch Aufsprühen oder Dispergieren der Wirkstofflösung in den Klebeteil eingearbeitet sein können. Die erfindungsgemäßen folienförmigen Arzneimittel bestehen dagegen aus einer einheitlichen Phase mit inkorporiertem Wirkstoff.

Aus der amerikanischen Patentschrift US-PS 38 03 300 sind salbenartige Folien (getrocknete Öl-in-Wasser-Emulsionen) bekannt. Im Gegensatz zu den gelartigen erfindungsgemäßen Arzneimitteln und Placebos enthalten die Folien gemäß US-PS 38 03 300 Öle oder Fette und Emulgatoren.

Ferner ist es bekannt, feste oral applizierbare Arzneimittel mit Überzügen zu versehen, die als Bindemittel sogenannte Filmbildner wie Harze oder Celluloseäther enthalten. Die wirkstofffreien Überzüge schützen das Arzneimittel vor Abrieb, vor Licht und Feuchtigkeit, sie wirken außerdem geruchs- und geschmackshemmend (Fiedler: »Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete «).

In der österreichischen Patentschrift AT-PS 2 79 035 werden Folien zur Erzeugung lokaler Anästhesie beschrieben. Aus einer großen Zahl genannter Folienbildner, die auch Celluloseäther einschließt, werden Polyvinylalkohol, Polyvinylpyrrolidon und Alkalimetallcarboxymethylcellulose besonders herausgestellt. Es hat sich gezeigt, daß die nach der österreichischen Patentschrift bevorzugten Folienbildner für unsere Zwecke wenig geeignet sind, da diese Folienbildner die Wirkstoffe teilweise einschließen und nur verzögert oder überhaupt nicht freigeben. Bei der Verwendung von Polyvinylalkohol als Folienbildner wird die Folie bei Temperaturen um 100°C gegossen und getrocknet; nach dem Abkühlen tritt eine Kristallisation des Wirkstoffes ein, wodurch eine gleichmäßige Wirkstoffverteilung in der Folie nicht mehr gewährleistet ist.

Es ist die Aufgabe der Erfindung, folienförmige Arzneimittel bereitzustellen, in denen bis zu 60% Wirkstoffe gleichmäßig verteilt sind bzw. in denen eine Kristallisation der Wirkstoffe verhindert wird. Die Aktivität der Wirkstoffe muß in der Folie erhalten bleiben, und die Folie darf sich beim Lagern nicht verändern. Das Folienmaterial darf die Wirkstoffe nicht einschließen und muß sie bei Anwendung wieder vollständig freigeben.

Die Aufgabe wird dadurch gelöst, daß man ein Trennmittel einsetzt und als Folienbildner einen nichtionogenen, wasserlöslichen Hydroxyalkyläther der Cellulose, Methylcellulose oder Äthylcellulose verwendet.

Als nichtionogene, wasserlösliche Hydroxyalkyläther der Cellulose seien beispielsweise Hydroxypropylcellulose, Hydroxyäthylcellulose und Methylhydroxypropylcellulose genannt.

Geeignete Trennmittel sind Polyoxyäthylenpolyoxypropylenpolymeres, Polyoxyäthylenstearate und alkyl- oder acylsubstituierte Polyadditionsprodukte des Äthylenoxids.

Außer Trennmittel, Folienbildner und Wirkstoffe können die erfindungsgemäßen Folien Füllstoffe enthalten.

Als Füllstoffe sind zum Beispiel Cellulose, Zucker, wie zum Beispiel Lactose, Dextrose, Rohrzucker usw., Stärken, Mannit, Calciumcarbonat, Calciumphosphat, Talkum und Farbstoffe in löslicher Form oder als Pigmente geeignet. Werden lösliche Füll- bzw. Wirkstoffe verwendet, entsteht eine transparente, glatte Folie; werden unlösliche Füll- bzw. Wirkstoffe verwendet, entsteht eine weiße oder farbige, papier-

artige Folie.

Es können alle in der Human- und Veterinärmedizin verwendeten Wirkstoffe eingesetzt werden. Für die innere Anwendung kommt insbesondere die orale Verabreichung infrage. Unter der äußeren Anwendung sollen insbesondere die topikale Verabreichung auf der Haut und in Körperhöhlungen wie Nase, Ohr, Vagina usw., verstanden werden. Als Wirkstoffe seien beispielsweise genannt: Gestagene, Östrogene, Gemische aus Gestagenen und Östrogenen, Tranquilizer, Antidiabetika, Sulfonamide, Antibiotika, Trichomonadenmittel, Entzündungshemmer, wie zum Beispiel Corticoide, usw.

Der Arzneimittelwirkstoff kann im Trägermaterial gelöst oder gleichmäßig suspendiert vorliegen. Der Wirkstoffanteil in der Folie kann bis zu 60% betragen. Als Einzeldosis (Einheit) werden Flächen geschnitten bzw. perforiert, die Wirkstoffmengen enthalten wie sie üblicherweise auch in Tabletten, Dragees, Salben, Zäpfchen usw. enthalten sind. So kann die Wirkstoffmenge pro Einzeldosis je nach Anwendungsart beliebig hoch sein und zwischen etwa 1 µg und 0,5 g betragen, wobei die untere und obere Dosis leicht unter- oder überschritten werden können.

Zur Herstellung der erfindungsgemäßen folienförmigen Arzneimittel werden bis zu 60% Wirkstoffe, bezogen auf getrocknete Arzneimittel, und das Trennmittel gelöst bzw. suspendiert, der Folienbildner und gegebenenfalls der Füllstoff eingetragen, gegebenenfalls homogenisiert und die Lösung bzw. Suspension auf einer Folienziehmaschine zu einem Ausstrich ausgezogen. Die durch Trocknung des Ausstrichs erhaltene Folie wird durch Schneiden bzw. Perforieren in Einzeldosen geteilt.

In der Lösung bzw. Suspension wird der Folienbildner in Gewichtsmengen von 6 – 20%, der Füllstoff in Gewichtsmengen von 0 – 30% und das Trennmittel in Gewichtsmengen von 0,01 – 2% eingesetzt.

Das Lösungs- bzw. Suspensionsmittel ist zu etwa 48 – 84 Gewichtsprozent enthalten und besteht aus Wasser und/oder einem oder mehreren organischen Lösungsmitteln. Als organische Lösungsmittel kommen physiologisch verträgliche Lösungsmittel oder solche Lösungsmittel in Betracht, die bei der Trocknung bis auf einen physiologisch unbedenklichen Rest entfernt werden können. Solche Lösungsmittel sind zum Beispiel Äthylalkohol, Isopropanol, Methylenchlorid usw. und ihre Mischungen. Wasser und Äthylalkohol bzw. Gemische aus Wasser und Äthylalkohol werden bevorzugt angewandt.

Die Schichtdicke des nassen Ausstrichs beträgt etwa 0,1 – 2 mm und die der trockenen Folie etwa 0,05 – 1 mm, vorzugsweise 0,07 – 0,3 mm.

Das Verfahren zur Herstellung des Arzneimittels in Folienform in einem Arbeitsgang (kontinuierliches Verfahren) bietet den Vorteil, daß der Wirkstoff homogen und gleichmäßig verteilt in dem Wirkstoffträger vorliegt. Durch die Konzentration des Wirkstoffs im Träger, die Dicke der Folie und die Fläche kann man die Einzeldosis sehr einfach variieren.

Beispiel 1

Herstellung für 1000 Einheiten:

0,25 g D-Norgestrel
0,05 g Äthinylöstradiol
und
0,84 g Polyoxyäthylenpolyoxypropylenpolymeres
werden in
95,00 g Äthylalkohol unter Rühren gelöst, in diese Lösung wird eine Pulvermischung aus
16,93 g Hydroxypropylcellulose und
16,93 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,25 mg D-Norgestrel
0,05 mg Äthinylöstradiol
0,84 mg Polyoxyäthylenpolyoxypropylenpolymeres
16,93 mg Hydroxypropylcellulose
16,93 mg Cellulose
35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm². Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 2

Herstellung für 1000 Einheiten:

1,10 g Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 Mol Äthylenoxid auf 1 Mol Glycerid) werden in
152,00 g Wasser gelöst. In dieser Lösung werden
0,25 g mikronisiertes D-Norgestrel und
0,05 g mikronisiertes Äthinylöstradiol suspendiert und evtl. homogenisiert. In diese Suspension werden
22,10 g Hydroxypropylcellulose und
16,50 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,25 mg D-Norgestrel
0,05 mg Äthinylöstradiol
1,10 mg Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 ml Äthylenoxid auf 1 Mol Glycerid)
22,10 mg Hydroxypropylcellulose
16,50 mg Cellulose
40,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 3

Herstellung für 1000 Einheiten:

0,03 g D-Norgestrel und
0,84 g Polyoxyäthylenmonostearat-40 werden in
95,00 g Äthylalkohol unter Rühren gelöst.
In diese Lösung wird eine Pulvermischung aus
16,93 g Hydroxypropylcellulose und
17,20 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,03 mg D-Norgestrel
0,84 mg Polyoxyäthylenmonostearat-40
16,93 mg Hydroxypropylcellulose
17,20 mg Cellulose

35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 4

Herstellung für 1000 Einheiten:

1,10 g Polyoxyäthylenpolyoxypropylenpolymeres werden in
152,00 g demineralisiertem Wasser gelöst.
In dieser Lösung werden
0,03 g mikronisiertes D-Norgestrel suspendiert und evtl. homogenisiert.
In die Suspension werden
22,10 g Hydroxypropylcellulose und
16,77 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,03 mg D-Norgestrel
1,10 mg Polyoxyäthylenpolyoxypropylenpolymeres
22,10 mg Hydroxypropylcellulose
16,77 mg Cellulose

40,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 5

Herstellung für 1000 Einheiten:

10,00 g 7-Chlor-2-methylamino-5-phenyl-3H-1,4-benzo-diazepin-4-oxid und
0,84 g Polyoxyäthylenpolyoxypropylenpolymeres werden in
95,00 g Äthylalkohol gelöst.
In diese Lösung wird ein Pulvergemisch aus
16,93 g Hydroxypropylcellulose und
7,23 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

10,00 mg 7-Chlor-2-methylamino-5-phenyl-3H-1,4-benzo-diazepin-4-oxid

0,84 mg Polyoxyäthylenpolyoxypropylenpolymeres
16,93 mg Hydroxypropylcellulose
7,23 mg Cellulose

35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: gelb, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 6

Herstellung für 1000 Einheiten:

1,00 g Norethisteronacetat
0,03 g Äthinylöstradiol und
0,84 g Polyoxyäthylenpolyoxypropylenpolymeres werden in
95,00 g Äthylalkohol gelöst.
In diese Lösung wird ein Pulvergemisch aus
16,93 g Hydroxypropylcellulose und
16,20 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

1,00 mg Norethisteronacetat
0,03 mg Äthinylöstradiol
0,84 mg Polyoxyäthylenpolyoxypropylenpolymeres
16,93 mg Hydroxypropylcellulose
16,20 mg Cellulose

35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 7

Herstellung für 1000 Einheiten:

1,00 g Norethisteronacetat
0,03 g Äthinylöstradiol und
0,84 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einem Gemisch aus
101,60 g Methylenchlorid und
25,40 g Äthylalkohol gelöst.
In diese Lösung wird ein Pulvergemisch aus
16,93 g Hydroxyäthylcellulose und
16,20 g Stärke eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

1,00 mg Norethisteronacetat
0,03 mg Äthinylöstradiol
0,84 mg Polyoxyäthylenpolyoxypropylenpolymeres
16,93 mg Hydroxyäthylcellulose und
16,20 mg Stärke

35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 8

Herstellung für 1000 Einheiten:

1,00 g Norethisteronacetat
0,03 g Äthinylöstradiol und
0,84 g Polyoxyäthylenmonostearat-40 werden in
95,00 g Äthylalkohol gelöst.
In diese Lösung wird ein Pulvergemisch aus
16,93 g Hydroxypropylcellulose
8,10 g Lactose und
8,10 g Maisstärke eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

1,00 mg Norethisteronacetat
0,03 mg Äthinylöstradiol
0,84 mg Polyoxyäthylenmonostearat-40
16,93 mg Hydroxypropylcellulose
8,10 mg Lactose
8,10 mg Maisstärke
35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 9

Herstellung für 1000 Einheiten:

25,0 g 5-Morpholinomethyl-3-(5-nitro-1-methyl-2-imidazolyl)-methylenamino-2-oxazolidinon · HCl
werden in
2,1 g Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 Mol Äthylenoxid auf 1 Mol Glycerid) gelöst in
152,0 g Alkohol und Wasser 1 : 1 suspendiert. In diese Suspension werden
42,3 g Methylhydroxypropylcellulose und
18,1 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und getrocknet.

Zusammensetzung für eine Einheit:

25,0 mg 5-Morpholinomethyl-3-(5-nitro-1-methyl-2-imidazolyl)-methylenamino-2-oxazolidinon · HCl
2,1 mg Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 Mol Äthylenoxid auf 1 Mol Glycerid)
42,3 mg Methylhydroxypropylcellulose
18,1 mg Cellulose
87,5 mg

Eine Einheit entspricht einer Fläche von ca. 8 cm².
Aussehen der Folie: hellgelb, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 10

Herstellung für 1000 Einheiten:

4,0 g Glisoxepid in mikronisierter Form werden in
0,9 g Polyoxyäthylenmonostearat-40 gelöst in
152,0 g Wasser suspendiert und eventuell homogenisiert.
In die Suspension werden
15,0 g Hydroxyäthylcellulose und
15,1 g Calciumcarbonat eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und getrocknet.

Zusammensetzung für eine Einheit:

4,00 mg Glisoxepid
0,90 mg Polyoxyäthylenmonostearat-40
15,00 mg Hydroxyäthylcellulose
15,10 mg Calciumcarbonat
35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

(19) BUNDESREPUBLIK DEUTSCHLAND

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Patentansprüche:

1. Folienförmiges Arzneimittel auf Basis filmbildender Celluloseäther gemäß Patentanmeldung P 24 32 925.7-41, dadurch gekennzeichnet, daß die Folie nebeneinander Dosierungseinheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff aufweist.

2. Verfahren zur Herstellung eines folienförmigen Arzneimittels auf Basis filmbildender Celluloseäther durch Ausziehen von Lösungen bzw. Suspensionen auf einer Folienziehmaschine, durch nachträgliches Trocknen des nassen Ausstrichs und Teilen der Folie in Abschnitte gemäß Patentanmeldung P 24 32 925.7-41, dadurch gekennzeichnet, daß man zwei oder mehrere unterschiedliche Lösungen bzw. Suspensionen aus Trennmittel, Folienbildner und gegebenenfalls Füllstoffen und/oder Wirkstoffen herstellt, die unterschiedlichen Lösungen bzw. Suspensionen mit Hilfe eines Spezialrakels, das aus zwei oder mehreren Kammern besteht, zu einem Ausstrich auszieht und die durch Trocknung des Ausstrichs erhaltene Folie in Einheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff teilt.

Gegenstand der Patentanmeldung P 24 32 925.7-41 sind folienförmige Arzneimittel mit gleichmäßiger Wirkstoffverteilung bzw. folienförmige Placebos auf Basis filmbildender Celluloseäther, dadurch gekennzeichnet, daß sie bis zu 60% Wirkstoffe, ein Trennmittel und als Folienbildner einen nicht-ionogenen, wasserlöslichen Hydroxyalkyläther der Cellulose, Methylcellulose oder Äthylcellulose enthalten sowie ein Verfahren zu deren Herstellung.

In Weiterentwicklung des Gegenstandes der Patentanmeldung P 24 32 925.7-41 betrifft die vorliegende Erfindung das in den Ansprüchen näher gekennzeichnete folienförmige Arzneimittel und dessen Herstellung.

Es werden in einem Ausstrich Folien hergestellt, die nebeneinander Dosierungseinheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff aufweisen. Mit Hilfe eines Spezialrakels, das aus zwei oder mehreren Kammern besteht, werden unterschiedliche Lösungen bzw. Suspensionen ohne Vermischen zu einem zusammenhängenden Ausstrich ausgezogen. Die Breite und die Dicke des Ausstrichs ist für jede Kammer separat einstellbar. Gewünschtenfalls können Zonen (Streifen) mit unterschiedlichen Wirkstoffen bzw. verschiedenen Konzentrationen durch unterschiedliche Farbstoffe sichtbar gemacht werden. Durch Trocknung des nassen Ausstrichs wird eine Folie erhalten, die bei entsprechender Teilung, zum Beispiel durch Perforation, Einheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff liefert. Folien mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen werden zur Herstellung von Mehrphasenpräparaten benötigt, beispielsweise zur

Herstellung von Präparaten zur Konzeptionsverhütung.

Durch die Möglichkeit der räumlichen Trennung von miteinander inkompatiblen Wirkstoffen in einer Folieneinheit wird die Stabilität der einzelnen Wirkstoffe verbessert.

Das folienförmige Arzneimittel enthält ein Trennmittel und als Folienbildner einen nichtionogenen, wasserlöslichen Hydroxyalkyläther der Cellulose, Methylcellulose oder Äthylcellulose.

Als nichtionogene, wasserlösliche Hydroxyalkyläther der Cellulose seien beispielsweise Hydroxypropylcellulose, Hydroxyäthylcellulose und Methylhydroxypropylcellulose genannt.

Geeignete Trennmittel sind u. a. Polyoxyäthylenpolyoxypropylenpolymeres, Polyoxyäthylenstearate, alkyl- bzw. acylsubstituierte Polyadditionsprodukte des Äthylenoxids, zum Beispiel das Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 Mol Äthylenoxid auf 1 Mol Glycerid), Silikone, Silikontrennemulsionen und Metallseifen.

Außer Trennmittel und Folienbildner können die erfindungsgemäßen Folien Füllstoffe und Wirkstoffe enthalten.

Als Füllstoffe sind zum Beispiel Cellulose, Zucker, wie zum Beispiel Lactose, Dextrose, Rohrzucker usw., Stärken, Mannit, Calciumcarbonat, Calciumphosphat, Talkum und Farbstoffe in löslicher Form oder als Pigmente geeignet. Werden lösliche Füll- bzw. Wirkstoff verwendet, entsteht eine transparente, glatte Folie; werden unlösliche Füll- bzw. Wirkstoffe verwendet, entsteht eine weiße oder farbige, papierartige Folie.

Es können alle in der Human- und Veterinärmedizin verwendeten Wirkstoffe eingesetzt werden. Für die innere Anwendung kommt insbesondere die orale Verabreichung in Frage. Unter der äußeren Anwendung sollen insbesondere die topikale Verabreichung auf der Haut und in Körperhöhlungen wie Nase, Ohr, Vagina usw., verstanden werden. Als Wirkstoffe seien beispielsweise genannt: Gestagene, Östrogene, Gemische aus Gestagenen und Östrogenen, Tranquilizer, Antidiabetika, Sulfonamide, Antibiotika, Trichomonadenmittel, Entzündungshemmer, wie zum Beispiel Corticoide, usw.

Der Arzneimittelwirkstoff kann im Trägermaterial gelöst oder gleichmäßig suspendiert vorliegen. Der Wirkstoffanteil in der Folie kann 0 – 60% betragen. Als Einzeldosis (Einheit) werden Flächen geschnitten bzw. perforiert, die Wirkstoffmengen enthalten, wie sie üblicherweise auch in Tabletten, Dragées, Salben, Zäpfchen usw. enthalten sind. So kann die Wirkstoffmenge pro Einzeldosis je nach Anwendungsart beliebig hoch sein und zwischen etwa 1 µg und 0,5 g betragen, wobei die untere und obere Dosis leicht unter- oder überschritten werden können. Selbstverständlich können auch wirkstofffreie Träger (Placebos) hergestellt werden.

Zur Herstellung des folienförmigen Arzneimittels mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen werden zwei oder mehrere unterschiedliche Lösungen bzw. Suspensionen aus Trennmittel, Folienbildner und gegebenenfalls Füllstoffen und/oder Wirkstoffen bereitet, die unterschiedlichen Lösungen bzw. Suspensionen mit Hilfe eines Spezialrakels, das aus zwei oder mehreren Kammern besteht, auf einer Folienziehmaschine zu einem Ausstrich ausgezogen und die durch Trocknung des Ausstrichs erhaltene Folie in Einheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff geteilt.

Pro Lösung bzw. Suspension wird der Folienbildner in Gewichtsmengen von 6–20%, der Füllstoff in Gewichtsmengen von 0–30% und das Trennmittel vorzugsweise in Gewichtsmengen von 0,01–2% eingesetzt.

Das Lösungs- bzw. Suspensionsmittel ist zu etwa 48–84 Gewichtsprozent enthalten und besteht aus Wasser und/oder einem oder mehreren organischen Lösungsmitteln. Als organische Lösungsmittel kommen physiologisch verträgliche Lösungsmittel oder solche Lösungsmittel in Betracht, die bei der Trocknung bis auf einen physiologisch unbedenklichen Rest entfernt werden können. Solche Lösungsmittel sind zum Beispiel Äthylalkohol, Isopropanol, Methylenchlorid usw. und ihre Mischungen. Wasser und Äthylalkohol bzw. Gemische aus Wasser und Äthylalkohol werden bevorzugt angewandt.

Die Schichtdicke des nassen Ausstrichs beträgt etwa 0,1–2 mm und die der trockenen Folie etwa 0,05–1 mm, vorzugsweise 0,07–0,3 mm.

Das kontinuierliche Verfahren zur Herstellung des folienförmigen Arzneimittels bietet den Vorteil, daß der Wirkstoff homogen und gleichmäßig verteilt in dem Wirkstoffträger vorliegt. Durch die Konzentration des Wirkstoffs im Träger, die Dicke der Folie und die Fläche der Folie kann man die Einzeldosis sehr einfach variieren.

Beispiel 1

Zweiphasenpräparat

Teil 1: 21 Einheiten mit Wirkstoff
Teil 2: 7 Einheiten ohne Wirkstoff

Herstellung für 3000 Einheiten Teil 1

0,75 g D-Norgestrel,
0,15 g Äthinylöstradiol und
0,54 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
237,00 g Äthylalkohol und
12,00 g Wasser gelöst. In diese Lösung werden
44,28 g Hydroxypropylcellulose und
44,28 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 1000 Einheiten Teil 2

0,18 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
79,00 g Äthylalkohol und
4,00 g Wasser gelöst. In diese Lösung werden
14,91 g Hydroxypropylcellulose und
14,91 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Die so erhaltenen Suspensionen werden auf einem geeigneten Folienziehgerät mit einem Zweikammer-Spezialrakel (Breite der Kammern: 1 = 54 mm; 2 = 18 mm) zu einem Ausstrich von 0,5 mm ausgezogen und anschließend getrocknet. Bei entsprechender Teilung in Einheiten zu 18 × 18 mm, zum Beispiel durch Perforation, können über die Breite der Folie drei Einheiten mit Wirkstoff und eine wirkstofffreie Einheit abgeteilt werden. Aus dem Folienband lassen sich nun beliebig viele Abschnitte im Verhältnis von drei Einheiten mit Wirkstoff und einer Einheit ohne Wirkstoff herstellen.

Zusammensetzung für je eine Einheit:

Teil 1 (wirkstoffhaltig)		Teil 2 (wirkstofffrei)
0,25 mg	D-Norgestrel	–
0,05 mg	Äthinylöstradiol	–
14,76 mg	Hydroxypropylcellulose	14,91 mg
14,76 mg	Cellulose	14,91 mg
0,18 mg	Polyoxyäthylenpolyoxypropylenpolymeres	0,18 mg
30,00 mg	Gewicht pro Einheit	30,00 mg

Fläche pro Einheit: ca. 3 cm^2.
Aussehen: weiß.

Beispiel 2

Dreiphasenpräparat (Zweiwirkstoffstufenpräparat)

Teil 1: 11 Einheiten mit 0,05 mg D-Norgestrel
0,05 mg Äthinylöstradiol
Teil 2: 10 Einheiten mit 0,125 mg D-Norgestrel
0,050 mg Äthinylöstradiol
Teil 3: 7 Einheiten ohne Wirkstoff

Herstellung für 1100 Einheiten Teil 1:

0,055 g D-Norgestrel,
0,055 g Äthinylöstradiol und
0,198 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
86,900 g Äthylalkohol und
4,400 g Wasser gelöst. In diese Lösung werden
16,346 g Hydroxypropylcellulose und
16,346 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 1000 Einheiten Teil 2:

0,125 g D-Norgestrel,
0,050 g Äthinylöstradiol und
0,180 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
79,000 g Äthylalkohol und
4,000 g Wasser gelöst. In diese Lösung werden
14,823 g Hydroxypropylcellulose und
14,822 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 700 Einheiten Teil 3:

0,189 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
82,950 gÄthylalkohol und
4,200 g Wasser gelöst. In diese Lösung werden
15,656 g Hydroxypropylcellulose und
15,655 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Die so erhaltenen Suspensionen werden auf einem geeigneten Folienziehgerät mit einem Dreikammer-Spezialrakel (Breite pro Kammer 18 mm) zu einem Ausstrich ausgezogen und getrocknet. Bei entsprechender Teilung, zum Beispiel durch Perforation, zu Einheiten von 18 × 18 mm für Teil 1, 18 × 19,8 mm für Teil 2 und 18 × 28 mm für Teil 3 können über die Breite der Folie drei Einheiten mit unterschiedlichem Wirkstoffgehalt abgeteilt werden. Aus dem Folienband lassen sich Präparate mit 11 Einheiten Teil 1, 10 Einheiten Teil 2 und 7 Einheiten Teil 3 abtrennen.

Zusammensetzung pro Einheit:

Teil 1	Teil 2	Teil 3	Inhaltsstoffe
0,050 mg	0,125 mg	–	D-Norgestrel
0,050 mg	0,050 mg	–	Äthinylöstradiol
0,180 mg	0,180 mg	0,270 mg	Polyoxyäthylenpolyoxypropylenpolymeres
14,860 mg	14,823 mg	22,366 mg	Hydroxypropylcellulose
14,860 mg	14,822 mg	22,364 mg	Cellulose
30,000 mg	30,000 mg	45,000 mg	Gewicht pro Einheit
ca. 3 cm^2	ca. 3,5 cm^2	ca. 5 cm^2	Fläche pro Einheit
weiß	weiß	weiß	Aussehen

Beispiel 3

Dreiphasenpräparat

Teil 1: 11 Einheiten mit 0,05 mg D-Norgestrel
0,05 mg Äthinylöstradiol
Teil 2: 10 Einheiten mit 0,125 mg D-Norgestrel
0,050 mg Äthinylöstradiol
Teil 3: 7 Einheiten mit 50,00 mg Eisen(II)fumarat

Herstellung für 1100 Einheiten Teil 1:

0,066 g Lebensmittelgelb Nr. 2 (Tartrazin; E 102) werden in
4,400 g Wasser gelöst und anschließend in
86,900 gÄthylalkohol eingetragen. In dieser Lösung werden
0,055 g D-Norgestrel,
0,055 g Äthinylöstradiol und
0,198 g Polyoxyäthylenpolyoxypropylenpolymeres gelöst.
In diese Lösung werden
16,313 g Hydroxypropylcellulose und
16,313 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 1000 Einheiten Teil 2:

0,065 g Lebensmittelorange Nr. 2 (Sunset Yellow; E 110) werden in
4,000 g Wasser gelöst und anschließend in
79,000 ggÄthylalkohol eingetragen. In dieser Lösung werden
0,125 g D-Norgestrel,
0,050 g Äthinylöstradiol und
0,180 g Polyoxyäthylenpolyoxypropylenpolymeres gelöst.
In diese Lösung werden
14,790 g Hydroxypropylcellulose und
14,790 g Cellulose eingetragen und gegebenenfalls *homogenisiert*.

Herstellung für 700 Einheiten Teil 3:

0,042 g Saccharin,
0,042 g Sahne-Essenz und
0,406 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
55,300 gÄthylalkohol und
2,800 g Wasser gelöst. In diese Lösung werden
35,000 g Eisen(II)fumarat,
17,500 g Hydroxypropylcellulose,
5,950 g Kakao und
4,060 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Die so erhaltenen Suspensionen werden auf einem geeigneten Folienziehgerät mit einem Dreikammer-Spezialrakel (Breite pro Kammer 18 mm) zu einem Ausstrich ausgezogen und anschließend getrocknet. Bei entsprechender Teilung, zum Beispiel durch Perforation, zu Einheiten von 18 × 18 mm für Teil 1, 18 × 19,8 mm für Teil 2 und 18 × 28 mm für Teil 3 können über die Breite der Folie drei Einheiten mit unterschiedlichem Wirkstoffgehalt abgeteilt werden. Aus dem Folienband lassen sich Präparate mit 11 Einheiten Teil 1, 10 Einheiten Teil 2 und 7 Einheiten Teil 3 abtrennen.

Zusammensetzung pro Einheit:

Teil 1	Teil 2	Teil 3	Inhaltsstoffe
0,050 mg	0,125 mg	–	D-Norgestrel
0,050 mg	0,050 mg	–	Äthinylöstradiol
–	–	50,000 mg	Eisen(II)fumarat
0,180 mg	0,180 mg	0,580 mg	Polyoxyäthylenpolyoxypropylenpolymeres
0,060 mg	–	–	Lebensmittelgelb Nr. 2
–	0,065 mg	–	Lebensmittelorange Nr. 2
14,830 mg	14,790 mg	25,000 mg	Hydroxypropylcellulose
14,830 mg	14,790 mg	5,800 mg	Cellulose
–	–	8,500 mg	Kakao
–	–	0,060 mg	Saccharin
–	–	0,060 mg	Sahne-Essenz
30,000 mg	30,000 mg	90,000 mg	Gewicht pro Einheit
ca. 3 cm^2	ca. 3,5 cm^2	ca. 5 cm^2	Fläche pro Einheit
gelb	orange	braun	Aussehen

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(56) Für die Beurteilung der Patentfähigkeit in Betracht gezogene Druckschriften:
DE-OS 24 49 865
CH 6 24 846

(54) Dosierungsform für Wirkstoffe sowie Verfahren zu deren Herstellung

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Beschreibung

Arzneimittel können in Form von Pulvern, Tropflösungen, oder Säften oral verabreicht werden. Da bei diesen Abgabeformen eine genaue Dosierung jedoch schwierig ist, werden vom Hersteller dosierte Applikationsformen wie Tabletten, Dragees oder Kapseln generell bevorzugt. Auch Reagentien und andere Wirkstoffe, z. B. Süßstoffe, werden für eine genaue dosierte Anwendung häufig tablettiert. Die Herstellungstechnik für Tabletten, Dragees, Kapseln und dergleichen ist zwar weitgehend ausgereift, doch ist eine Reihe von systembedingten Nachteilen nicht zu übersehen.

Für niedrig dosierte Wirkstoffe muß ein großer Anteil an Hilfsstoffen zugesetzt werden, um zu einer handhabbaren Größe der Einzeldosis zu gelangen. Weiterhin ist eine genaue Kennzeichnung einzelner Tabletten oder Dragees praktisch nicht möglich. Es haben sich deshalb Durchdrückpackungen durchgesetzt, welche eine Mehrzahl von Tabletten, Dragees oder auch Kapseln enthalten und welche mit den notwendigen Informationen, insbesondere dem Namen des Präparates bedruckt sind. Die Herstellung solcher Verpackungen erfordert naturgemäß einen zusätzlichen Arbeitsgang und es werden Umverpackungen in Form von Faltschachteln benötigt, welche ein beträchtliches Leervolumen aufweisen und dadurch zusätzlich Lagerraum beanspruchen. Ein besonders gravierender Nachteil von Dragees und Kapseln besteht darin, daß eine Zerteilung praktisch unmöglich ist, die kleinste Dosis somit vorgegeben ist. Auch bei Tabletten ist eine genaue Zerteilung schwierig, lediglicht größere Tabletten mit einer Kerbe als Sollbruchstelle lassen sich allenfalls teilen, wobei häufig ungleichgroße Bruchstücke entstehen.

Es sind bereits Versuche zur Schaffung einer neuen Darreichungsform für die orale Verabreichung von Arzneimitteln bekannt geworden, welche aus wirkstoffhaltigen Folien bestehen. Gemäß der BE-PS 6 37 363 wird ein papierartiges Trägermaterial aus unlöslichen Zellulosefasern mit einer Wirkstofflösung getränkt bzw. beschichtet und eine Dosierung durch Perforation der Trägerfolie nach Art eines Briefmarkenbogens erreicht. Aus den deutschen Offenlegungsschriften 24 32 925 und 24 49 865 ist es bekannt, Arzneimittelwirkstoffe in Folienbildner einzuarbeiten, bei denen es sich vorzugsweise um wasserlösliche Verbindungen wie Methyl- und Ethylzellulose, insbesondere aber Hydroxypropylzellulose, Hydroxyethylzellulose oder Methylhydroxypropylzellulose handelt. Auch die so erhaltenen wirkstoffhaltigen Folien lassen sich durch Perforation in einzelne Abschnitte zur Dosierung aufteilen. In der CH-PS 6 24 846 wird vorgeschlagen, eine Einheitsdosierungsform dadurch zu schaffen, daß ein Arzneimittelwirkstoff zwischen mehreren Lagen aus eßbarem Trägermaterial angeordnet wird, um den Wirkstoff gegen Einflüsse von außen zu schützen. Darüber hinaus ermöglicht die Ausbildung in mehreren Lagen die Einbringung verschiedener Wirkstoffe in voneinander getrennten Schichten. Wie die Betonung der Eßbarkeit der Trägermaterialien verdeutlicht, soll die gesamte auf diese Weise erhaltene schichtförmige Dosierungsform zur oralen Applikation dienen.

Alle diese Vorschläge haben keinen Eingang in die Praxis gefunden und in dem neuesten Lehrbuch der "Arzneiformenlehre" von P. H. List, 4. Auflage, Stuttgart, 1985, finden sie keine Erwähnung. Dies beruht ersichtlich darauf, daß die bislang bekanntgewordenen Formen es nicht ermöglichen, die geforderte Gewichtskonstanz und gleichmäßige Wirkstoffverteilung zu erreichen, welche heute gefordert werden. Die Pharmakopoea Europea setzt zum Beispiel Maßstäbe für die Gleichförmigkeit des Gewichtes einzeldosierter Arzneiformen, wobei diese dem jeweiligen Durchschnittsgewicht entsprechend nach höchstzulässigen Abweichungen in % gestaffelt sind. Die Forderung liegt im allgemeinen bei +/—5% bis max. 10%. Entsprechende Werte für feste Arzneiformen bestehen auch hinsichtlich anderer Parameter wie Zerfallzeit und Lösungsgeschwindigkeit.

Die oben erwähnten Vorschläge des Standes der Technik führen zur Produkten ungenügender Akzeptanz durch die Patienten (Papierabschnitte lassen sich nur schlecht einnehmen) und erlauben keine exakte Dosierung pro Flächeneinheit, wie sie unbedingt gefordert werden muß. Bei Inkorporieren des Wirkstoffes in eine Folie bereitet nicht nur die genaue Dosierung Schwierigkeiten, sondern ein wesentlicher weiterer Nachteil besteht darin, daß für jeden Wirkstoff eine entsprechende Folie gesondert hergestellt werden muß, so daß die Wirtschaftlichkeit des Herstellungsverfahrens nicht gegeben ist.

Der Erfindung liegt demgegenüber die Aufgabe zugrunde, eine dünnflächige Dosierungsform zu schaffen, welche die genannten Nachteile nicht aufweist, sich leicht herstellen läßt und mit großer Flexibilität unter Verwendung verschiedener Wirkstoffe an die Anforderungen des Marktes angepaßt werden kann.

Gegenstand der Erfindung ist eine Dosierungsform für Wirkstoffe aus einem flächigen Trägermaterial mit einer wirkstoffhaltigen Beschichtung, wobei diese Dosierungsform dadurch gekennzeichnet ist, daß das Trägermaterial ein Trennpapier, ein Trennfilm oder eine Trennfolie ist und daß das Trägermaterial einseitig mit der wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

Die erfindungsgemäße Dosierungsform weist mehrere wesentliche Vorteile auf:

- Da der Träger im Gegensatz zu den vorbekannten Ausführungsformen keinen Teil der Darreichungsform bildet, kann er die erforderliche Festigkeit aufweisen, ohne die Akzeptanz des Arzneimittels durch Patienten zu beeinträchtigen,
- die wirkstoffhaltige Schicht kann bei hochwirksamen Arzneimitteln verhältnismäßig dünn sein, da das Trägermaterial die mechanische Festigkeit gewährleistet.
- mit Hilfe moderner Auftragverfahren läßt sich die wirkstoffhaltige Beschichtung mit konstanter Schichtdicke aufbringen, so daß die erforderlichen Toleranzen eingehalten werden können,
- falls eine Sterilisierung erforderlich ist, kann diese wegen der geringen Schichtdicke problemlos mittels Strahlenbehandlung erreicht werden,
- der Träger läßt sich auf der Vorder- und insbesondere der Rückseite mit verschiedenen Informationen bedrucken,
- aufgrund der relativ großen Fläche von beispielsweise 4 bis 10 cm^2 lassen sich ausführliche Informationen für den Benutzer auf das Trägermaterial vor oder auch nach der Beschichtung aufdrukken,
- die Dosiseinheiten lassen sich durch entsprechende Vorzerteilung flexibel gestalten, so daß für verschiedene Dosierungen (z. B. für Erwachsene

und Kinder) nur ein Produkt hergestellt werden muß; die Vorzerteilung kann ggf. auch erst in der Apotheke oder im Krankenhaus nach ärztlichen Angaben vorgenommen werden.

Mit den vorbekannten Darreichungsformen in Folienform hat die erfindungsgemäße Darreichungsform darüber hinaus den Vorteil des äußerst geringen Platzbedarfes gemeinsam. Statt Faltschachteln können daher beispielsweise Taschen oder Beutel aus Kunststoffolie oder kunststoffbeschichtetem Papier verwendet werden, in welche das Produkt eingesiegelt wird, ähnlich wie feuchte Erfrischungstücher.

Als Trägermaterialien eignen sich die verschiedensten Materialien, beispielsweise Papiere mit einem Gewicht von etwa 80 bis 120, vorzugsweise 100 g/m², Kunststoffilme bzw. -folien auf Basis von Polyethylen, Polyvinylchlorid, Polyvinylidenchlorid, Polyester und anderen indifferenten Polymeren oder dünne Metallfolien, beispielsweise solche aus Aluminium. Bevorzugt werden siliconisierte Papiere, welche in unterschiedlichen Qualitäten im Handel erhältlich sind, und welche insbesondere zur Abdeckung von selbstklebenden Produkten wie Pflastern, Klebebändern oder Haftetiketten Verwendung finden. Die an sich auch geeigneten, mit Wachs oder Paraffin beschichteten Trennpapiere sind dagegen in der Praxis weitgehend durch die mit inerten Siliconen beschichteten Papiere ersetzt worden. Bei einem Auftrag der wirkstoffhaltigen Beschichtung auf nur eine Seite der Trägerfolie reicht es aus, wenn nur diese mit einer nicht haftenden Beschichtung versehen ist. Die Rückseite sollte dagegen vorzugsweise so beschaffen sein, daß sie mit Informationen unterschiedlicher Art gut und dauerhaft bedruckbar ist.

Die Möglichkeit der vorder- und rückseitigen Bedruckung ist ein besonderer Vorteil der erfindungsgemäßen Darreichungsform. Beispielsweise können die Kennzeichnung, Angaben über die Inhaltsstoffe sowie Dosierungsangaben aufgedruckt werden. Gegebenenfalls läßt sich sogar der ganze Inhalt eines Beipackzettels rückseitig aufdrucken mit der Folge, daß ein separater Beipackzettel, der auch häufig verlorengeht, überflüssig wird. Bei Arzneimitteln, welche regelmäßig genommen werden müssen, beispielsweise bei hormonalen Contrazeptiva, kann der gesamte Verabreichungsplan so angebracht werden, daß eine einfache Einnahmekontrolle gewährleistet ist. Da die einzelnen Dosiseinheiten von dem Träger abgezogen werden, bleibt dieser bis zum vollständigen Aufbrauch des Arzneimittels erhalten und es gehen keine der aufgedruckten Informationen verloren.

Für die wirkstoffhaltige Beschichtung findet vorzugsweise eine wäßrige Beschichtungsmasse Verwendung, die physiologisch inert ist und deren Einzelkomponenten für Arzneimittel bzw. Lebensmittel geeignet sind. Dabei handelt es sich zum einen um wasserlösliche Quellstoffe in der Art polymerer Filmbildner, vorzugsweise Gelatine, Zellulosen oder Hemizellulosen, quellende oder lösliche Stärken. Vorzugsweise werden ferner Weichmacher zugesetzt, insbesondere mehrwertige Alkohole wie Glycerin oder Sorbitol. Zur Einstellung der gewünschten Viskosität der Beschichtungsmasse, welche etwa die Konsistenz eines Schleimes aufweist, finden polymere Quellstoffe Verwendung, vorzugsweise Alginate, Pectine, Chitine, Lecithine oder Polyethylenglykole. Diese letzteren Stoffe können gleichzeitig als Haftvermittler dienen. Andererseits können auch wasserlösliche Gumme oder Gummi arabicum zugesetzt werden, um die Haftung der Beschichtung auf dem Trägermaterial zu verbessern. Schließlich können noch Konservierungsmittel wie z. B. p-Hydroxybenzoesäureester, Farbstoffe (Lebensmittelfarbstoffe), Pigmente wie Titandioxid oder Aroma- und Süßstoffe zugesetzt werden.

Beschichtungsmassen mit einem Wassergehalt von ungefähr 50% und einer Viskosität von etwa 30 bis zu 10 000 mpa · s haben sich als besonders geeignet erwiesen. Die Rezeptur und Herstellung ähnelt derjenigen eines Arzneimittelsaftes, in welchem der Wirkstoff bzw. die Wirkstoffkombination gelöst oder gleichmäßig dispergiert wird. Die Beschichtungsmasse muß ausreichende Homogenität und galenische Stabilität aufweisen, damit ein gleichmäßiger Wirkstoffgehalt der fertigen Beschichtung sichergestellt ist.

Folgende Rahmenrezeptur hat sich bewährt:

Gelatine	8 bis 10 g
Stärke	3 bis 8 g
Glycerin	1 bis 2 g
Wasser	30 bis 50 g

In dieser Grundmasse wird der Wirkstoff gelöst bzw. dispergiert. Im Fall der Verwendung einer Dispersion muß der Wirkstoff für eine gleichmäßige Verteilung äußerst feinteilig sein. Vorzugsweise liegt die mittlere Teilchengröße im Bereich von etwa 1 bis 20 µm.

Die gewünschte Dosis des Wirkstoffes und die angestrebte Fläche der Dosiseinheiten bestimmen letztlich die Dicke der Schicht, wobei der Feuchtigkeitsgehalt der Beschichtungmasse und der fertigen Beschichtung zu berücksichtigen sind.

Im Rahmen der Erfindung ist es auch möglich, die Beschichtungsmasse zu einer wirkstoffhaltigen Folie zu verarbeiten und diese anschließend, gegebenenfalls unter Verwendung eines physiologisch einsetzbaren inerten Klebstoffes, auf das Trägermaterial aufzukaschieren. Diese Ausführungsform kommt insbesondere dann in Betracht, wenn die wirkstoffhaltige Beschichtung eine größere Dicke aufweisen soll, so daß die Verarbeitung zu einer Folie möglich und sinnvoll ist.

Die erfindungsgemäße Darreichungsform ist besonders geeignet für Arzneimittel, welche niedrig dosiert verabreicht werden, d. h. bei welchen die Einzeldosis für die orale Applikation zwischen 0 mg (Placebo) und etwa 20 mg liegt. Geeignete Arzneimittelwirkstoffe finden sich in allen Bereichen der oralen Therapie; hervorzuheben sind u. a. Analeptika, Antibiotika, Antidiabetika, Antiemetika, Antiepileptika, Antihypertonika, Cortikoide, Geriatrika, Hypnotika, Cardiaka, Hypostatika und Biowirkstoffe.

Die Beschichtung kann einen oder mehrere Arzneimittelwirkstoffe enthalten. Falls bei Verwendung mehrerer Wirkstoffe diese nicht ohne weiteres miteinander verträglich sind, ist es bei der erfindungsgemäßen Darreichungsform möglich, die Beschichtung in mehreren Schichten unterschiedlicher Zusammensetzung aufzubringen und die Wirkstoffe dadurch voneinander zu trennen, wobei erforderlichenfalls eine wirkstofffreie Zwischenschicht vorgesehen werden kann. Weiterhin ist es möglich, über der wirkstoffhaltigen Schicht noch eine weitere Schutzschicht vorzusehen, welche den/die Wirkstoff(e) gegen eine Berührung mit der Atmosphäre und/oder gegen Licht schützt. In diesen Fällen muß die Schutzschicht demgemäß luft- und feuchtigkeitsundurchlässig und/oder durch Zusatz entsprechender

Farbstoffe bzw. Pigmente lichtundurchlässig sein.

Weiterhin kann durch entsprechenden Aufbau der Beschichtung die Wirkstoffabgabe nach Verabreichung des Arzneimittels gesteuert werden. Beispielsweise ist es möglich, eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten anzuordnen, welche die Wirkstoffresorption im Magen/Darmtrakt in an sich bekannter Weise steuern. Dabei kann die Wirkstoffschicht z. B. zwischen zwei säureunlöslichen Schichten angeordnet werden, so daß bei Verabreichung der Magen passiert wird und die Resorption erst im Darmtrakt erfolgt. In ähnlicher Weise können unterschiedliche Wirkstoffe in verschiedenen Schichten übereinander auf die Trägerfolie aufgebracht werden, damit die Resorption nacheinander und/oder verzögert erfolgt. Ähnliche pharmakokinetische Effekte lassen sich durch das Einarbeiten (z. B. Suspendieren) von unterschiedlich vorbehandelten mikroverkapselten Wirkstoffen erzielen.

Die Aufbringung der wirkstoffhaltigen Beschichtungen auf den Träger, z. B. auf ein Trennpapier oder eine Trenn-Kunststoffolie, erfolgt vorzugsweise mit Hilfe eines Glattwalzen-Beschichtungsverfahrens. Die vorzugsweise auf ca. 60 bis 80°C erwärmte Beschichtungsmasse wird dabei bei geschlossenem Auftragsystem auf eine beheizte Walze in dünner Schicht übertragen. Mit verzögertem Gleichlauf in bestimmten wählbaren Verhältnissen wird die Masse auf eine parallel angeordnete Walze übertragen, wobei eine Reduzierung der Schichtdicke im Verhältnis 1 : 2 bis 1 : 10 erfolgen kann, wodurch gleichzeitig die Toleranzen bei der Auftragung um diese Faktoren verringert werden. Im Gleichlauf erfolgt dann über ein weiteres Walzensystem die Beschichtung des Trägermaterials. Bei einer Anpassung der Wirkstoffbeschichtungsmasse an den Release-Wert des Trägermaterials kann auf den Zusatz eines Klebemittels völlig verzichtet werden. Gegebenenfalls können jedoch auch geeignete Haftvermittler zugesetzt werden.

Bei Aufbringung mehrerer Schichten, wie dies oben bereits beschrieben wurde, werden diese nacheinander aufgebracht, wobei ggf. jede Beschichtung zuvor eine Trocknungsstation durchläuft. Diese kann beispielsweise aus einem temperierten Walzenpaar und einem in Sektionen steuerbaren Trockentunnel bestehen. Nach dem letzten Beschichtungsvorgang wird das beschichtete Material auf Rollen aufgewickelt.

Die wirkstoffhaltige Beschichtung wird anschließend in Dosiseinheiten vorzerteilt, welche ähnlich wir Haftetiketten vom Trägermaterial abziehbar sind. Normalerweise wird diese Vorzerteilung beim Arzneimittelhersteller erfolgen; es ist jedoch auch denkbar, das beschichtete Material beispielsweise an Krankenhäuser oder Apotheken auszuliefern, wo dann die Vorzerteilung dosisabhängig oder auch individuell nach ärztlicher Vorgabe durchgeführt werden kann.

Die Vorzerteilung erfolgt in besonders einfacher Weise durch Stanzung, wobei es möglich ist, diesen Schritt mit der Bedruckung des Trägermaterials zu kombinieren. In vielen Fällen wird es allerdings günstiger sein, die Bedruckung des Trägermaterials vor der Beschichtung vorzunehmen.

Vor oder besser nach Vorzerteilung der wirkstoffhaltigen Beschichtung in Dosiseinheiten wird das beschichtete Trägermaterial zu gebrauchsfertigen Abschnitten zerschnitten, welche eine bestimmte Anzahl von Dosiseinheiten enthalten. Es ist auch denkbar, das Material auf Rollen zu schmalen Bändern zu zerschneiden. Vor einer solchen Einzelrolle können dann die einzelnen Dosiseinheiten ähnlich wie einzelne Haftetiketten abgezogen werden.

Vorstehend wurde die Erfindung im wesentlichen im Zusammenhang mit Arzneimitteln beschrieben, worauf sie jedoch keineswegs beschränkt ist. Beispielsweise lassen sich in derselben Weise auch Dosierungsformen für chemische Reagentien, Aromastoffe und dergleichen herstellen.

Zur näheren Erläuterung der Erfindung sollen die nachfolgenden Ausführungsbeispiele dienen.

Beispiel 1

Herstellung eines Cardiakum

Zum Naßauftrag auf ein Trennpapier (Siliconpapier mit einem Flächengewicht von 100 g/m²) wurde eine Beschichtungsmasse gemäß folgender Rezeptur hergestellt:

Gelatine	10,0 Gew.-Teile	= 22,22%
Kartoffelstärke	3,0 Gew.-Teile	= 6,67%
Glycerin	1,5 Gew.-Teile	= 3,33%
Titandioxid	0,3 Gew.-Teile	= 0,67%
α-Acetyldigoxin	0,2 Gew.-Teile	= 0,44%
Wasser	30,0 Gew.-Teile	= 66,67%

Diese Beschichtungsmasse wurde in einer Schichtdikke von 90 g/m² mittels Walzen auf das Trennpapier aufgebracht. Nach dem Trocknen wies die Beschichtung einen Restwassergehalt von 11,76% auf. Das Beschichtungsgewicht lag bei 34 g/m², was einem Arzneimittelanteil von 0,4 g/m² entspricht. Ein Abschnitt von 2 cm × 2,5 cm = 5 cm² (entsprechend den Abmessungen einer üblichen Briefmarke) enthält 0,2 mg α-Acetyldigoxin, was mit dem Gehalt der handelsüblichen Tabletten übereinstimmt.

Beispiel 2

Herstellung eines Contrazeptivum

Zum Naßauftrag auf ein Trennpapier (einseitig silikonisiertes Papier von 110 g/m²) wurde eine Beschichtungsmasse von schleimartiger Konsistenz nach folgender Rezeptur hergestellt:

Gelatine	10,00 Gew.-Teile	= 22,222%
Maisstärke	3,17 Gew.-Teile	= 7,044%
Glycerin	1,50 Gew.-Teile	= 3,333%
Titandioxid	0,30 Gew.-Teile	= 0,667%
Levonorgestrel	0,03 Gew.-Teile	= 0,067%
Wasser	30,00 Gew.-Teile	= 66,663%

Die Beschichtungsmasse wurde mittels eines Walzenübertragungsverfahrens mit einem Beschichtungsgewicht von 45 g/m² auf das Trennpapier aufgebracht. Nach dem Trocknen wies die Beschichtung einen Restwassergehalt von 11,76% auf. Bei einem Beschichtungsgewicht von 17 g/m² betrug der Arzneimittelanteil 0,03 g/m².

Ein Abschnitt von 2,5 × 4 cm bzw. zwei Abschnitte von je 2,5 cm × 2 cm, also 10 cm² der Beschichtung, enthalten somit 0,03 Levonorgestrel, was dem Gehalt der handelsüblichen Dragees entspricht.

Patentansprüche

1. Dosierungsform für Wirkstoffe aus einem flächigen Trägermaterial mit einer wirkstoffhaltigen Beschichtung, **dadurch gekennzeichnet,** daß das Trägermaterial ein Trennpapier, ein Trennfilm oder eine Trennfolie ist und daß das Trägermaterial einseitig mit der wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

2. Dosierungsform nach Anspruch 1, dadurch gekennzeichnet, daß das Trägermaterial ein silicon- oder wachsbeschichtetes Trennpapier ist.

3. Dosierungsform nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die wirkstoffhaltige Beschichtung durch Stanzung in Dosiseinheiten vorzerteilt ist.

4. Dosierungsform nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß die Beschichtung einen oder mehrere Arzneimittelwirkstoffe enthält.

5. Dosierungsform nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß die Beschichtung wasserlösliche Quellstoffe als polymere Filmbildner und gegebenenfalls Weichmacher enthält.

6. Dosierungsform nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß die Beschichtung zur Viskositätseinstellung polymere Quellstoffe enthält, welche gleichzeitig als Haftvermittler dienen können.

7. Dosierungsform nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß die Beschichtung in mehreren Schichten unterschiedlicher Zusammensetzung aufgebracht ist.

8. Dosierungsform nach Anspruch 7, dadurch gekennzeichnet, daß miteinander inkompatible Wirkstoffe in getrennten Schichten nacheinander auf das Trägermaterial aufgebracht sind.

9. Dosierungsform nach Anspruch 7, dadurch gekennzeichnet, daß eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten angeordnet ist, welche die Wirkstoff-Resorption im Magen/Darmtrakt in an sich bekannter Weise steuern.

10. Dosierungsform nach Anspruch 7, dadurch gekennzeichnet, daß über der Wirkstoffschicht eine weitere Schicht aufgebracht ist, die den Wirkstoff gegen Berührung mit der Atmosphäre und/oder gegen Licht schützt.

11. Dosierungsform nach einem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß die Rückseite des Trägermaterials mit die Wirkstoffzusammensetzung und/oder deren Einnahme betreffenden Informationen bedruckbar ist.

12. Verfahren zur Herstellung der Dosierungsform der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß man eine wirkstoffhaltige Zusammensetzung mit Hilfe von Walzen auf die nichthaftend ausgerüstete Seite eines Trennpapiers, eines Trennfilms oder einer Trennfolie bringt.

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Description

This invention relates to an oral bandage that can be adhered to the oral mucosa to prevent a drug administered to the oral mucosa from running out and to cover or protect the affected part of the oral mucosa, and to oral preparations comprising such a bandage having incorporated therein a topical drug.

In the field of dental and oral surgery, various topical preparations in the form of ointments or solutions have hitherto been administered to the oral mucosa for prophylaxis and therapy of oral diseases, such as periodontal disease, stomatitis, etc. The most serious problem in administering drugs to the oral mucosa is that the drug runs away in a short time by salivary secretion or through eating or drinking, thereby failing to fully exert its medical effects.

On the other hand, protection of the affected part in the oral cavity has scarcely been conducted because no effective oral bandage has been developed. As mentioned above, the continuous salivary secretion and taking of foods and drinks constitute an insuperable barrier to the protection of the oral mucosa.

In recent years, many proposals have been made in an attempt to effectively administer a drug to the mucosa of the oral cavity, so as to overcome the above-described problems. Among them, proposals relevant to the present invention relate to preparations adhesive to the oral mucosa, which contain water-soluble high-molecular substances as an adhesive. When water-soluble high-molecular substances absorb a small amount of water, they become a viscous aqueous solution or gel having adhesion, though varying in extent with their kind. Making use of this property, various preparations adhesive to the oral mucosa have been proposed, including pastes as disclosed in Japanese Patent Publication No. 27491/81, sponges as disclosed in Japanese Patent Publication No. 25211/81, tablets as disclosed in Japanese Patent Publication No. 7605/83, sheets as disclosed in Japanese Patent Publication No. 16676/69 and Japanese Patent Application (OPI) No. 186913/84 (the term "OPI" has herein used means "unexamined published application").

However, these conventional preparations only are intended to have enough adhesion to allow them to remain in position for a period of time enough to administer the drug to the mucosa. In other words, these preparations do not possess strong adhesion for an extended period of time as required for an oral bandage. On the contrary, an oral bandage is intended to prevent running-off of the administered drug or to provide protection by adhesion to the affected or injured part of the oral cavity. Therefore, it is required to have strong and long-lasting adhesion to the oral mucosa which may be less adherable due to the administered drug or stomatorrhagia. Since both adhesive strength and duration of adhesion of the aforesaid conventional preparations adhesive to the oral mucosa are not so high as demanded for an oral bandage, application of bases used in these preparations to an oral bandage can never satisfy the above-described requirements of an oral bandage. The conventional adhesive tapes which are intended to be applied to the skin cannot be, of course, used as an oral bandage because they have no adhesion to a wet surface such as oral mucosa.

Japanese Patent Application (OPI) No.186913/84 is directed to an invention that four components of gelatin or agar, gluten, carboxyvinyl polymer, and vinyl acetate resin or gum are essential. It is therefore apparent that the cited reference differs from the present application in which a homogeneous state is maintained by a two component system.

In the JPA document a water-soluble material and a water-insoluble material are mixed together with water in such a manner that a water content is 0.5-20 w/w%. From this fact, it is apparent that a homogeneous state cannot be obtained.

Even if a base material having such a state is adhered to the oral mucosa, water at the adhering portion is not absorbed uniformly with respect to the base material, resulting in an ununiform absorption, and as a result, the system of the base material tends to break, and its adhesion is not maintained for a long period of time.

On the other hand, in the homogeneous state as in the present invention, absorption of water from the adhering portion is uniformly conducted over the whole base material. Consequently, it is difficult to proceed breakage of the system, and the adhesion is sufficiently maintained over a long period of time.

An oral bandage is required to have not only strong and long-lasting adhesion to the oral mucosa as described above but also softness sufficient to be adhered to any desired site of complicated shape in the oral mucosa and, in addition, safety from worsening of the injury due to irritation. However, an oral bandage having such performance characteristics has not yet been developed.

The present invention is intended to meet the above-described situations.

Accordingly, an object of this invention is to provide an oral bandage having high adhesive strength for a prolonged period of time and softness with which to adhere to desired site of the oral mucosa or teeth.

Another object of this invention is to provide an oral preparation adhesive to the oral mucosa by which an active ingredient can be surely and effectively administered to the oral mucosa.

According to the invention we provide an oral bandage comprising a soft adhesive film consisting of a mixture of (a) an acrylic acid polymer, methacrylic acid polymer and/or maleic anhydride polymer and (b) a vinyl acetate polymer, the polymers (a) and (b) being uniformly dissolved in each other without regions of phase separation, so as to be substantially water-insolubilized; and optionally a basic substance capable of neutralizing said polymers (a) and an oral preparation comprising such an oral bandage having incorporated therein a topical drug.

The term "compatible state" as herein used means such a state that the polymers (a) and (b) (hereinafter simply referred to as "polycarboxylic acids") and the vinyl acetate polymer (hereinafter referred to as polyvinyl acetate) are uniformly dissolved in each other without forming small individual regions due to phase separation.

Water-soluble high-molecular compounds, such as polycarboxylic acids and polycarboxylic acid anhydrides have per se a shape-retention property. When they absorb a small amount of water, they exhibit strong adhesiveness but soon take up excess water to cause reduction in viscosity and degradation, thus resulting in losing their adhesiveness by being substantially dissolved in water. Moreover, since polycarboxylic acids in a dissolved state are acidic, they heavily irritate the sensitive injured part of the oral mucosa to cause worsening of the condition.

The present inventors have conducted extensive investigations on water-insolubilization of the above-described water-soluble high-molecular compounds, such as polycarboxylic acids, polycarboxylic acid anhydrides, etc., aiming at effective utilization of these compounds exhibiting excellent adhesion upon absorption of water as an oral bandage, while eliminating the above-described disadvantages, i.e., loss of adhesion due to over-absorption of water and irritation of the injured part. As a result, it has now been found that polycarboxylic acids and polyvinyl acetate are compatible with each other, and mixing of these two components in a compatible state substantially realizes water-insolubilization of the polycarboxylic acids without impairing the strong adhesion upon water absorption. Therefore, even if such a compatible mixture of the two components is shaped into a thin and soft film, it can exert strong adhesion for an extended period of time without undergoing degradation due to water absorption in a wet state.

It has further been found that incorporation of a basic substance (salt or base) capable of neutralizing the polycarboxylic acids into the above-described compatible mixture can further relieve the irritation on the injured part of the oral mucosa.

It has furthermore been found that incorporation of topical drugs into adhesive film and/or film support comprising the above-described compatible mixture can provide film-like oral preparations retaining the strong adhesion, by which the drug can be surely, simply and effectively administered to the oral mucosa, thus permitting prevention and treatment of oral diseases.

In the accompanying drawing:

The graph is a characteristic curve of (dissolved amount)/(total dissolved amount) of a drug, over a period of time.

A soft film comprising a compatible mixture of the polycarboxylic acids and polyvinyl acetate according to the present invention does not show adhesion in a dry state but comes to exhibit strong adhesion upon water absorption, such adhesion being substantially unchangeable even when immersed in water. Such a characteristic can first be manifested when the polycarboxylic acids and polyvinyl acetate are in a compatible state, not appearing when they are not in a compatible state.

As described above, the mixture of the polycarboxylic acids and polyvinyl acetate in a compatible state exhibit characteristics unpredictable from those of a mixture in a phase-separated state. More specifically, a film in a phase-separated state is turbid, whereas a film in a compatible state has such a high transparency that no independent small region is observed under an optical microscope. Further, when immersed in water, the polycarboxylic acids is dissolved out from the film in a phase-separated state, resulting in degradation as a whole; while the film in a compatible state only undergoes uniform swelling with very little elution of the polycarboxylic acids into water, which indicates that the polycarboxylic acids is substantially water-insolubilized. The compatible state (compatibility) of the polycarboxylic acids and polyvinyl acetate can be determined by making use of insolubilization of the polycarboxylic acids.

When a basic substance capable of neutralizing polycarboxylic acids is mixed with the above-described compatible mixture, the state of its mixing has no substantial influence on the adhesion property. Therefore, the basic substance may be mixed either in a compatible state or in a coarse dispersion.

Compatibility between the polycarboxylic acids and polyvinyl acetate can be clearly observed if the

mixture consists of only these two components as mentioned above. However, differrences in compatibility become unclear in those mixtures containing a basic substance having a neutralizing effect. In other words, in a mixture containing a basic substance, the mixing state of the basic substance being not restricted, even if the polycarboxylic acids and polyvinyl acetate are in a compatible state, the basic substance, if being mixed in a coarse dispersion, makes the film turbid. Thus, the mixing state of the polycarboxylic acids and polyvinyl acetate cannot always be observed visually or under an optical microscope.

Nevertheless, as described above, it has been confirmed that water-solubility of polycarboxylic acids can be markedly inhibited in a compatible mixture with polyvinyl acetate and that such a compatible mixture is uniformly swollen without degradation even when immersed in water for a considerably long period of time. This property can be recognized irrespective of whether a basic substance having a neutralizing effect be present or not.

Accordingly, this property can be made use of in determination of compatibility between polycarboxylic acids and polyvinyl acetate. This method of determination can be regarded reasonable from the fact that the oral bandage according to the present invention can be adhered to the oral mucosa for a long period of time owing to the limited water-solubility of the polycarboxylic acids.

In the present invention, the compatibility between polycarboxylic acids and polyvinyl acetate is determined from the amount of dissolved polycarboxylic acids. That is, the compatible state as herein referred to specifically means that the dissolution ratio of polycarboxylic acids as obtained by the following method is 40% by weight or less. In the case of an oral bandage containing a salt having a neutralizing effect, it means that the dissolution ratio of polycarboxylic acids as obtained by the following method is 50% by weight or less, taking into account dissolving of the salt.

Method of determing Dissolution Ratio:

A film comprising polycarboxylic acids and polyvinyl acetate is ground and weighed. The ground sample is put in a mesh bag and left to stand still in 300 times or more the weight of pure water at 20 °C for one hour. The bag is then taken out, and the amount of polycarboxylic acids dissolved out into the water is determined by neutralization titration or the like technique. This value is divided by the amount of the polycarboxylic acids initially contained in the film to obtain the dissolution ratio.

In the case when the film contains a basic substance, the dissolution ratio is obtained in the same manner as above except that the bag after the immersion is weighed to obtain the total amount of dissolved polycarboxylic acids and dissolved salt from, for example, weight reduction and this value is divided by the sum of the polycarboxylic acids and the basic substance initially contained in the film to obtain the dissolution ratio.

Since the oral bandage in accordance with the present invention comprises a soft film which is not adhesive in a dry state but shows adhesion only upon absorption of water, it can be stored as such without requiring any special storage conditions. On use, the oral bandage is stuck onto the oral mucosa whereupon it absorbs saliva or moisture of the mucous membrane to rapidly exerts strong adhesion to the mucous membrane. Thus, it firmly adheres to the affected part or injured part of the oral cavity that is less adherable due to the drug administered, stomatorrhagia, and the like. This adhesion lasts for a markedly prolonged period of time, which is a well-marked characteristic of the present invention. Such adhesion of long duration can first be attained by the adhesive film comprising the polycarboxylic acids and polyvinyl acetate in a compatible state as set forth above.

The mechanism accounting for the long-lasting adhesion is not clear, but it is believed that the polycarboxylic acids contributes to adhesiveness to the wet mucosa and the polyvinyl acetate contributes to water resistance in a compatible mixture thereof, thus functioning together to give adhesion of long duration.

The mixing state of the basic substance capable of neutralizing polycarboxylic acids has no influence on the adhesion, but the kind of the basic substance to be used exerts delicate influences on the adhesion and the like. For example, polyvalent metal salts, e.g., zinc oxide, calcium oxide, etc., function to reduce adhesion and to enhance water resistance, while monovalent metal salts, e.g., sodium acetate, etc., or a monovalent base, e.g., sodium hydroxide, triethanolamine, etc., functions to reduce water resistance and to enhance adhesion.

As described above, since the oral bandage in accordance with the present invention has adhesion of long duration, it can prevent the drug administered to the affected part of the oral cavity from running off to accelerate healing with a remarkably increased absorption of the drug and also give protection to the injured part of the oral cavity for a long period of time to expedite recovery.

Further, since the irritation due to eluted polycarboxylic acids can be reduced by adding a basic substance having a neutralizing effect to the adhesive film, a situation wherein the injured part of the oral

cavity becomes worse due to application of the oral bandage can be avoided.

In addition, the adhesive film according to the present invention is not merely composed of a water-soluble high-molecular substance but comprises a substantially water-insoluble soft film, in which polycarboxylic acids and polyvinyl acetate exist in a compatible state. Therefore, adhesion of long duration can be produced in a very thin film. In other words, too a thin film solely made of a water-soluble high-molecular substance is readily dissolved out in saliva in a short time to rapidly lose its adhesiveness so that a film made of such a material should have a considerably large thickness. However, a thick film produces a feeling foreign to the applied part and also reduces softness of the oral bandage. On the contrary, the oral bandage of the present invention does not require such a large thickness, thus giving no uncomfortable feeling.

The oral bandage according to the present invention can be produced by, for example, dissolving polycarboxylic acids and polyvinyl acetate in a solvent common to both and rapidly flow-casting the solution in a thin film, followed by drying.

The oral bandage containing a basic substance having a neutralizing effect according to the present invention can be produced by, for example, dissolving polycarboxylic acids and polyvinyl acetate in a solvent common to both, adding a basic substance capable of neutralizing the polycarboxylic acids to the solution, and rapidly flow-casting the mixture in a thin film, followed by drying. Incorporation of the basic substance may be carried out by dissolving in the solution or by dispersing a powderous basic substance in the solution. The above-described flow casting method is advantageous to easily produce a very thin film.

In the present invention, a topical drug can be incorporated into the oral bandage of the invention to obtain oral preparations. The method of incorporation is not particularly restricted, and usually comprises adding the topical drug directly or in the form of a solution to the solution of polycarboxylic acids and polyvinyl acetate, rapidly casting the composition in a thin film and drying. the acrylic polymers include an acrylic acid homopolymer and copolymers of acrylic acid and acrylic esters, e.g., butyl acrylate, 2-ethylhexyl acrylate,
methacrylic esters, e.g., methyl methacrylate,
or vinyl monomers, e.g., vinyl acetate, and copolymers, e.g., carboxyvinyl polymer. Examples of the methacrylic polymers include a methacrylic acid homopolymer and copolymers of methacrylic acid and comonomers as enumerated for the acrylic polymers. Specific examples of the maleic anhydride polymers include copolymers of maleic anhydride and methyl vinyl ether,

These compounds can be used either individually or in combination of two or more thereof. It is preferable that these Polycarboxylic acids contain 20% by weight or more of a -COOH group in case of methacrylic polymers or 16% by weight or more or a -CO-O-CO- group in case of maleic anhydride polymers.

The vinyl acetate polymer which can be used in the present invention typically includes a vinyl acetate homopolymer. In addition, copolymers of vinyl acetate and vinyl monomers, e.g., acrylic esters, and partial saponification products of a vinyl acetate homopolymer may also be employed. These vinyl acetate polymers may be used either individually or in combinations of two or more thereof. The polyvinyl acetate preferably has an average molecular weight (viscosity-average molecular weight) of not less than 60,000. Use of polyvinyl acetate having an average molecular weight less than 60,000 reduces water resistance of the adhesive, resulting in failing of the expected effects.

The basic substance which can be used for neutralizing polycarboxylic acids includes not only salts but bases. Typical examples of the salt include salts of metals and weak acids, metal oxides, metal hydroxides, amines, and mixtures thereof. Specific examples of the salt of metals and weak acids are salts of sodium, potassium, calcium, magnesium, etc. and carboxylic acids, e.g., acetic acid, lactic acid, citric acid, etc. Specific examples of the metal oxides are zinc oxide, calcium oxide, magnesium oxide, etc. Specific examples of the metal hydroxides are sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, etc. Specific examples of the amines are triethanolamine, diisopropanolamine, etc. These compounds can be used either alone or in combination. A preferred amount of the basic substance to be added varies widely depending on the kind thereof. In the case of using a polyvalent metal salt, for example, it is preferably added in an amount of from 0.2 to 0.8 equivalent based on the polycarboxylic acids. If its amount is less than 0.2 equivalent, the effect to relieve irritation on the injured part of the oral mucosa becomes insufficient. If it exceeds 0.8 equivalent, sufficient duration of adhesion can hardly be attained. In case of using a monovalent metal salt or a monovalent base, it is preferably added in an amount of from 0.03 to 0.2 equivalent based on the polycarboxylic acids. Amounts less than 0.03 equivalent reduce the effect of relieving irritation on the injured part, and amounts exceeding 0.2 equivalent reduce water resistance of the adhesive film, resulting in difficulty in obtaining sufficient adhesion.

The solvent common to the polycarboxylic acids and polyvinyl acetate includes lower alcohols, such as

methanol, ethanol, etc.; mixed solvents comprising a lower alcohol in a larger proportion and a compatible organic solvent, such as acetone, ethyl acetate, etc.; and mixed solvents comprising a lower alcohol or the above-described mixed solvent and water. The mixed solvent of a lower alcohol and an organic solvent preferably contains not more than 30% by weight of the organic solvent because the organic solvent of more than 30% by weight makes it difficult to dissolve polycarboxylic acids. The mixed solvent of a lower alcohol or a lower alcohol-organic solvent mixed solvent and water preferably contains not more than 30% by weight of water because a water content exceeding 30% by weight is liable to make it difficult to dissolve the polyvinyl acetate.

In the preparation of the oral bandage or oral; preparations of the invention, it is preferable that the polycarboxylic acids to polyvinyl acetate mixing ratio fall within such a range that the value A as obtained according to the following formula ranges from 15 to 45:

$$A = \frac{\left(\begin{array}{c}\text{Weight of -COOH} \\ \text{in Adhesive Film}\end{array}\right) + \frac{5}{4}\left(\begin{array}{c}\text{Weight of -CO-O-CO-} \\ \text{in Adhesive Film}\end{array}\right)}{\left(\begin{array}{c}\text{Weight of Polycarboxylic Acids in Adhesive Film} \\ \text{+ Weight of Polyvinyl Acetate in Adhesive Film}\end{array}\right)} \times 100$$

As the value A becomes larger, the adhesion to the mucous membrane increases, but the duration of adhesion tends to decrease. To the contrary, the smaller the value A, the lesser the ahesion, but the duration of adhesion tends to increase. If the value A is less than 15, sufficient adhesion is hard to obtain. If it exceeds 45, it becomes difficult to obtain sufficient duration of adhesion. Accordingly, the mixing ratio of polycarboxylic acids and polyvinyl acetate is preferably adjusted so that the value A falls within a range of from 15 to 45. Taking the case of using polyacrylic acid as a polycarboxylic acid for instance, with the proportion of polyacrylic acid in the adhesive film being between 24 and 72% by weight, the value A falls within the above-recited range to obtain good results.

When the polycarboxylic acids and polyvinyl acetate are dissolved in a common solvent, care should be taken so as to sufficiently dissolve the both components. On this occasion, concentrations of the polycarboxylic acids, polyvinyl acetate, etc. are not particularly limited. However, too a high concentration of the high-molecular substance makes the resulting solution highly viscous, and such a viscous solution is difficult to flow-cast in a film. Therefore, it is preferable to give care that the concentrations of the high-molecular substances may not exceed 40% by weight.

In the preparation of the adhesive film according to the present invention, the solution comprising the polycarboxylic acids and polyvinyl acetate and, if necessary, a basic substance and/or a topical drug is cast on an appropriate film, such as polyethylene-laminated paper, having been subjected to releaseability-imparting treatment, and the casted film is rapidly dried with hot air in a drying oven or a drying tower. Suitable time and temperature in drying vary depending on the composition of a common solvent used, solid content of the solution, thickness of the cast film, the pressure and the like but, in general, preferably range from 60° to 120° C in temperature and from 1 to 20 minutes in time under an atmospheric pressure. A very thin film that can be, as such, used as an oral bandage can be thereby produced. The thickness of the resulting film is preferably be adjusted to a range of from 5 to 100 μm by controlling the amount of the casting solution, and the like. If a film thickness is less than 5 μm, it is difficult to obtain sufficient adhesion. A film having a thickness exceeding 100 μm tends to produce a feeling foreign to the mouth and to impair softness of the film.

As described above, the adhesive film in accordance with the present invention comprises a polycarboxylic acids and a vinyl acetate polymer not in a merely mixed state but in a compatible state with each other, in which the polycarboxylic acids is substantially water-insolubilized. Hence, even being very thin, it exerts strong adhesion for an extended period of time without suffering degradation due to water absorption. Besides, the film can easily be deformed according to the form of the oral mucosa and adhered thereto simply by pressing because of its softness.

The oral bandage and oral preparations according to the present invention may solely comprise the adhesive film but may further comprise a soft film support in combination.

A composite comprising the adhesive film and a support can be produced by laminating the adhesive film on a soft film support in a usual manner, such as hot pressing or by the use of an adhesive. Alternatively, the lamination can be carried out simultaneously with the preparation of the adhesive film by casting the film-forming composition on a soft film support, followed by drying. The latter process has an advantage over the former in simplifying the production procedure since hot pressing or adhesion with an adhesive is unnecessary.

The soft film support which can preferably be used in the present invention is substantially impermeable to water. Such a support typically includes plastic films, such as polyethylene, polyvinyl acetate resin, an ethylene-vinyl acetate copolymer, polyvinyl chloride, polyurethane, etc., metal foils, such as aluminum foil, tin foil, etc., laminates of cloth or paper and a plastic film, and the like. Of these, plastic films are preferred in view of safety and feeling in use. A preferred thickness of the film support is from 10 to 100 μm in view of handling properties and freedom from a foreign feeling on use. A thickness of the composite film, i.e., a total thickness of the adhesive film and the film support, is preferably in the range of from 30 to 150 μm. If it is less than 30 μm, handling properties and operation properties are deteriorated. A thickness exceeding 150 μm is liable to give a foreign feeling on use.

When the oral bandage of the invention contains a topical drug to obtain an oral preparation as described before, the topical drug may be incorporated into the adhesive film and/or the above-described film support. In the latter case, incorporation of the drug can be carried out by kneading with a resin material for the support, mixing the drug in the form of its solution with a resin material, absorbing onto a support, impregnating into a support, or a like method.

The topical drug which can be used in the present invention may be either solid or liquid at room temperature as long as it may be incorporated into the adhesive film or the film support by dissolving or dispersing.

Specific examples of the topical drugs to be used in the present invention are adrenal corticosteroids, e.g., Triamcinolone acetonide, Dexamethasone, Betamethasone, Prednisolone, Fluocinolone, Hydrocortisone, Beclomethasone, etc. and salts thereof; anti-inflammatory agents, e.g., Flurbiprofen, Ibuprofen, Diclofenac, Indomethacin, Bendazac, Flufenamic acid, Bufezamac, Cyclospoline, Clidanac, Glycyrrhizin, Ketoprofen, Piroxicam, Pranoprofen, Benzydamine, Ibuprofenpiconol, Etofenamate, Lysozyme, Chymotrypsin, Epidihydrocholesterine, Hinokitiol, α-Amylase, Azulene, Chlorophllin, Cromoglic acid, Tranilast, Serratiopeptidase, Pronase, Glucanase, Lithospermi Radix extract, etc. and salts thereof; antimicrobial agents, e.g., Acrynol, Cetyl pyridinium, Chlorhexidine, Domifen, Iodine, Monensin, Sanginalline, Metronidazol, Dequalinium, Tetracycline, Minocycline, Ofloxacin, Penicilline, Doxycycline, Oxycycline, Cefatrizin, Nystatin, Clindamycin, Fradiomycin, sulfate, etc. and salts thereof; analgesics, e.g., Ethyl aminobenziate, Camphor, Eugenol, Dibucaine, Phenol, Menthol, Creosote, Diphenhydramine, Lidocaine, Tetracaine, Procaine, Cocaine, Piprocaine, Mepivacaine, Promoxin, Dicronin, Guaiacol, etc. and salts thereof; hemostatics, e.g., Tranexamic acid, ε-Aminocapronic acid, Alginic acid, Bioflavonoide, Ascorbic acid, Thrombin, oxidized Cellulose, Cetraxate, Epinephrine, Ferric chloride, Fibrinogen, Carbazochrome, Adrenochrome, etc. and salts thereof; vasodilators, e.g., Inositol hexanicotinate, Cyclanderate, Cinnarizine, Tolazoline, Acetylcholine, etc. and salts thereof; agents activaing cellular function, e.g., Solcoseryl, Proglumide, Sucralfate, Gefarnate, Nicametate, Glutamine, Aceglutamide aluminum, Ethylcysteine, Chitin, Tocopherol nicotinate, Ubidecarenone, etc. and salts thereof; antiviral agents, e.g., Aciclovir, Idoxuridine, Betrabin, Amantadine, etc. and salts thereof; agents affecting calcium metabolism, e.g., Vitamin D, Endotoxin, Hydroxyapatite, Collagen, Cataboline, 2-Chloroadenosine, Norcardia, Calcitriol, Prostaglandins for alveolar bone, Osteoclast activating factors for alveolar bone, Parathormone for alveolar bone, Calcitonine for alveolar bone, etc. and salts thereof; astringents, e.g., Tannin, Tanninc acid, Zinc fluoride, Sodium fluoride, Strontium fluoride, Potassium nitate, Stannous fluoride, Aluminum potassium sulfate, Berberine, Bismuth compounds, Strontium chloride, Aluminum lactate, etc. and salts thereof.

The amount of these topical drugs to be incorporated in the oral preparation varies depending on the kind thereof, but from considerations of pharmacological effects and adhesion to the mucous membrane, it usually ranges from 0.0001 to 35% by weight, and preferably from 0.0002 to 20% by weight, based on the preparation. When positive administration of the drug to the oral mucosa is expected, the drug is preferably present in the adhesive film side. In the treatment of bad breath, and the like, it may be prevent in the support side.

The composite film composed of the adhesive film and the support has enhanced strength while retaining the excellent adhesion of long duration. As an additional effect, the composite film can present adhesion of foreign matters, such as foods, onto the back side of the oral bandage or oral preparations. Further, use of a substantially water-impermeable support effectively prevents permeation of water through the back side to thereby prolong the duration of adhesion.

The adhesive film or support of the oral bandage or oral preparations according to the present invention may further contain other additives, such as coloring matters, flavoring materials, softening agents, and the like, as long as they do not impair adhesiveness or pharmacological effects. For example, when both the adhesive film and the support are colorless, incorporation of a coloring matter in one of them makes it easy to distinguish the surface or back of the bandage or preparation.

According to the present invention, both of the adhesive film and the composite film composed of the

adhesive film and a support are very soft and, when applied to the oral mucosa, absorb water in the oral cavity to get further softened. Therefore, they can be easily fitted to any site of the oral cavity to thereby produce strong adhesion for an extended period of time. The adhesive strength of the adhesive film or the composite film of the invention was measured using a crosslinked collagen swollen with water as a substitute for the oral mucosa at a peel angle of 180° and, as a result, was found to be from 25 to 200 g/2.5 cm-width. Adhesive strength smaller than 25 g/2.5 cm-width cannot ensure adhesion to the oral mucosa for a long period of time, and that greater than 200 g/2.5 cm-width is liable to injure the mucous membrane upon peeling. Taking these facts into account, the oral bandage or preparations according to the present invention can be reasonably regarded as exhibiting the optimum adhesive strength.

The above-described adhesive strength is naturally subject to variations depending on the kind of adherends. That is, the adhesive film exerts sufficient adhesion to mucous membranes, the teeth, the skin, cross-linked collagen films, and the like, with the adhesive strength being not impaired even when immersed in water. But the adhesive film scarcely shows adhesion to plastics material or regenerated cellulose film, and the adhesion thereto is very weak and rapidly disappears in water. This property is entirely favorable for storage of prodducts. No special moisture-proof packaging is needed because the products do not adhere to packaging materials, storage cases, etc. Further, it is not necessary to cut the oral bandage or oral preparations into small lengths for storage, and they can be formed in a tape and wound on a spool without sticking to each other. They may be stored as they are, but if there is a fear of contamination, the surface that is to be adhered can be protected with paper or a plastic film.

The oral bandage and oral preparations containing a basic substance for neutralization according to the present invention are highly safe from harm to the injured part of the oral cavity due to the irritant polycarboxylic acids which are dissolved out when applied to the injured parts. That is, the adhesive film of the invention containing no basic substance for neutralization may be applied to the skin of shaved guinea pigs, the eye mucous membrane of rabbits, the oral mucosa of healthy persons, etc. without causing any substantial irritation. However, irritation is noted when it is applied to the injured skin of a shaved guinea pig caused by stripping the corneum with an adhesive tape. To the contrary, the products containing a basic substance for neutralization cause substantially no irritation on such an injured skin as well as on the normal mucous membranes.

The oral bandages or preparations according to the present invention possess excellent water resistance attributed to substantial water-insolubilization of the polycarboxylic acids constituting the adhesive film so that they are only swollen but not degraded even when immersed in water. Therefore, they retain adhesiveness for a long period of time, generally 3 to 4 hours or even more, e.g., for one day, onto the oral mucosa.

Further, the oral preparations comprising the oral bandage of the invention having incorporated therein a topical drug are effective in producing pharmacological effects and very easy to handle since they can be adhered to the wet surface of affected parts of the oral cavity simply by pressing thereonto for the prevention or treatment of oral diseases.

This invention will now be illustrated in greater detail with reference to the following examples, are not intended to limit the present invention. In these examples, all the parts and percents are given by weight unless otherwise indicated.

EXAMPLE 1

Five parts of a carboxyvinyl polymer as a polycarboxylic acid and 5 parts of polyvinyl acetate (degree of polymerization: ca. 1,500) were poured in 90 parts of methanol as a common solvent, followed by mixing to form a uniform solution. The resulting solution was flow-casted on a release paper, dried, and peeled off to obtain an adhesive film having a thickness of 30 μm. The value A of this film was 31.3. The dissolution ratio of the polycarboxylic acid, that is a criterion of the compatible state, was 9%, indicating that the film had a compatible state.

The adhesive film thus prepared was laminated on 15 μm thick aluminium foil by hot pressing to obtain an oral bandage.

COMPARATIVE EXAMPLE 1

Five parts of polyvinyl acetate (degree of polymerization: ca. 1,500) were dissolved in 20 parts of toluene, and to the solution was added 5 parts of a toluene-insoluble carboxyvinyl polymer, followed by thoroughly stirring to prepare a uniform suspension. The suspension was then flow-casted on a release paper, dried, hot pressed and peeled off to obtain an adhesive film having a thickness of 30 μm. The

resulting film had the same value A as in Example 1 but a ratio of dissolution of the polycarboxylic acid of 67%, which indicated that the carboxylvinyl polymer and polyvinyl acetate were in a phase-separated state.

The adhesive film thus prepared was laminated on 15 μm thick aluminum foil by hot pressing to obtain an oral bandage.

COMPARATIVE EXAMPLE 2

Five parts of a carboxyvinyl polymer were dissolved in 45 parts of pure water. Separately, 5 parts of polyvinyl acetate (degree of polymerization: ca. 1,500) was dissolved in 20 parts of toluene. The both solutions were mixed and then stirred in a small-sized stirrer at 5,000 rpm for 3 minutes to obtain a suspension. The resulting suspension was flow-casted on a release paper, dried and peeled off to obtain an adhesive film having a thickness of 30 μm. The value A of this film was the same as in Example 1, but the dissolution ratio of the polycarboxylic acid was 79%, indicating that the carboxyvinyl polymer and polyvinyl acetate were in a phase-separated state.

The resulting film was laminated on 15 μm thick aluminum foil by hot pressing to obtain an oral bandage.

The compatible state of each of the samples obtained in the foregoing examples was evaluated by macroscopic observation to see the appearance of the film and also under an optical microscope to observe whether small independent regions of the polycarboxylic acid or polyvinyl acetate were formed or not. Formation of such small regions indicates phase separation.

Further, each of the samples was cut in a size of 5 x 5 cm, immersed in water at 37° C for 10 minutes, dried and weighed to determine weight reduction. The weight reduction (%) as an average of 10 runs was taken as a parameter of solubility of the film.

Furthermore, the dissolution ratio of the polycarboxylic acid after 2 hour- and 4-hour immersion in the same manner as described above for the dissolution ratio after 1 hr-immersion.

The results obtained are shown in Table 1 below. In Table 1, the solubility (weight reduction) is an average of 10 sample pieces. The dissolution ratio after 1 hr-immersion as measured in the foregoing examples is also shown in Table 1.

TABLE 1

	Example 1	Comparative Example 1	Comparative Example 2
Compatible State:			
Appearance	trans-parent	turbid	turbid
Formation of Small Regions	no small regions observed	small regions observed	small regions observed
Solubility (%)	0.1	6.9	7.7
Dissolution Ratio (%):			
1 Hr-Immersion	9	67	79
2 Hr-Immersion	10	-	-
4 Hr-Immersion	12	-	-

As is apparent from Table 1 above, in the adhesive film of Example 1, the polycarboxylic acid and polyvinyl acetate are in a good compatible state, making a contrast to those of Comparative Examples 1 and 2. In particular, the results of polycarboxylic acid dissolution ratios reveal that the most of the

polycarboxylic acid, an adhesive component, in the films of Comparative Examples 1 and 2 is dissolved out into water through immersion for one hour, whereas the dissolution ratio of the film of Example 1 after 1 hour-immersion is as low as 9%, which increases only to 12% even by immersion for 4 hours, said ratio showing no further increase through additional immersion, though not shown in Table 1. It can be seen from these results that a major proportion of the total amount of the dissolved polycarboxylic acid is dissolved out during the first one-hour immersion. The change in the proportion of the dissolved amount to the total dissolved amount with time is shown in Figure 1.

Then, the oral bandages obtained in the foregoing examples were subjected to adhesion test and peel test at a peel angle of 180° C in accordance with the following test methods.

Adhesion Test:

A sample was cut out round to a diameter of 10 mm. The cut piece was attached to a crosslinked collagen film swollen with water which was fixed on a phenolic resin plate and immersed in water at 37° C to observe the state of the film.

Peel Test:

A sample was cut into a strip of 2.5 cm in width and 15 cm in length. The strip was attached to a collagen film and immersed in water in the same manner as in the adhesion test, and a peel strength at a peel angle of 180° C was measured by means of a Schopper type tensile strength tester.

The results obtained are shown in Table 2 below.

TABLE 2

	Example 1	Comparative Example 1	Comparative Example 2
State of Film And Adhesion in Water	No change observed except a swelling of the periphery. Firmly adhered for 5 hrs.	Remarkable swelling from the periphery. Spontaneously separated from the adherend in 0.5 to 1.5 hrs.	Gradual swelling all over the film. Still adhered for 30 mins but with little adhesion. Spontaneously separated from the adherend in 1.5 to 2.0 hrs.
Peel Strength (g/2.5cm-width): Immersion Time:			
10 mins	110	12	20
30 mins.	105	unmeasurable	unmeasurable
60 mins.	95	"	"
120 mins.	85	"	"
240 mins.	90	"	"

As can be seen from Table 2, the samples of Comparative Examples 1 and 2 peel apart from the adherend in the early stage of immersion in water, becoming unmeasurable for peel strength when immersed for 30 minutes. On the contrary, the sample according to the present invention exhibits excellent adhesion in water, with its peel strength after 4 hour-immersion showing about 80% of the initial value. These results prove that the oral bandage of the present invention exerts strong adhesion of extremely long

duration.

EXAMPLE 2

A 10% methanolic solution of a carboxyvinyl polymer (CVP) and a 10% methanolic solution of polyvinyl acetate (PVAc) (degree of polymerization: ca. 2,500) were mixed at a CVP to PVAc ratio as shown in Table 3. The mixed solution was flow-casted on a release paper and dried to obtain an adhesive film having a thickness of 20 μm. The value A of each sample thus prepared is shown in Table 3.

The resulting film was laminated on a 50 μm thick film of polyvinyl acetate (degree of polymerization: ca. 2,500) by hot pressing to obtain an oral bandage.

Each of the samples thus obtained was determined for the dissolution ratio of the polycarboxylic acid (immersion time: 1 hour), adhesiveness in water and peel strength at a peel angle of 180° C after 10 minutes-immersion in accordance with the methods as described in Example 1. The adhesiveness in water was expressed in terms of the time until the sample was spontaneously separated from the adherend. These test results are shown in Table 3.

TABLE 3

Mixing Ratio (CVP:PVAc)	2:8	3:7	5:5	7:3	8:2
Value A	12.5	18.8	31.3	43.8	50.0
Dissolution Ratio (%)	2	5	8	22	35
Adhesion Time (hr)	>8	>8	>8	3.2	1.5
Peel Strength (g/2.5 cm-width)	20	60	110	160	200

It can be seen from Table 3 above that when the value A falls within the range of from 15 to 45 with the CVP:PVAc ratio being from 3:7 to 7:3, the films are excellent in both adhesion time and peel strength as well as in dissolution ratio of the polycarboxylic acid, indicating usefulness as an oral bandage. However, the film having a CVP:PVAc ratio of 2:8 has the value A smaller than 15 and shows poor adhesion. On the other hand, the film having a CVP:PVAc ratio of 8:2 has a short adhesion time and a high polycarboxylic acid dissolution ratio due to the value A exceeding 45. Accordingly, these films out of the scope of the present invention are regarded as hard to use with exceptions for special purposes of use.

EXAMPLE 3

Four parts of an alternating copolymer of methyl vinyl ether and maleic anhydride and 6 parts of polyvinyl acetate (degree of polymerization: ca. 1,000) were dissolved in 90 parts of methanol. The resulting solution was flow-casted on a release paper, dried at 80° C and peeled to obtain an adhesive film having a thickness of 60 μm. The value A of this film was 23.0, and the dissolution ratio (immersion time: 1 hour) was 12%.

The oral bandage thus obtained was cut into a circle having a diameter of 10 mm. The cut piece was adhered to the palatine mucosa of 10 panel members, and the time until the sample was separated apart (peeling time) was determined. As a result, the average peeling time was 4.0 hours.

EXAMPLE 4

Six parts of polyacrylic acid (degree of polymerization: ca. 5000) and 14 parts of partially saponified polyvinyl acetate (degree of saponification: 20 mol%; degree of polymerization: ca. 1,500) were dissolved in 80 parts of methanol, and the resulting solution was flow-casted on a release paper, dried at 80° C and

peeled off to obtain an adhesive film having a thickness of 70 μm. The value A of this film was 37.5, and the dissolution ratio of the polycarboxylic acid (immersion time: 1 hour) was 37%.

Separately, an ethylene-vinyl acetate copolymer (vinyl acetate content: 30 mol%) was hot-pressed to form a film support having a thickness of 80 μm. The above obtained adhesive film and the film support were laminated by the use of a hot laminator to produce an oral bandage.

The resulting oral bandage was cut in a strip of 7 mm in width and 20 mm in length. The cut piece was adhered to the gingival mucosa of 10 panel members, and the time until the strip was separated therefrom (peeling time) was measured. As a result, the average peeling time was 7.6 hours.

EXAMPLE 5

Four parts of a carboxyvinyl polymer and 6 parts of polyvinyl acetate (degree of polymerization: ca. 2,000) were dissolved in 92 parts of isopropanol, and 2 parts of titanium dioxide was added thereto as a coloring matter was added thereto, followed by thoroughly mixing with stirring. The mixture was flow-casted on a release paper, dried at 90° C and peeled off to obtain an adhesive film having a thickness of 15 μm. The value A of this film was 25, and the dissolution ratio of the polycarboxylic acid (immersion time: 1 hour) was 6%. Separately, 0.1 part of Food Red 3 aluminum lake was added to 100 parts of a 20% ethyl acetate solution of polyvinyl acetate (degree of polymerization: ca. 2,000), followed by thoroughly mixing while stirring. The mixture was flow-casted on a release paper, dried at 180° C and peeled off to prepare a film support having a thickness of 30 μm. The above prepared adhesive film and the film support were laminated by hot pressing to obtain an oral bandage.

The thus obtained oral bandage was cut in a circle having a diameter of 20 mm. The cut piece was adhered to the buccal mucosa of 10 panel members, and the time until the bandage was separated therefrom (peeling time) was determined. As a result, an average peeling time was 5.6 hours.

The performance of the oral bandage to prevent running-off of a drug administered was evaluated using a food dye as a model of a drug and a crosslinked collagen film swollen with water as an adherend as follows. That is, 9.5 parts of lactose and 5 parts of Food Red 102 were ground in a mortar, and the mixture was pounched out into tablets of 5.0 mm in diameter and 0.5 mm in thickness. One of the tablets was placed on a water-swollen crosslinked collagen film that was fixed on a phenolic resin plate, and the oral bandage cut round to a diameter of 15 mm was adhered thereonto so as to cover the tablet. The sample was then immersed in water at 37° C. As a result, the time required for the dye in the tablet to be dissolved out into water was 4.1 hours as an average of 10 runs, indicating a sufficient performance property to prevent running-off of a drug administered.

Thereafter, the storage stability of the oral bandage was evaluated as follows. The oral bandage was cut in a tape of 18 mm in width and 3 m in length. The tape was rolled up, wrapped with a cellophane film, packed in a paper box of 6 cm x 6 cm x 2 cm and preserved under ambient conditions for 3 months. As a result, no change in shape or adhesion properties was noted, to confirm excellent storage stability of the oral bandage.

EXAMPLE 6

Three parts of a carboxyvinyl polymer, 2 parts of a methyl vinyl ether-maleic anhydride copolymer and 5 parts of polyvinyl acetate (degree of polymerization: ca. 2,000) were dissolved in 90 parts of methanol. The resulting mixed solution was flow-casted on a release paper, dried at 60° C and peeled off to obtain an adhesive film having a thickness of 15 μm. The value A of this film was 30.3, and the dissolution ratio of the polycarboxylic acid (immersion time: 1 hour) was 10%.

The thus obtained film was laminated on a 30 μm thick film support of polyvinyl acetate (degree of polymerization: ca. 1,500) by hot pressing to obtian an oral bandage.

The resulting oral bandage was cut round to a diameter of 10 mm, adhered to the gingival mucosa of 10 panel members, and the time until the bandage was separated therefrom (peeling time) was measured. As a result, the peeling time was 5.4 hours in average.

EXAMPLE 7

Into 90 parts of methanol were poured 4.7 parts of a carboxyvinyl polymer and 4.7 parts of polyvinyl acetate (degree of polymerization: ca. 1,500), and 0.6 part of diisopropanolamine was further added thereto, followed by mixing to form a uniform solution. The resulting solution was flow-casted on polyethylene-laminated paper dried in a drier at 80° C for 8 minutes and peeled off to prepare an adhesive film having a

thickness of 40 μm. The value A of this film was 31, and the dissolution ratio of the polycarboxylic acid was 12%, which value indicated the compatible state of the film.

The thus obtained adhesive film was laminated on a 40 μm polyvinyl acetate film (degree of polymerization: ca. 2,000) by hot pressing at 100 ° C to obtain an oral bandage.

COMPARATIVE EXAMPLE 3

In 30 parts of toluene were dissolved 4.7 parts of polyvinyl acetate (degree of polymerization: ca. 1,500) and 0.6 parts of diisopropanolamine, and 5 parts of a toluene-insoluble carboxyvinyl polymer powder was added to the solution, followed by sufficiently mixing while stirring to prepare a uniformly dispersed suspension. The resulting suspension was flow-casted on polyethylene-laminated paper dried in a drier at 100 ° C for 10 minutes and peeled off to obtain an adhesive film having a thickness of 40 μm. The value A of this film was equal to that of the adhesive film of Example 7, but the dissolution ratio of the polycarboxylic acid was 72%, indicating that the carboxyvinyl polymer and the polyvinyl acetate were in a phase-separated state.

The adhesive film thus obtained was laminated on a 40 μm thick polyvinyl acetate film by hot pressing at 100 ° C in the same manner as in Example 7 to obtain an oral bandage.

COMPARATIVE EXAMPLE 4

In 45 parts of pure water were dissolved 4.7 parts of a carboxyvinyl polymer and 0.6 part of diisopropanolamine. Separately, 4.7 parts of polyvinyl acetate (degree of polymerization: ca. 1,500) was dissolved in 30 parts of toluene. The two solutions were mixed and stirred in a small-sized stirrer at 5,000 rpm for 5 minutes to prepare a suspension. The resulting suspension was flow-casted on polyethylene-laminated paper, dried in a drier at 100 ° C and peeled off to obtain an adhesive film having a thickness of 40 μm. The value A of this film was equal to that of the film of Example 7, but the dissolution ratio of the polycarboxylic acid was 77%, indicating that the carboxyvinyl polymer and the polyvinyl acetate were in a phase-separated state.

The film thus obtained was laminated on a 40 μm thick polyvinyl acetate film by hot pressing at 100 ° C in the same manner as in Example 7 to obtain an oral bandage.

Each of the samples obtained in Example 7 and Comparative Examples 3 and 4 was evaluated for the compatible state, the adhesiveness (adhesion time) and the peel strength. The compatible state was observed in the same manner as in Example 1, and the adhesiveness and peel strength were determined in the same manner as in Example 2. Further, each sample cut round to a diameter of 10 mm was adhered to the palatine mucosa of 5 healthy male panel members, and the time until the sample was separated therefrom was measured. The adhesion was effected after lunch, and the panel members were allowed to drink and talk, ad lib. The results obtained are shown in Table 4 below.

TABLE 4

	Example 7	Comparative Example 3	Comparative Example 4
Compatible State:			
Appearance	trans-parent	turbid	turbid
Formation of Small Regions	no small regions observed	small regions observed	small regions observed
Adhesiveness (Adhesion Time) (min)	185[1)]	70[2)]	55[2)]
Peel Strength (g/2.5 cm-width)	35	10	12
Peeling Time (min)	210	25	40

Note: 1): Strong adhesion was retained for 60 minutes.

2): Only slight adhesion was noted with insubstantial adhesive strength after 60 minutes.

As is apparent from the results of Table 4, the polycarboxylic acid and the polyvinyl acetate in the film of Example 7 are in a good compatible state, making a contrast to the films of Comparative Examples 3 and 4. More specifically, the films of Comparative Examples 3 and 4 are separated from the adherend in the early stage of the adhesion test and undergo great reduction in adhesion through immersion in water for 10 minutes in the peel test. Further, these comparative samples are separated from the adherend in the test using a panel. To the contrary, the oral bandage according to the present invention exhibits excellent results in the adhesion test, peel test and panel test, demonstrating strong adhesion of long duration.

COMPARATIVE EXAMPLE 5

In order to ascertain high safety of the oral bandage of the present invention, a comparative adhesive film containing no diisopropanolamine was prepared as follows.

Carboxyvinyl polymer	5.0 parts
Polyvinyl acetate (degree of polymerization: ca. 2,000)	5.0 parts
Methanol	90.0 parts

The above components were mixed while stirring to prepare a uniform solution. The solution was flow-casted on polyethylene-laminated paper, dried in a drier at 80° C for 8 minutes and peeled off to obtain an

adhesive film having a thickness of 40 μm. The resulting film was laminated on a 40 μm thick polyvinyl acetate film (degree of polymerization: ca. 2,000) by hot pressing at 100°C to obtain a comparative oral bandage.

Irritation of the oral bandage as obtained in Example 7 on the normal skin and injured skin of a guinea pig was determined as compared with the above obtained comparative sample in accordance with the following test method.

The back of female Hartley guinea pigs (body weight: 300 to 400 g) was shaved with an electric clipper and an electric shaver to expose the normal skin. An adhesive tape was attached to the normal skin followed by peeling 7 times, whereby the stratum corneum was removed therefrom to form injured skin.

The sample was cut round to a diameter of 10 mm, dipped in water and adhered to each of the normal skin and the injured skin. The adhered sample was covered with absorbent cotton and further closely covered thereon with an adhesive tape for tight covering. Six hours later, the sample was removed, and irritation score was judged after 1 hour and 24 hours from the removal according to the following four grades:

0 : No change
0.5: Slight Erythema
1 : Moderate Erythema
2 : Severe erythema with edema

The results obtained are shown in Table 5 below. Each score shown in Table 5 is an average of 6 runs.

TABLE 5

	Normal Skin		Injured Skin	
	1 Hr	24 Hrs	1 Hr	24 Hrs
Example 7	0.3	0.3	0.5	0.5
Comparative Example 5	0.3	0.4	0.4	2.0
Non-Treated Group	0.1	0.2	0.2	0.3

The results of Table 5 above demonstrate that the sample according to the present invention causes no irritation on not only the normal skin but the injured skin as compared with the comparative sample, although there is no difference in irritation on the normal skin between the sample of the invention and the comparative sample.

EXAMPLE 8

Carboxyvinyl polymer	8.0 parts
Polyvinyl acetate (degree of polymerization: ca. 1,500)	2.0 parts
ZnO	3.6 parts
Methanol	26.4 parts

The above components were kneaded to obtain a uniform mixture. The mixture was flow-casted on polyethylene-laminated paper having been subjected to releasability-imparting treatment, dried in a drier at 100°C for 3 minutes and peeled off to obtain an adhesive film having a thickness of 10 μm. The value A of this film was 50. The resulting film was then laminated on a 40 μm thick film of a mixture of polyvinyl acetate (degree of polymerization: ca. 800) and polybutene (95:5) by hot pressing at 100°C to obtain an oral bandage.

The sample was evaluated for peel strength, peeling time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results obtained are as follows:

Peel Strength: 60 g/2.5 cm-width
Peeling Time: 186 minutes
Irritation Score: 0.6

EXAMPLE 9

Carboxyvinyl polymer	3.4 parts
Polyvinyl Acetate (Degree of polymerization: ca. 1,000)	8.4 parts
Sodium citrate ($Na_3C_6H_5O_7$)	0.2 part
Methanol	71.0 parts
Pure water	17.0 parts

The above components were mixed to obtain a uniform solution, and the solution was flow-casted on a polyethylene terephthalate film, dried in a drier at 80° C for 15 minutes and peeled off to obtain an adhesive film having a thickness of 80 μm. The value A of this film was 18. The resulting film was then laminated on 15 μm thick aluminum foil by hot pressing at 100° C to obtain an oral bandage.

The sample was evaluated for peel strength, peel time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results obtained are as follows:

Peel Strength: 25 g/2.5 cm-width
Peeling Time: 258 minutes
Irritation Score: 0.3

EXAMPLE 10

Methyl vinyl ether/maleic anhydride alternating copolymer	4.0 parts
Polyvinyl acetate (degree of polymerization: ca. 1,500)	6.0 parts
Sodium hydroxide	0.5 part
Methanol	67.5 parts
Ethyl acetate	22.0 parts

The above components were mixed to prepare a uniform solution, and the solution was flow-casted on 15 μm thick aluminum foil and dried in a drier at 60° C for 15 minutes to obtain a composite oral bandage having a total thickness of 35 μm. The value A of the adhesive film constituting the composite oral bandage was 23.

The sample was evaluated for peel strength, peeling time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results obtained are as follows:

Peel Strength: 54 g/2.5 cm-width
Peeling Time: 222 minutes
Irritation Score: 0.5

EXAMPLE 11

Polyacrylic acid	7.0 part
Saponified polyvinyl acetate (saponification degree: 20 mol%)	3.0 parts
ZnO	0.8 part
Methanol	89.2 parts

The above components were mixed to prepare a uniform solution. The solution was flow-casted on polyethylene-laminated paper, and dried in a drier at 80° C for 10 minutes to obtain a composite oral bandage having a thickness of 50 μm. The value A of the adhesive film constituting the composite was 44.

The sample was evaluated for peel strength, peeling time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results obtained are as follows:

Peel Strength: 70 g/2.5 cm-width
Peeling Time: 166 minutes
Irritation Score: 1.0

EXAMPLE 12

Carboxyvinyl polymer	4.0 parts
Polyvinyl acetate (degree of polymerization: ca. 2,000)	6.0 parts
Diisopropanolamine	0.7 part
ZnO	1.4 parts
Methanol	87.9 parts

The above components were mixed to prepare a uniform solution. The solution was flow-casted on a polyethylene terephthalate film, dried in a drier at 80° C for 15 minutes and peeled off to obtain an adhesive film having a thickness of 30 μm. The value A of this film was 25.

Polyvinyl acetate (degree of polymerization: ca. 2,000)	80.0 parts
Titanium white	19.5 parts
Food Red 3 aluminum lake	0.5 part

The above components were mixed and formed into a film of 30 μm in thickness, and the above prepared adhesive film was laminated thereon by hot pressing at 100° C to obtain an oral bandage.

The resulting sample was evaluated for peel strength, peeling time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results obtained are as follows:

Peel Strength: 35 g/2.5 cm-width
Peeling Time: above 300 minutes
Irritation Score: 0.4

EXAMPLE 13

Carboxyvinyl polymer	3.0 parts
Methyl vinyl ether/maleic anhydride alternating copolymer	2.0 parts
Polyvinyl acetate (degree of polymerization: ca. 1,500)	4.3 parts
Triethanolamine	0.7 part
Methanol	80.0 parts
Pure water	10.0 parts

The above components were mixed to prepare a uniform solution. The solution was flow-cast on polyethylene-laminated paper, dried in a drier at 80°C for 10 minutes and peeled off to obtain an adhesive film having a thickness of 25 μm. The value A of this film was 33.

The resulting film was laminated on a 30 μm thick polyvinyl acetate film (degree of polymerization: ca. 1,500) by hot pressing at 100°C to obtain an oral bandage.

The resulting sample was evaluated for peel strength, peeling time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results are as follows:

Peel Strength: 42 g/2.5 cm-width
Peeling Time: 190 minutes
Irritation Score: 0.4

EXAMPLES 14 to 19

Oral preparations comprising an adhesive film or a composite of an adhesive film and a support, in which the adhesive film and/or the support contained a topical drug as shown in Table 6 below, were prepared using the materials shown in Table 6. In each example, the adhesive film and the support were prepared in the same manner as described in the corresponding example shown in the column of "material" in Table 6 except for film thickness.

TABLE 6

Example No.	Adhesive Film Material	Adhesive Film Drug and Its Content (wt%)	Adhesive Film Thickness (μm)	Support Material	Support Drug and Its Content (wt%)	Support Thickness (μm)
14	Example 1	Mepivacaine 5	30	Example 1	-	15
15	Example 2 (CVP/PVAc= 5/5)	-	20	Example 2	Cetylpyridinium chloride 2 ℓ-Menthol 3	50
16	Example 3	Lithospermi Radix extract 60		PVAc*	-	30
17	Example 4	Chlorhexidine-hydrochloride 2	100	-	-	-
18	Example 5	Predonisolone 0.2	40	Example 5	-	30
19	Example 6	Sodium azulene-sulfonate 0.5	20	Example 6	-	30

Note: *: Polyvinyl acetate having a degree of polymerization of about 2,000.

EXAMPLES 20 to 37

Oral preparations comprising an adhesive film and a support, in which the adhesive film or both the adhesive film and the support contained a topical drug as shown in Table 7 below, were prepared using the film materials shown in Table 7. In each example, the adhesive film and the support were prepared in the same manner as described in the corresponding example shown in the column of "material" in Table 7 except for film thickness.

TABLE 7

Example No.	Adhesive Film			Support		
	Material	Drug and Its Content (wt%)	Thickness (μm)	Material	Drug and Its Content (wt%)	Thickness (μm)
20	Example 7	Triamcinolone acetonide 0.05	30	Example 7	-	40
21	Example 7	Dipotassium glycyrrhetinate 1.0	30	Example 7	-	40
22	Example 7	Fradiomycin sulfate 1.0 Hydrocortisone acetate 0.5	30	Example 7	-	40
23	Example 7	Ethyl aminobenzoate 10.0	30	Example 7	-	40
24	Example 7	Tocopherol nicotinate 2.0 Cetylpyridinium chloride 0.2	30	Example 7	-	40
25*	Example 8	Tetracycline hydrochloride 3	20	Example 8	-	30
26*	Example 8	Strontium chloride 5	20	Example 8	-	30
27*	Example 8	Tranexamic acid 0.1	20	Example 8	-	30

* Dried at 70°C for 15 minutes

TABLE 7 (cont'd)

Example No.	Adhesive Film: Material	Adhesive Film: Drug and Its Content (wt%)	Adhesive Film: Thickness (μm)	Support: Material	Support: Drug and Its Content (wt%)	Support: Thickness (μm)
28	Example 9	Dexamethasone 0.1	60	Example 9	-	9
29	Example 9	Sodium fluoride 5	60	Example 9	-	9
30	Example 9	Lysozyme chloride 0.5	60	Example 9	-	9
31	Example 11	Lidocaine 5	50	Ethylene-vinyl acetate copolymer (vinyl acetate content: 28 wt%)	-	60
32	Example 12	Aluminum lactate 5	60	Example 12	-	30
33	Example 13	Dibucaine hydrochloride 0.5	30	Example 13	Dibucaine hydrochloride 0.5	30
34	Example 13	Dequalinium hydrochloride 2	30	Example 13	Dequalinium hydrochloride 2	30
35	Example 13	Calcitriol 0.001	40	Example 13	-	30
36	Example 13	1α,(OH)-vitamin D_3 0.005	40	Example 13	-	30
37	Example 13	1α,24(R)-(OH)$_2$-vitamin D_3 0.005	40	Example 13	-	30

The effects of the oral preparations obtained in Example 14 to 37 were evaluated by the following clinical examples.

CLINICAL EXAMPLE 1

Effect on Stomatitis

A patient (50-year-old, female) suffered from stomatitis of 5 mm in diameter on her buccal mucosa. The oral preparation of Example 20 was applied on the affected part three times a day. The inflammation subsided on the third day.

CLINICAL EXAMPLE 2

Effect on Stomatitis

A patient (27-year-old, male) with stomatitis of 6 mm in diameter on his gingival mucosa had much pain at meals. The oral preparation of Example 3 was prescribed to him with a direction to apply to the affected part at meals. He had no pain on the injured site during a meal.

CLINICAL EXAMPLE 3

Effect on the injured site by toothbrushing

A patient (8-year-old, female) had a injured site on her gingival mucosa due to brushing with a toothbrush. The oral preparation of Example 21 was applied to the injured part three times a day, while toothbrushing instructions were given to the patient. The wound healed on the 2nd day.

CLINICAL EXAMPLE 4

Effect on Halitosis

A patient (21-year-old, female) complained of bad breath. Ten oral bandages of Example 15 were prescribed to her with directions to apply to the cervix dentis of the jaw twice a day. On re-examination after 1 week, subjective symptoms disappeared.

CLINICAL EXAMPLE 5

Prophylactic Effect on Infection

⌈456 Flap operation was performed on a patient (39-year-old, male) with adult periodontitis having deep pockets. The oral preparation of Example 22 was applied on the operated part, and a pack was further applied thereon. When the pack was removed on the third day, granulation was found to be normal. The patient further received only the oral preparation twice a day for 4 days, and the postoperative course was uneventful.

CLINICAL EXAMPLE 6

Effect on Periodontal Disense

The oral preparation of Example 24 was applied to ⌈345 of a patient (45-year-old, male) with adult periodentitis having deep pockets once a day for 4 weeks. As a control, ⌈345 were not treated with the oral preparation.

As a result, in the treated part, the gingival index decreased from 2 to 1 and the pocket depth decreased from 5.5 mm to 4.0 mm. On the other hand, almost no improvement of symptoms was noted in the control part.

CLINICAL EXAMPLE 7

Effect on Dentin Hyperesthesia

A patient (36-year-old, female) complained of dentin hyperesthesia accompanied by sharp pain in ⌈4. Thirty units of the oral preparation of Example 26 were prescribed to her with a direction to apply to the affected part twice a day.

On re-examination after 3 weeks, the symptoms completely disappeared.

CLINICAL EXAMPLE 8

Effect on dentin hyperesthesia

A patient (56-year-old, female) complained of dentin hyperesthesia accompanied by sharp pain in ⌈2. The oral preparation of Example 9 were applied to the affected part twice a day.

On re-examination after four weeks, the symptoms completely disappered.

CLINICAL EXAMPLE 9

Local Anesthetic Effect

The oral preparation of Example 31 was preoperatively applied to the gingiva of a patient (41-year-old, female) with proliferative gingivitis. Thereafter, gingivectomy was performed on the patient, but the patient experienced neither pain during the operation nor paresthesia in the part where the oral preparation was not administered. Further, the postoperative course was uneventful.

Claims

1. An oral bandage comprising a soft adhesive film consisting of a mixture of (a) an acrylic acid polymer, methacrylic acid polymer and/or maleic anhydride polymer and (b) a vinyl acetate polymer, the polymers (a) and (b) being uniformly dissolved in each other without regions of phase separation, so as to be substantially water-insolubilized; and optionally a basic substance capable of neutralizing said polymers (a).

2. An oral bandage as claimed in Claim 1, wherein the weight ratio of the polymer(s) (a) to polymer (b) in the film is such that the value obtained from the following formula is from 15 to 45:

$$\frac{(\text{weight of } -COOH) + \frac{5}{4}(\text{Weight of } -CO-O-CO-)}{\text{Total weight of polymers (a) and (b)}} \times 100$$

3. An oral bandage as claimed in Claim 1 or 2, wherein said vinyl acetate polymer has an average molecular weight determined by viscosity of at least 60,000.

4. An oral bandage as claimed in any preceding claim, wherein said acrylic or methacrylic polymer contains 20% by weight or more of -COOH group and said maleic anhydride polymer contains 16% by weight or more of -CO-O-CO- group.

5. An oral bandage as claimed in any preceding claim, wherein said mixture was obtained by dissolving the polymers (a) and (b) in a solvent common to both.

6. An oral bandage as claimed in Claim 5, wherein said solvent is selected from lower alcohols, mixtures of a lower alcohol in a larger proportion and a compatible organic solvent, mixtures of a lower alcohol in a larger proportion and water, and mixtures of a lower alcohol in a larger proportion, a compatible organic solvent and water.

7. An oral bandage as claimed in Claim 6, wherein said mixture of a lower alcohol and an organic solvent contains not more than 30% by weight of the organic solvent.

8. An oral bandage as claimed in Claim 6, wherein said mixture of a lower alcohol and water or of a lower alcohol, an organic solvent and water contains not more than 30% by weight of water.

9. An oral bandage as claimed in any preceding claim wherein said basic substance (c) is at least one salt or base.

10. An oral bandage as claimed in Claim 9, wherein said basic substance is a monovalent metal salt or monovalent base and is present in an amount of from 0.03 to 0.2 equivalent based on the said

polymers (a).

11. An oral bandage as claimed in any preceding claim, wherein said oral bandage further comprises a soft film support.

12. An oral preparation comprising an oral bandage as defined in any preceding claim and a topical drug incorporated therein.

Revendications

1. Emplâtre pour la cavité buccale comprenant un film adhésive souple consistant en un mélange de (a) un polymère d'acide acrylique, un polymère d'acide méthacrylique et/ou un polymère d'anhydride maléique et (b) un polymère d'acétate de vinyle, les polymères (a) et (b) étant uniformément dissous l'un dans l'autre sans régions de séparation de phase de manière à être substantiellement rendus insolubles dans l'eau, et à choix une substance basique capable de neutraliser les dits polymères (A).

2. Emplâtre buccal selon la revendication 1, dans lequel le rapport du poids du/des polymère(s) (a) au polymère (b) dans le film est tel que la valeur obtenue par la formule ci-jointe va de 15 à 45:

$$\frac{(\text{poids du } -COOH) + \frac{5}{4}(\text{poids du } -CO-O-CO-)}{\text{poids total des polymères (a) et (b)}} \times 100$$

3. Emplâtre buccal selon la revendication 1 ou 2, dans lequel le dit polymère d'acétate de vinyle a un poids moléculaire moyen déterminé par la viscosité d'au moins 60'000.

4. Emplâtre buccal selon l'une quelconque des revendications précédentes, dans lequel le dit polymère acrylique ou méthacrylique contient 20% en poids ou plus du groupe -COOH et le dit polymère d'anhydride maléique contient 16% en poids ou plus du groupe -CO-O-CO.

5. Emplâtre buccal selon l'une quelconque des revendications précédentes, dans lequel le dit mélange a été obtenu par dissolution des polymères (a) et (b) dans un solvant qui leur est commun à tous deux.

6. Emplâtre buccal selon la revendication 5, dans lequel le dit solvant est sélectionné parmi les alcools inférieurs, les mélanges d'un alcool inférieur dans une proportion plus grande et d'un solvant compatible, les mélanges d'un alcool inférieur dans une proportion plus grande et d'eau, et les mélanges d'un alcool inférieur dans une portion plus grande, d'un solvant organique compatible et d'eau.

7. Emplâtre buccal selon la revendication 6, dans lequel le dit mélange d'un alcool inférieur et d'un solvant organique ne contient pas plus de 30% en poids de solvant organique.

8. Emplâtre buccal selon la revendication 6, dans lequel le dit mélange d'un alcool inférieur et d'eau ou d'un alcool inférieur, d'un solvant organique et d'eau ne contient pas plus de 30% en poids d'eau.

9. Emplâtre buccal selon l'une quelconque des revendication précédentes, dans lequel la substance basique (c) est au moins un sel ou une base.

10. Emplâtre buccal selon la revendication 9, dans lequel la dite substance basique est un sel de métal monovalent ou une base monovalente et est présente dans une quantité allant de 0,03 à 0,2 équivalente sur la base des dits polymères (a).

11. Emplâtre buccal selon l'une des revendications précédentes, dans lequel le dit emplâtre buccal comprend de plus un support souple de film.

12. Préparation pour la cavité de la bouche comprenant un emplâtre buccal selon l'une quelconque des revendications précédentes et un médicament topique qui lui est incorporé.

Patentansprüche

1. Oraler Verband, enthaltend einen weichen Klebefilm, bestehend aus einer Mischung von (a) einem Acrylsäurepolymer, Methacrylsäurepolymer und/oder Maleinanhydridpolymer und (b) einem Vinylacetatpolymer, wobei die Polymere (a) und (b) einheitlich ineinander aufgelöst sind, ohne Zonen von Phasentrennung, so dass sie im wesentlichen wasserinsolubilisiert sind; und gegebenenfalls eine basische Substanz, die fähig ist, die genannten Polymere (a) zu neutralisieren.

2. Oraler Verband gemäss Anspruch 1, worin das Gewichtsverhältnis des (der) Polymer(e) (a) zu Polymer (b) im Film so ist, dass der Wert, der von folgender Formel erhalten wird, 15 bis 45 ist:

$$\frac{(\text{Gewicht von } -COOH) + \frac{5}{4}(\text{Gewicht von } -CO-O-CO)}{\text{Gesamtgewicht der Polymere (a) und (b)}} \times 100$$

3. Oraler Verband gemäss Anspruch 1 oder 2, worin das genannte Vinylacetatpolymer ein mittleres durch Viskosität bestimmtes Molekulargewicht von mindestens 60'000 besitzt.

4. Oraler Verband gemäss einem der vorhergehenden Ansprüche, worin das genannte Acryl- oder Methacrylpolymer 20 Gew.-% oder mehr -COOH-Gruppen aufweist und das genannte Maleinanhydridpolymer 16 Gew.-% oder mehr -CO-O-CO-Gruppen aufweist.

5. Oraler Verband gemäss einem der vorhergehenden Ansprüche, worin die genannte Mischung durch Auflösen der Polymere (a) und (b) in einem für beide üblichen Lösungsmittel erhalten wurde.

6. Oraler Verband gemäss Anspruch 5, worin das genannte Lösungsmittel ausgewählt ist aus niederen Alkoholen, Mischungen von niederen Alkohlen in einem grösseren Anteil und einem verträglichen organischen Lösungsmittel, Mischungen eines niederen Alkoholes in einem grösseren Anteil und Wasser, Mischungen eines niederen Alkoholes in einem grösseren Anteil, einem verträglichen organischen Lösungsmittel und Wasser.

7. Oraler Verband gemäss Anspruch 6, worin die genannte Mischung eines niederen Alkohols und einem organischen Lösungsmittel nicht mehr als 30 Gew.-% des organischen Lösungsmittels enthält.

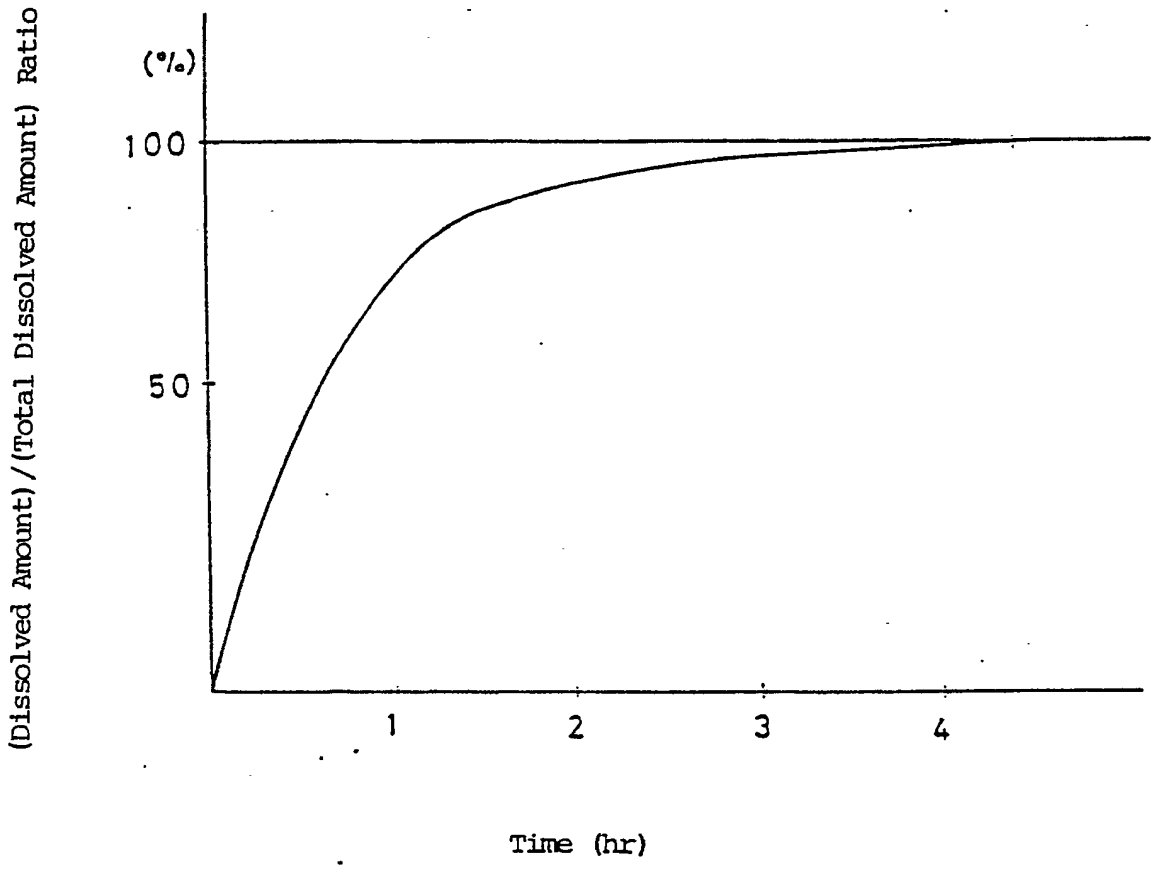
8. Oraler Verband gemäss Anspruch 6, worin die genannte Mischung eines niederen Alkohols und Wasser oder eines niederen Alkohols, eines organischen Lösungsmittels und Wasser nicht mehr als 30 Gew.-% Wasser enthält.

9. Oraler Verband gemäss einem der vorhergehenden Ansprüche, worin die genannte basische Substanz (c) mindestens ein Salz oder eine Base ist.

10. Oraler Verband gemäss Anspruch 9, worin die genannte basische Substanz ein monovalentes Metallsalz oder eine monovalente Base ist und in einem Anteil von 0,03 bis 0,2 Aequivalenten auf Basis des genannten Polymers (a) vorhanden ist.

11. Oraler Verband gemäss einem der vorhergehenden Ansprüche, worin der genannte orale Verband im weiteren einen weichen Trägerfilm aufweist.

12. Orale Zubereitung, enthaltend einen oralen Verband gemäss der Definition eines der vorhergehenden Ansprüche und eines einverleibten topischen Medikamentes.



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(54) **Verfahren zur Herstellung einer Darreichungs- und Dosierungsform für Arzneimittel-Wirkstoffe, Reagentien oder andere Wirkstoffe.**

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Beschreibung

Arzneimittel können in Form von Pulvern, Tropflösungen oder Säften oral verabreicht werden. Da bei diesen Abgabeformen eine genaue Dosierung jedoch schwierig ist, werden vom Hersteller dosierte Applikationsformen wie Tabletten, Dragees oder Kapseln generell bevorzugt. Auch Reagentien und andere Wirkstoffe, z.B. Süßstoffe oder Aromastoffe, werden für eine genaue dosierte Anwendung häufig tablettiert. Die Herstellungstechnik für Tabletten, Dragees, Kapseln und dergleichen ist zwar weitgehend ausgereift, doch sind eine Reihe von systembedingten Nachteilen nicht zu übersehen.

Für niedrig dosierte Wirkstoffe muß ein großer Anteil an Hilfsstoffen zugesetzt werden, um zu einer handhabbaren Größe der Einzeldosis zu gelangen. Weiterhin ist eine genaue Kennzeichnung einzelner Tabletten oder Dragees praktisch nicht möglich. Es haben sich deshalb Durchdrückpackungen durchgesetzt, welche eine Mehrzahl von Tabletten, Dragees oder auch Kapseln enthalten und welche mit den notwendigen Informationen, insbesondere dem Namen des Präparates bedruckt sind. Die Herstellung solcher Verpackungen erfordert naturgemäß einen zusätzlichen Arbeitsgang und es werden Umverpackungen in Form von Faltschachteln benötigt, welche ein beträchtliches Leervolumen aufweisen und dadurch zusätzlich Lagerraum beanspruchen. Ein besonders gravierender Nachteil von Dragees und Kapseln besteht darin, daß eine Zerteilung praktisch unmöglich ist, die kleinste Dosis somit vorgegeben ist. Auch bei Tabletten ist eine genaue Zerteilung schwierig, lediglich größere Tabletten mit einer Kerbe als Sollbruchstelle lassen sich allenfalls teilen, wobei häufig ungleichgroße Bruchstücke entstehen.

Es sind bereits Versuche zur Schaffung einer neuen Darreichungsform für die orale Verabreichung von Arzneimitteln bekannt geworden, welche aus wirkstoffhaltigen Folien bestehen. Gemäß der BE-A 637 363 wird ein papierartiges Trägermaterial aus unlöslichen Zellulosefasern mit einer Wirkstofflösung getränkt bzw. durch Auftragen oder -streuen beschichtet und eine Dosierung durch Perforation der Trägerfolie nach Art eines Briefmarkenbogens erreicht. Die Wirkstoffdosierung ist dabei zwangsläufig äußerst ungenau. Aus den DE-A 2 432 925 und DE-A 2 449 865 ist es bekannt, Arzneimittelwirkstoffe in Folienbildner einzuarbeiten, bei denen es sich vorzugsweise um wasserlösliche Verbindungen wie Methyl- und Ethylzellulose, insbesondere aber Hydroxypropylzellulose, Hydroxyethylzellulose oder Methylhydroxypropylzellulose handelt. Daneben können die Folien Füllstoffe und Trennmittel enthalten. Die DE-A 2 746 414 beschreibt ebenfalls die Verarbeitung von wirkstoffhaltigen Folienmassen auf Basis von beispielsweise Gelatine oder Zellulosederivaten und weiteren Zusätzen wie Stärke zu Folien, in die der Wirkstoff eingearbeitet ist. Die erhaltenen wirkstoffhaltigen Folien lassen sich zur Dosierung durch Perforation in einzelne Abschnitte aufteilen.

Aus der GB-A 1 061 557 ist es bekannt, Gelatinefolien oder Reispapier mit einer Wirkstofflösung zu imprägnieren oder mit einer Wirkstofflösung bzw. -schmelze zu beschichten. Die Beschichtung erfolgt durch Besprühen mit der Lösung oder durch Laminieren von zwei Trägerfolien mit der dazwischen liegenden Wirkstoffschmelze. Diese Herstellungsverfahren ermöglichen keine exakte Dosierung des Wirkstoffes: Beim Aufsprühen einer Wirkstofflösung kann ebenso wie beim Beschichten mit einer Schmelze eine völlig gleichmäßige Schichtdicke nicht sichergestellt werden. Darüber hinaus haftet die nur aus dem Wirkstoff bestehende Beschichtung häufig schlecht auf der Trägerfolie.

Die JA-A 76/54 917 erwähnt die Möglichkeit, eßbare Folien, z.B. Gelatinefolien, mit Wirkstofflösungen zu bedrucken, welche Verdickungsmittel wie Hydroxylpropylzellulose enthalten. Auch bei dieser Vorgehensweise erhält man häufig nur schlecht haftende Beschichtungen.

Alle diese Vorschläge haben keinen Eingang in die Praxis gefunden und in dem neuesten Lehrbuch der "Arzneiformenlehre" von P.H. List, 4. Auflage, Stuttgart, 1985, finden sie keine Erwähnung. Dies beruht ersichtlich darauf, daß die bislang bekanntgewordenen Vorschläge es nicht ermöglichen, die geforderte Gewichtskonstanz und gleichmäßige Wirkstoffverteilung zu erreichen, welche heute gefordert werden. Die Pharmakopoea Europae setzt zum Beispiel Maßstäbe für die Gleichförmigkeit des Gewichtes einzeldosierter Arzneiformen, wobei diese dem jeweiligen Durchschnittsgewicht entsprechend nach höchstzulässigen Abweichungen in % gestattelt sind. Die Forderung liegt im allgemeinen bei +/– 5 bis max. 10%. Entsprechende Werte für feste Arzneiformen bestehen auch hinsichtlich anderer Parameter wie Zerfallzeit und Lösungsgeschwindigkeit.

Die oben erwähnten Vorschläge des Standes der Technik führen zu Produkten ungenügender Akzeptanz durch die Patienten (z.B. lassen sich Papierabschnitte nur schlecht einnehmen) und erlauben keine exakte Dosierung pro Flächeneinheit, wie sie unbedingt gefordert werden muß. Bei Inkorporieren des Wirkstoffes in eine Folie bereitet nicht nur die genaue Dosierung Schwierigkeiten, sondern ein wesentlicher weiterer Nachteil besteht darin, daß für jeden Wirkstoff eine entsprechende Folie gesondert hergestellt werden muß, so daß die Wirtschaftlichkeit des Herstellungsverfahrens nicht gegeben ist.

Der Erfindung liegt demgegenüber die Aufgabe zugrunde, eine "zweidimensionale" Darreichungs- und Dosierungsform zu schaffen, welche die genannten Nachteile nicht aufweist, sich leicht herstellen läßt und mit großer Flexibilität an die Anforderungen des Marktes und verschiedener Wirkstoffe angepaßt werden kann.

Gegenstand der Erfindung ist ein Verfahren zur Herstellung einer Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder andere Wirkstoffe in Form einer wasserlöslichen Folie auf Basis von Stärken, Gelatinen, Glycerin und/oder Sorbit sowie gegebenenfalls natürlichen und/oder synthetischen Harzen und Gummen, welches dadurch gekennzeichnet ist, daß man

a) eine wäßrige Zusammensetzung, deren Rezeptur derjenigen der Trägerfolie entspricht, aus dem Wirkstoff sowie Stärken, Gelatinen, Glycerin und/oder Sorbit sowie gegebenenfalls natürlichen und/oder synthetischen Harzen und Gummen herstellt, und

b) diese Beschichtungsmasse kontinuierlich mittels eines Walzenauftragsverfahrens in genau vorbestimmter Menge (Schichtdicke) auf mindestens eine Seite der wasserlöslichen wirkstofffreien Folie aufbringt.

Die erfindungsgemäß hergestellte Darreichungsform weist eine Reihe wesentlicher Vorteile auf:

– Eine Trägerfolie kann für die verschiedensten Wirkstoffe verwendet werden und somit in größerer Menge wirtschaftlich produziert werden,

– die wirkstoffhaltige Schicht kann bei hochwirksamen Arzneimitteln sehr dünn sein, da das Trägermaterial die ausreichende mechanische Festigkeit gewährleistet,

– die Beschichtung haftet hervorragend auf der Trägerfolie, weil beide dieselbe Rezeptur aufweisen,

– mit Hilfe der modernen Walzen-Auftragverfahren läßt sich die wirkstoffhaltige Beschichtung mit konstanter Schichtdicke aufbringen, so daß die erforderlichen Toleranzen eingehalten werden können,

– falls eine Sterilisierung erforderlich ist, kann diese wegen der geringen Schichtdicke problemlos mittels Strahlenbehandlung erreicht werden,

– der Träger läßt sich auf der Vorder- und insbesondere der Rückseite unter Verwendung physiologisch verträglicher Druckfarben mit verschiedenen Informationen bedrucken,

– aufgrund der relativ großen Fläche von beispielsweise 4 bis 10 cm^2 lassen sich ausführliche Informationen für den Benutzer auf das unbeschichtete Trägermaterial oder auch nachträglich aufdrucken,

– die Dosiereinheiten lassen sich durch entsprechende Vorzerteilung, z.B. eine Perforierung, flexibel gestalten, so daß für verschiedene Dosierungen (z.B. für Erwachsene und Kinder) nur ein Produkt hergestellt werden muß; die Vorzerteilung kann ggf. auch erst in der Apotheke oder im Krankenhaus nach ärztlichen Angaben vorgenommen werden.

Mit den früher beschriebenen Darreichungsformen in Folienform hat die erfindungsgemäße darüberhinaus den Vorteil des äußerst geringen Platzbedarfes gemeinsam. Statt Faltschachteln können daher beispielsweise Taschen oder Beutel aus Kunststoffolie oder kunststoffbeschichtetem Papier verwendet werden, in welche das Produkt eingesiegelt wird, ähnlich wie feuchte Erfrischungstücher.

Die Herstellung der Trägerfolie erfolgt in an sich bekannter Weise mit einer kontinuierlich arbeitenden Folienmaschine auf Rollenbasis. Das Streichverfahren zur Herstellung der Trägerfolie arbeitet nach dem Walzenprinzip, d.h. die wasserhaltige Zusammensetzung für die Trägerfolie wird mittels Rollen und Rakel angetragen und zu dünnen Bahnen ausgestrichen, auf der Rolle vorgetrocknet und im Haupttrockengang auf die gewünschte Endfeuchte nachgetrocknet. Das erhaltene Endprodukt ist so fest und elastisch, daß es auf Rollen gewickelt werden kann und lagerfähig ist, wenn die Restfeuchtigkeit nicht zu hoch ist (Gefahr der Schimmelbildung).

Die Folienbreite kann beliebig sein und wird günstigerweise auf die Breite der Beschichtungsmaschine zugeschnitten. Es bietet sich jedoch an, bereits bei der Herstellung beide Breiten aufeinander abzustimmen.

Es ist technisch auch möglich, die Folienherstellung und die Beschichtung zeitlich nacheinander auf derselben Anlage vorzunehmen, wodurch die Wirtschaftlichkeit wesentlich erhöht werden kann.

Die verwendete Zusammensetzung wird unter Umpumpen bei der gewünschten Temperatur, Viskosität und Homogenität gehalten. Die Trocknung der Folie erfolgt anschließend in einem Wärmetunnel. Die so gewonnene Trägerfolie stellt den indifferenten Träger für die spätere Beschichtung mit verschiedene Wirkstoffe enthaltenden Beschichtungsmassen dar.

Zur Herstellung der wasserlöslichen Trägerfolie dient eine physiologisch unbedenkliche Zusammensetzung. Die "Wasserlöslichkeit" soll dabei so definiert sein, daß die Herstellung der Folie aus einer wäßrigen Zusammensetzung erfolgt und daß sich die fertige Folie später bei der Anwendung wiederum in Wasser bzw. im Magensaftmilieu löst oder darin quillt.

Als Folienbildner kommen insbesondere Gelatinen sowie Stärken (Kartoffelstärke, Weizenstärke, Maisstärke) sowie ferner Poly-N-vinylpyrrolidon (PVP), Methyl- und Ethylzellulose sowie Polyvinylalkohol (PVA) infrage. Ferner können wässerlösliche Acrylharzdispersionen Verwendung finden. Geeignete Weichmacher sind insbesondere polyfunktionelle Alkohole wie Glycerin und Sorbit (Karion®).

Die Komponenten werden in geeigneter Weise mit Wasser kalt angemischt und unter leichtem Erwärmen und ständigem Rühren zu einem streichfähigen Schleim verarbeitet. Das Einrühren von Luft muß soweit wie möglich vermieden werden, um eine klare, allenfalls leicht opaleszierende Masse zu erhalten.

Die Stärke der Trägerfolie beträgt vorzugsweise zwischen etwa 50 und 250 µm. Sie ist in weitem Maße steuerbar. Auch die Eigenschaften der Trägerfolie lassen sich durch entsprechende Kombination der Folienbildner und Weichmacher qualitativ stark beeinflussen. Die Trägerfolie soll eine möglichst gleichmäßige Stärke aufweisen (vorzugsweise z.B. 100 µm), leicht elastisch und knickfähig sein, ohne zu brechen. Dabei sollte der Stärkeanteil ausreichend hoch sein, damit beim Aufbringen der Beschichtungsmasse Feuchtigkeit aufgenommen wird, ohne daß es zu einem Kleben der Oberfläche oder zum Erweichen der ganzen Folie kommt.

Folgende Rahmenrezeptur hat sich für die Trägerfolie bewährt:

Gelatine 8 bis 10 g
Stärke 4 bis 8 g
Glycerin 1 bis 2 g

Polyvinyl-pyrrolidon 1 bis 2 g
Wasser 30 bis 50 g

Wasserlösliche natürliche und/oder synthetische Harze, z.B. Acrylharze, und Gumme sind ebenfalls geeignet. Ggf. können der Masse noch übliche weitere Stoffe zugefügt werden, z.B. Konservierungsmittel wie p-Hydroxybenzoesäure-Ester, inerte lösliche oder unlösliche Füllstoffe, Geschmackstoffe, Zucker oder andere Süßungsmittel, weitere Weichmacher, insbesondere Polyole, Wachse oder Farbstoffe.

Die Möglichkeit der vorder- und rückseitigen Bedruckung der Trägerfolie ist ein besonderer Vorteil der erfindungsgemäßen Darreichungsform. Beispielsweise können die Kennzeichnung, Angaben über die Inhaltsstoffe sowie Dosierungsangaben aufgedruckt werden. Gegebenenfalls läßt sich sogar der ganze Inhalt eines Beipackzettels rückseitig aufdrucken mit der Folge, daß ein separater Beipackzettel, der auch häufig verlorengeht, überflüssig wird. Bei Arzneimitteln, welche regelmäßig genommen werden müssen, beispielsweise bei hormonalen Contrazeptiva, kann der gesamte Verabreichungsplan so angebracht werden, daß eine einfache Einnahmekontrolle gewährleistet ist. Zur Bedruckung müssen physiologisch verträgliche Farben (Lebensmittelfarben) verwendet werden, da die Trägerfolie einen Teil der oral verabreichten Darreichungsformen bildet.

Für die wirkstoffhaltige Beschichtungsmasse findet eine wäßrige Zusammensetzung Verwendung, die physiologisch inert ist und deren Einzelkomponenten für Arzneimittel bzw. Lebensmittel geeignet sind. Wesentlich ist die gegenseitige physikalisch-chemische Affinität und Verträglichkeit zwischen Beschichtungsmasse und Trägerfolie, welche besonders gut ist, weil die verwendeten Komponenten gleich sind bzw. sehr ähnliche Eigenschaften besitzen. Unter Berücksichtigung des zugeführten Wirkstoffes entspricht die Rezeptur der Beschichtungsmasse demgemäß der oben für die Trägerfolie genannten, wobei die genaue Einstellung auf Feststoffgehalt und Viskosität mittels indifferenter Quell- und Füllstoffe erfolgt.

Die Masse enthält somit einmal polymere Filmbildner, vorzugsweise Gelatine und quellende oder lösliche Stärken sowie ggf. Zellulosen oder Hemizellulosen. Ferner werden Weichmacher zugesetzt, insbesondere mehrwertige Alkohole wie Glycerin oder Sorbit. Zur Einstellung der erwünschten Viskosität der Beschichtungsmasse, welche die Konsistenz eines Schleimes aufweist, finden polymere Quellstoffe Verwendung, vorzugsweise Alginate, Pectine, Chitine, Lecithine oder Polyethylenglykole. Diese letzteren Stoffe können gleichzeitig als Haftvermittler dienen. Andererseits können auch wasserlösliche synthetische oder natürliche Harze oder Gumme oder Gummi arabicum zugesetzt werden, um die Haftung der Beschichtung auf dem Trägermaterial zu verbessern. Schließlich können noch Konservierungsmittel wie z.B. p-Hydroxybenzoesäureester, Farbstoffe (Lebensmittelfarbstoffe), Pigmente wie Titandioxid oder Aroma- und Süßstoffe zugesetzt werden.

Coatingmassen mit einem Wassergehalt von ungefähr 50% und einer Viskosität von etwa 30 bis zu 10 000 cPs haben sich als besonders geeignet erwiesen. Die Rezeptur und Herstellung ähnelt derjenigen eines Arzneimittelsaftes, in welchem der Wirkstoff bzw. die Wirkstoffkombination gelöst oder gleichmäßig dispergiert wird. Die Beschichtungsmasse muß ausreichende Homogenität und galenische Stabilität aufweisen, damit ein gleichmäßiger Wirkstoffgehalt der fertigen Beschichtung sichergestellt ist.

In dieser Grundmasse wird der Wirkstoff gelöst bzw. dispergiert. Im Fall der Verwendung einer Dispersion muß der Wirkstoff für eine gleichmäßige Verteilung äußerst feinteilig sein. Vorzugsweise liegt die mittlere Teilchengröße im Bereich von etwa 1 bis 20 µm.

Die gewünschte Dosis des Wirkstoffes und die angestrebte Fläche der Dosiseinheiten bestimmen letztlich die Dicke der Schicht, wobei der Feuchtigkeitsgehalt der Beschichtungsmasse und der fertigen Beschichtung zu berücksichtigen sind.

Die erfindungsgemäße Darreichungsform ist besonders geeignet für Arzneimittel, welche niedrig dosiert verabreicht werden, d.h. bei welchen die Einzeldosis für die orale Applikation zwischen 0 mg (Placebo) und etwa 20 mg liegt. Geeignete Arzneimittelwirkstoffe finden sich in allen Bereichen der oralen Therapie; hervorzuheben sind u.a. Analeptika, Antibiotika, Antidiabetika, Antiemetika, Antiepileptika, Antihypertonika, Cortikoide, Geriatrika, Hypnotika, Cardiaka, Hypostatika und Biowirkstoffe.

In einem Beschichtungsgang lassen sich ca. 4 bis 20 g Wirkstoff je m^2 (= 10.000 cm^2) Trägerfolie aufbringen, so daß 10 cm^2 (= 2 übliche Briefmarken) bis zu 20 mg Wirkstoff aufnehmen können.

Die Beschichtungsmasse wird normalerweise auf eine Seite der Trägerfolie aufgebracht, doch ist auch eine beidseitige Beschichtung, insbesondere bei zwei verschiedenen Wirkstoffen möglich. Jede Beschichtung kann einen oder mehrere Arzneimittelwirkstoffe enthalten. Falls bei Verwendung mehrerer Wirkstoffe diese nicht ohne weiteres miteinander verträglich sind und in einer Beschichtungsmasse enthalten sein können, ist es bei der erfindungsgemäßen Darreichungsform möglich, die Beschichtung in mehreren Schichten unterschiedlicher Zusammensetzung aufzubringen und die Wirkstoffe dadurch voneinander zu trennen, wobei erforderlichenfalls eine wirkstofffreie Zwischenschicht vorgesehen werden kann. Weiterhin ist es möglich, über der wirkstoffhaltigen Schicht noch eine weitere Schutzschicht vorzusehen, welche den/die Wirkstoff(e) genen eine Berührung mit der Atmosphäre und/oder gegen Licht schützt. In diesen Fällen muß die Schutzschicht demgemäß luft- und feuchtigkeitsundurchlässig und/oder durch Zusatz entsprechender Farbstoffe bzw. Pigmente lichtundurchlässig sein.

Weiterhin kann durch entsprechenden Aufbau der Beschichtung die Wirkstoffabgabe nach Verabreichung des Arzneimittels gesteuert werden. Beispielsweise ist es möglich, eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten anzuordnen, welche die Wirkstoffresorption im Magen/Darmtrakt in an sich bekannter Weise steuern.

Dabei kann die Wirkstoffschicht z.B. zwischen zwei säureunlöslichen Schichten angeordnet werden, so daß bei Verabreichung der Magen passiert wird und die Resorption erst im Darmtrakt erfolgt. In ähnlicher Weise können unterschiedliche Wirkstoffe in verschiedenen Schichten übereinander auf die Trägerfolie aufgebracht werden, damit die Resorption nacheinander und/oder verzögert erfolgt.

Ähnliche pharmakokinetische Effekte lassen sich durch das Einarbeiten (z.B. Suspendieren) von unterschiedlich vorbehandelten mikroverkapselten Wirkstoffen erzielen.

Die Beschichtung des Trägermaterials mit der wirkstoffhaltigen Beschichtungsmasse erfolgt mittels eines Walzenauftragverfahrens. Dieses für die quantitative Beschichtung besonders geeignete Verfahren arbeitet nach einem dem Tiefdruck ähnlichen Verfahren, welches als "Akkugravur" bezeichnet wird. Hierfür geeignete Maschinen sind im Handel (Fa. Pagendarm, Hamburg) und erlauben Auftragsgewichte bis zu 80 g/m² bei Bahngeschwindigkeiten von mehreren 100 m/min. Die reproduzierbare Gewichtskonstanz liegt für 20 g/m² bei nur +/- 2,5% für 1 g/m² und für ca. +/- 10% über die gesamte Fläche. Der Auftrag der Beschichtungsmasse erfolgt kontinuierlich über Walzen mit spezieller Feingravur, wobei die eingravierten Rillen zur Laufrichtung der Trägerfolie vorzugsweise einen Winkel von 30 bis 60, insbesondere 45° bilden. In die Walzen können 27 bis 80 Rillen/cm eingeätzt sein. Entsprechend ihrer Form und Tiefe kann die Gravur eine definierte Menge der Beschichtungsmasse aufnehmen und anschließend an die Trägerfolie weitergeben. Durch Variation der Vorlaufgeschwindigkeit, der Laufrichtung und der Gravur sowie durch indirektes Auftragen über eine weitere geschwindigkeitsvariable Walze lassen sich die Beschichtungsmengen sehr exakt einstellen.

Eine zweiseitige Beschichtung ergibt häufig Vorteile, da Probleme durch Verwerfen des Trägermaterials und durch unterschiedliche Hygroskopizität ausgeglichen werden. Mehrfach- und auch Streifenbeschichtungen, ja sogar Druckbildbeschichtungen, sind möglich und bieten bei der Verarbeitung von inkompatiblen Wirkstoffen eine große Variabilität.

Ein anderes geeignetes Auftragverfahren entspricht dem Streichen von Papier oder von Folien. Dabei werden Rohpapiere dadurch verbessert, daß sie ein- oder zweiseitig mit Coatingmaterialien beschichtet werden. Die wässrigen Beschichtungsmassen gelangen zunächst auf ein Walzwerk, welches sie mittels einer rotierenden Walze aufnimmt, mit einen Rakel bestimmten Abstandes auf eine definierte Schichtdicke abstreift, worauf die Walze die Beschichtungsmasse auf den Träger abgibt. Die Trägerfolie, welche 0,30 bis 7,50 m breit sein kann, durchläuft anschließend einen Trockentunnel und wird dann auf Rollen aufgewickelt. Dieser Vorgang ist in einem oder mehreren Schritten ein- oder zweiseitig wiederholbar, wobei auch eine bereits beschichtete Fläche nochmals beschichtet werden kann. Das Gewicht des Trägermaterials nimmt um das der Trockenmasse zu. Die Genauigkeit des Auftragverfahrens mittels dieses Rakel-Verfahrens liegt reproduzierbar bei +/- 5%. Sie ist abhängig von der jeweiligen Schichtdicke, die variabel zwischen 4 und 40 g/m² betragen kann. Innerhalb der einzelnen Fertigungen kann eine Gewichtstoleranz pro Flächeneinheit bis unter +/- 1 % erreicht werden.

Bei Aufbringung mehrerer Schichten, wie dies oben bereits beschrieben wurde, werden diese nacheinander aufgebracht, wobei ggf. jede Beschichtung zuvor eine Trocknungsstation durchläuft. Diese kann beispielsweise aus einem temperierten Walzenpaar und einem in Sektionen steuerbaren Trockentunnel bestehen. Nach dem letzten Beschichtungsvorgang wird das beschichte Material auf Rollen aufgewickelt.

Die wirkstoffbeschichtete Trägerfolie wird anschließend in Dosiseinheiten vorzerteilt, welche ähnlich wie Briefmarken abtrennbar sind. Normalerweise wird diese Vorzerteilung beim Arzneimittelhersteller erfolgen, es ist jedoch auch denkbar, das beschichtete Material beispeilsweise an Krankenhäuser oder Apotheken auszuliefern, wo dann die Vorzerteilung dosisabhängig oder auch individuell nach ärztlicher Vorgabe durchgeführt werden kann.

Die Vorzerteilung erfolgt in besonders einfacher Weise durch Perforierung oder Stanzung, wobei es möglich ist, diesen Schritt mit der Bedruckung des Trägermaterials zu kombinieren. In vielen Fällen wird es allerdings günstiger sein, die Bedruckung des Trägermaterials vor der Beschichtung vorzunehmen.

Vor oder besser nach Vorzerteilung der wirkstoffhaltigen Beschichtung in Dosiseinheiten wird das beschichtete Trägermaterial zu gebrauchsfertigen Abschnitten zerschnitten, welche eine bestimmte Anzahl von Dosiseinheiten enthalten. Es ist auch denkbar, das Material auf Rollen zu schmalen Bändern zu zerschneiden. Von einer solchen Einzelrolle können dann die einzelnen Dosiseinheiten ähnlich wie einzelne Briefmarken abgetrennt werden.

Da als Grundstoffe für die Herstellung der erfindungsgemäßen Darreichungsform überwiegend Naturstoffe wie Stärken und Gelatine verwendet werden, erhält man insgesamt Produkte, welche den bekannten Oblaten ähneln und deren orale Einnahme keinerlei Schwierigkeiten bereitet. Wichtig ist, daß das Fertigprodukt weitgehend von Wasser befreit ist, d.h. einen Wassergehalt von wengier als 10 und vorszugsweise von weniger als 2% aufweist, da sonst Schimmelbildung auftreten kann.

Vorstehend wurde die Erfindung im wesentlichen im Zusammenhang mit Arzneimitteln beschrieben, worauf sie jedoch keineswegs beschränkt ist. Beispielsweise lassen sich in derselben Weise auch Dosierungsformen für chemische Reagentien, Aromastoffe und dergleichen herstellen.

Zur näheren Erläuterung der Erfindung soll das nachfolgende Ausführungsbeispiele dienen.

Beispiel

Herstellung einer Arzneimittel-Darreichungsform in Form einer beschichteten Folie.

Zur Herstellung einer wasserlöslichen Trägerfolie wurde von folgender Zusammensetzung ausgegangen:
Gelatine 10,0 Gew.-Teile = 25%
Kartoffelstärke 8,0 Gew.-Teile = 20%
Glycerin 1,5 Gew.-Teile = 3,75%
gereinigtes Wasser 20,5 Gew.-Teile = 51,25%

Die Viskosität der schleimartigen Zusammensetzung betrug bei 50°C ca. 3000 cPs. Mit Hilfe des Streichverfahrens wurde die Masse zu einer Folie verarbeitet, welche nach dem Trocknen noch 9,3% Restwasser enthielt.

Unter Verwendung derselben Grundstoffe wie für die Trägerfolie wurde die Beschichtungsmasse gemäß folgender Rezeptur hergestellt:
Gelatine 10,0 Gew.-Teile = 18,2%
Kartoffelstärke 5,0 Gew.-Teile = 9,1%
Glycerin 1,0 Gew.-Teile = 1,8%
Wirkstoff 5,0 Gew.-Teile = 9,1%
gereinigtes Wasser 34,0 Gew.-Teile = 61,8%

Die Viskosität der schleimartigen Zusammensetzung betrug temperatur- und wirkstoffabhängig zwischen 4.000 und 10.000 cPs. Zur Herstellung der Beschichtungsmasse wurde zunächst die Gelatine in einer ausreichenden Menge Wasser gelöst. Dazu wurde Wasser von 90 bis 95°C vorgelegt, in das die Gelatine unter Rühren eingetragen wurde. In einem getrennten Ansatz wurde der Wirkstoff zusammen mit dem Glycerin in Wasser gelöst. Schließlich wurde die Kartoffelstärke bei 50 bis 60°C unter Rühren in einer ausreichenden Menge Wasser angerührt. Die Gelatinelösung und die Kartoffelstärkesuspension wurden zusammengegeben und die Wirkstoffsuspension wurde in die Mischung langsam eingerührt, wobei Lufteinschlüsse vermieden wurden. Die Temperatur wurde auf 55 bis 60°C gehalten. Zuletzt wurde der gewünschte Wassergehalt durch Zugabe von weiterem Wasser eingestellt.

Die Beschichtungsmasse wurde mittels Akkugravur mit einem Naßbeschichtungsgewicht von 55 g/m² auf die Trägerfolie aufgebracht. Nach dem Trocknen betrug das Beschichtungsgewicht 23 g/m² entsprechend einem Wirkstoffgehalt von 5 g/m². Die wirkstoffbeschichtete Folie wurde anschließend kastenartig perforiert, so daß die einzelnen Abschnitte bei Abmessungen von 2 x 2,5 cm eine Fläche von 5 cm² aufwiesen. Ein solcher Abschnitt enthielt 2.5 mg Wirkstoff.

Nach dem Trocknen lag die Restfeuchtigkeit des Produktes bei 8,6%.

Es wurde eine Darreichungsform erhalten, welche bei oraler Einnahme im Mund rasch quillt und zergeht und sich demgemäß leicht schlucken läßt.

Patentansprüche

1. Verfahren zur Herstellung einer Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder andere Wirkstoffe in Form einer wasserlöslichen Folie auf Basis von Stärken, Gelatinen, Glycerin und/oder Sorbit sowie gegebenenfalls natürlichen und/oder synthetischen Harzen und Gummen, dadurch gekennzeichnet daß man
   a) eine wässrige Zusammensetzung, deren Rezeptur derjenigen der Trägerfolie entspricht, aus dem Wirkstoff sowie Stärken, Gelatinen, Glycerin und/oder Sorbit sowie gegebenenfalls natürlichen und/oder synthetischen Harzen und Gummen herstellt, und
   b) diese Beschichtungsmasse kontinuierlich mittels eines Walzenauftragsverfahrens in genau vorbestimmter Menge (Schichtdicke) auf mindestens eine Seite der wasserlöslichen wirkstofffreien Folie aufbringt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß man der Zusammensetzung für die Trägerfolie und die Beschichtung zusätzlich inerte lösliche und/oder unlösliche Füllstoffe, Zucker und/oder andere Süßungsmittel, weitere Weichmacher, insbesondere Polyole, Wachse, Farbstoffe, Geschmacksstoffe und/oder Konservierungsmittel zusetzt.

3. Verfahren nach einem der Ansprüche 1 oder 2, dadurch gekennzeichnet, daß man für die Herstellung der Trägerfolie und der Beschichtungsmasse eine Zusammensetzung verwendet, die 8 bis 10 Gew.-Teile Gelatine, 4 bis 8 Gew.-Teile Stärke, 1 bis 2 Gew.-Teile Glycerin und 20 bis 50 Gew.Teile Wasser enthält.

4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß man eine Beschichtungsmasse einsetzt, die bis zu 10 Gew.-Teile des Wirkstoffes enthält.

5. Verfahren nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß man der Beschichtungsmasse zur Einstellung der Viskosität indifferente Quell- und Füllstoffe zusetzt.

6. Verfahren nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß man die Beschichtungsmasse kontinuierlich mittels Rasterwalzen, welche eine genau definierte Menge der Beschichtungsmasse aufnehmen und wieder abgeben, auf die Trägerfolie aufbringt.

7. Verfahren nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß man die Beschichtungsmasse kontinuierlich mittels glatter Walzenpaare, welche in geschwindigkeitsversetztem Gleichlauf die Masse aufnehmen und in definierter Menge abgeben, auf die Trägerfolie aufbringt.

8. Verfahren nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß man zur Herstellung eines Kombinationspräparates auf die Ober- und die Unterseite der Trägerfolie unterschiedliche Wirkstoffe aufbringt.

Claims

1. Process for the manufacture of a presentation and dosage form for pharmaceutical active substances, reagents or other active substances in the form of a water-soluble foil based on starches, gelatines, glycerin and/or sorbite and also in some cases on natural and/or synthetic resins and gums, characterized in that
   a) an aqueous composition, the formulation of which corresponds to that of the carrier foil, is manufactured from the active substance and from starches, gelatines, glycerin and/or sorbite and also in some cases from natural and/or synthetic resins and gums, and that

b) this coating substance is applied continuously in a precise pre-determined quantity (layer thickness) to at least one side of the active-substance-free-water-soluble foil by means of a roller coating process.

2. Process according to claim 1, characterized in that inert, soluble and/or insoluble fillers, sugars and/or other sweeteners, other softeners, particularly polyols, waxes, colorants, flavouring agents and/or preservatives are also added to the composition for the carrier foil and the coating.

3. Process according to one of claims 1 or 2, characterized in that, for the manufacture of the carrier foil and the coating substance, a composition is used which contains 8 to 10 parts by weight of gelatine, 4 to 8 parts by weight of starch, 1 to 2 parts by weight of glycerin and 20 to 50 parts by weight of water.

4. Process according to claim 3, characterized in that a coating substance is used which contains up to 10 parts by weight of the active substance.

5. Process according to one of claims 1 to 4, characterized in that inert swelling agents and fillers are added to the coating substance to regulate the viscosity.

6. Process according to one of claims 1 to 5, characterized in that the coating substance is continuously applied by means of grid rollers which take up and then release a precisely defined quantity of the coating substance.

7. Process according to one of claims 1 to 5, characterized in that the coating substance is applied to the carrier foil continuously by means of smooth pairs of rollers synchronized but out of phase which take up the substance and release a pre-defined quantity.

8. Process according to one of claims 1 to 7, characterized in that different active substances are applied to the top and bottom of the carrier foil for the manufacture of a compound preparation.

Revendications

1. Procédé de fabrication d'une forme d'administration et de dosage pour des principes actifs de médicaments, des réactifs ou d'autres substances actives, sous forme d'une feuille hydrosoluble à base d'amidons, de gélatines, de glycérol et/ou de sorbitol, et éventuellement de résines et gommes naturelles et/ou synthétiques, procédé caractérisé en ce que l'on

a) fabrique une composition aqueuse, dont la formulation correspond à celle de la feuille support, à partir de la substance active ainsi que d'amidons, de gélatines, de glycérol et/ou de sorbitol, et éventuellement de résines et gommes naturelles et/ou synthétiques, et

b) dépose en continu, à l'aide d'un cylindre d'enduction, cette masse, en quantité exactement prédéterminée (épaisseur de couche), sur au moins une des faces de la feuille hydrosoluble dépourvue de substance active.

2. Procédé selon la revendication 1, caractérisé en ce que l'on ajoute en plus, à la composition pour la feuille support et le revêtement, des charges inertes solubles et/ou insolubles, des sucres et/ou d'autres édulcorants, en outre des plastifiants, en particulier des polyols, des cires, des colorants, des aromatisants et/ou des conservateurs.

3. Procédé selon l'une des revendications 1 ou 2, caractérisé en ce que, pour la fabrication de la feuille support et du revêtement, on utilise une composition qui renferme de 8 à 10 parties en poids de gélatine, 4 à 8 parties en poids d'amidon, 1 à 2 parties en poids de glycérol et 20 à 50 parties en poids d'eau.

4. Procédé selon la revendication 3, caractérisé en ce que l'on met en œuvre une masse d'enduction qui renferme jusqu'à 10 parties en poids de la substance active.

5. Procédé selon l'une des revendications 1 à 4, caractérisé en ce que l'on ajoute des agents gonflants et charges inertes à la masse d'enduction, pour ajuster la viscosité.

6. Procédé selon l'une des revendications 1 à 5, caractérisé en ce que l'on dépose en continu la masse d'enduction sur la feuille support, à l'aide de cylindres à trame, qui prennent puis rétrocèdent une quantité exactement définie de la masse d'enduction.

7. Procédé selon l'une des revendications 1 à 5, caractérisé en ce que l'on dépose en continu la masse d'enduction sur la feuille support, à l'aide de paires de cylindres lisses, qui prennent la masse avec un syndrome décalé de la vitesse et la rétrocèdent en quantité définie.

8. Procédé selon l'une des revendications 1 à 7, caractérisé en ce que, pour fabriquer une préparation combinée, on dépose différentes substances actives sur la face supérieure et sur la face inférieure de la feuille support.

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EP-A- 0 135 022
EP-A- 0 184 389
DE-A- 3 432 573
FR-A- 2 148 045
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Description

This invention relates to a pharmaceutical composition which is applied to a periodontal pocket or paradentium for the purpose of treating periodontal diseases. The pharmaceutical composition may be provided in the form of gel, sheet, film or bar-like formulation to release a controlled and effective amount of an active ingredient at the periodontal pocket or paradentium.

The "periodontal diseases" is a general term of various inflammatory diseases of paradentium. The diseases include a series of diseases exhibiting various syndromes which vary from each other according to the stage or situation of the diseases or the age of the patient, and have not been definitely subclassified. Since, however, the term "periodontal diseases" is given to any inflammatory disease which initially occurs at a marginal gingiva area and finally reaches an alveolar bone, the diseases can be roughly divided, on the basis of the degree of the inflammation, into "gingivitis" in which the inflammation is limited to the gingiva tissue, and "paradentitis" in which the inflammation is chronic and found even in an alveolar bone. However, peculiar diseases such as "juvenile paradentitis" and "acute necrotizing ulcerative gingivitis" are also included in the periodontal diseases.

The paradentitis, which was once called "alveolar pyorrhea", is characterized by remarkable symptoms such as inflammation of gingiva, formation of periodontal pockets, bleeding and pus discharge from said periodontal pockets, and it brings about resorption of alveolar bone, loose teeth, and shedding of teeth.

The consensus of most investigators is that periodontal diseases are caused by bacteria present in dental plaques formed in periodontal pockets. Efforts have been concentrated on the discovery of pathogenic bacteria responsible for said diseases. At the present time, an attributable major pathogen is recognized to be certain nigral pigment-producing bacteria, such as genus Bacteroides. However, other genera of bacteria including Actinobacillus, Capnocytophaga, Fusobacterium and Spirochetes may be included in the causative pathogens. In any case, it is an established theory that the periodontal diseases should not be attributed to all bacteria present in the dental plaque.

The periodontal diseases have previously been treated in several ways, such as exhaustive scaling of plaques in periodontal pockets, root planing, gingivectomy to eliminate the periodontal pocket, or surgical curettage to excise inflammatory tissues. These treatments have been effective to some extent but not satisfactory.

On the other hand, pharmacotherapy has also been conducted using drugs, for example germicides, antiinflammatory agents, plaque solubilizing agents, and hemostyptics. These drugs are used in the form of formulations suited for internal use or massotherapy (e.g., dentifrices and ointments). However, they are not satisfactory for the purpose of treatment of periodontal diseases because the internal use hardly permits the selective migration of the drug to the lesional region, and the massotherapy is not successful in solubilizing the plaques which are present beneath the gingival margin.

Recently, strips which comprise polymers and active ingredients for treatment of periodontal diseases have been developed. These strips are said to be useful for the treatment of plaques and inflammation beneath the gingival margin. The strips can be applied directly to the lesional region to be treated, and therefore, the active ingredient can be concentrated to the desired site selectively. This modified therapeutic method has been proved to be more effective than any conventional pharmacotherapy. For instance, J. M. Goodson et al. disclose the implantation of "hollow fiber", which contains germicides, into the gingival region (J. Clinical Periodontology, 1979: 6: 83-92). M. Addy et al. have reported the insertion of strips, which were prepared from a mixture of an insoluble polymer such as polyethylmethacrylate and germicides, into periodontal pockets (J. Periodontal, 693, Nov. 1982). In addition, insertion of the strips, prepared from a mixture of a soluble polymer and a drug, into the lesional region, such as periodontal pockets, is also reported (Japan Patent Publication No. 59-222406).

The formulations mentioned above comprise a mixture of an active ingredient and a homogeneous polymer base. Accordingly, where such formulation is designed to contain two or more active ingredients which differ from each other in terms of pharmacological activity and therapeutically effective dose, it has been impossible to prepare a formulation in which each of the plural ingredients may release independently and provide its suitable concentration as desired.

The use of the hollow fiber or insoluble polymer, as a base, causes irritation or pain to patients, and moreover, it necessitates the removal of the base after release of an active ingredient, which is often annoying. On the other hand, the strip which comprises a soluble polymer as a base or carrier permits a rapid release of an active ingredient. Accordingly, it does not afford a constant therapeutic effect and, therefore, has a poor practical use.

As the result of an extensive study for seeking a novel therapeutical composition for periodontal diseases, which suitably controls the release of one or more active ingredients and which does not give any uncomfortable feelings to patients, it has been

found that the use of a two-phase carrier base, which consists of particles comprising a polymer having a limited solubility in water and a water soluble polymer used for dispersing such particles, meets the requirements just mentioned above.

DE-A-3 432 573 and US-A-4 693 887 disclose pharmaceutical composition having two polymeric phases, one hydrophobic and one hydrophilic, the combination being insoluble in water and thus suitable for water-insoluble implants. A drug partitions itself between the phases. The hydrophilic phase has a different composition from the discontinuous phase employed in the present

Thus the present invention provides:

a controlled-release pharmaceutical composition in the form of gel, sheet, film, or bar to be inserted or placed into a periodontal pocket for treating a periodontal disease, said composition comprising a therapeutically effective amount of at least one active ingredient effective for the treatment of the periodontal disease, said active ingredient being dispersed in a two-phase carrier consisting of

(a) a continuous phase consisting of a water-soluble polymer capable of dissolving in water at a concentration of more than 1% by weight irrespective of pH, and

(b) a discontinuous phase consisting of solid particles composed of a polymer capable of dissolving in water at a concentration of at least about 0.1% and not more than about 1.0% by weight; or solid particles composed of a polymer capable of dissolving in water at a concentration of more than 1% by weight only at a pH higher than 4 or lower than 6

said particles having an average size ranging from 1 μm to 500 μm and being dispersed in said water-soluble polymer, with the weight ratio of said particles to said water-soluble polymer ranging from 1:99 to 99:1 on a dry weight basis, said water-soluble polymer being selected from the

methyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, sodium alginate, propylene glycol alginate, pullulan, tragacanth, xanthan gum, chitosan, polyethylene oxide, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, and salts thereof, and said solid particles being selected from

poly(glycolic acid), poly(lactic acid), polytetramethylglycolide, polydiethylglycolide, poly-ε-caprolactone, poly(DL-decalactone), poly(alkyleneadipate), methylacrylate/ methacrylic acid copolymer, methylacrylate/ methacrylic acid/ octylacrylate copolymer, ethylacrylate/ methacrylic acid copolymer, methylacrylate/ methacrylic acid/ methylmethacrylate copolymer, methylmethacrylate/ methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate maleate, starch acetate phthalate, amylose acetate phthalate, methyl cellulose phthalate, hydroxypropylmethyl cellulose phthalate, hydroxyethyl ethylcellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylethyl cellulose, polyvinylalcohol phthalate, polyvinyl acetate phthalate, polyvinylacetal phthalate, polyvinylbutylate phthalate, methylmethacrylate/ dimethylaminoethyl methacrylate copolymer, and polyvinylacetal/ dimethylamino acetate.

Brief Description of the Drawing

Fig. 1 shows the dissolution profile of two active ingredients contained in the pharmaceutical composition of the invention which is in the form of a film. Fig. 2 shows the dissolution profile of two active ingredients contained in a conventional composition.

"Water soluble polymer" or "soluble polymer" denotes any polymer which dissolves in an aqueous medium, particularly in water, in a concentration of more than 1% by weight, irrespective of pH.

For the purpose of simplicity, the polymers usable for the discontinuous phase are hereinafter referred to as "non-soluble polymer" as a whole.

The soluble polymer used in the present invention must be fabricated into a semi-solid or a solid material. The non-soluble polymer should have a property suitable for being fabricated into particles. Both soluble and non-soluble polymers employed in the present application should be, of course, physiologically acceptable.

The pharmaceutical composition of the present invention may be prepared by dispersing one or more of active ingredients into a non-soluble polymer, or both of a soluble polymer and a non-soluble polymer, and mixing these polymers, and finally forming the resultant mixture into a solid material of a film, sheet or bar-like shape, or into a semi-solid material such as gel or ointment.

In more detail, one or more non-soluble polymers is dissolved, as the first step, in an appropriate organic solvent. To the resultant solution is dissolved or dispersed one or more active ingredients, and the mixture is formed into film or sheet by casting method. The resultant solid material is ground into particles.

The particles are also obtainable by spray drying, Wuster coating, Coacervation, or Drying in liquid phase. The average particle size may range from 1μm to 500μm depending on the contemplated release pattern of the active ingredient. However, the size range between 1μm and 300μm is generally preferred.

On the other hand, one or more water soluble

polymers are dissolved in a suitable solvent. The solvent may contain, if desired, one or more active ingredients. Subsequently, the pH of the mixture is adjusted, if necessary, and the particles obtained above are uniformly suspended in the mixture. The pharmaceutical composition of the invention in the form of gel is thus obtained.

The composition of the invention in the form of film or sheet is obtained by deaerating the just mentioned gel, and subjecting the same to the casting process. The film or sheet may also be prepared by compression molding, extrusion or calendering. The most suitable forming process among others is selected depending on the physico-chemical properties of the polymers employed.

The bar-like composition of the invention is prepared in the similar manner as the film or sheet, but through extrusion.

The weight ratio of the particles to the soluble polymer ranges from 1:99 to 99:1 on the basis of dry weight. The composition of the particles: soluble polymer in a ratio of 10:90-70:30 is preferred.

Therapeutically active ingredient or ingredients used for the preparation of the composition of the invention are selected from those effective for prevention or treatment of periodontal diseases, for example, germicides, such as chlorhexidine, Ag protein, glyceryl iodide, phenol, benzalkonium chloride, and cetylpyridinium chloride; antimicrobial agents, such as ampicillin, tetracycline, benzylpenicillin, clindamycin, cefalexin, erythromycin, chloramphenicol, and fragiomycin sulfate; anti-inflammatory agents, such as ibuprofen, indomethacin, ketoprofen, mefenamic acid, antipyrine, pranoprofen, ibufenac, tiaramide hydrochloride, prednisolon, dexamethasone, triamcinolone acetonide, and prostaglandine; plaque solubilizing agents, such as dextranase, protease, and amylase; collagenase inhibitors obtained from the extraction of crude drugs, such as gambir-catechu known by the name of "asenyaku"; local anesthetics, such as tetracaine hydrochloride and ethyl aminobenzoate; antihistaminic agents, such as chlorphenilamine maleate and diphenhydramine; and hemostatic agents such as tranexamic acids.

The solid composition of the invention in the form of film, sheet or bar can be prepared in different sizes. However, the convenient size of the film or sheet may be 0.1-0.5 mm in thickness, 0.5-3 mm in width, and 10-50 mm in length. The size of the bar may generally range from 0.5 to 1.5 mm in diameter and from 10 to 50 mm in length. Furthermore, the composition of the invention may be cut in suitable size by the user depending on several factors, such as severity of the disease, and the width and depth of the locus to be applied. The composition of the invention can be applied to the periodontal pocket or paradentium by insertion, injection, or rubbing according to the type of formulation.

The pharmaceutical composition of the invention exhibits a desirably controlled release pattern of the active ingredient(s). Such controlled release is attained by careful selection of a particular condition with respect to the following variables.

(1) Distribution ratio of an active ingredient between the particles and the soluble polymer.

(2) The particle size to be dispersed in the soluble polymer.

(3) Selection of non-soluble polymer or polymers which permits the modification of both the solubility of particles and diffusion velocity of an active ingredient in the particles in the manner as desired.

(4) The use of one or more kind(s) of particles which differ from each other in their solubilities.

(5) The ratio of the amounts of particles and soluble polymer to be combined.

(6) Selection of soluble polymer or polymers having desired viscosity.

By selection of suitable conditions in regard to the above variables, there is obtained the pharmaceutical composition of the invention which releases one or more of active ingredients in the manner as contemplated. Since the surface of the composition of the invention is mainly composed of water soluble polymer, it does not give any uncomfortable feeling to patients.

The following examples are presented by way of illustration of specific embodiments of the pharmaceutical composition of the invention. In examples, part or parts are represented by weight basis.

Example 1

Poly(lactic acid) (10 parts) and tetracycline hydrochloride (2 parts) are dissolved in methylene chloride (100 parts). Flow casting of the resultant mixture yields a sheet, which is ground into particles having an average size of 50μm.

The particles (10 parts) and hydroxypropyl cellulose (10 parts) are uniformly admixed. The mixture is blended with water, extruded with pressure, and dried. The bar-like shaped product of 1.0 mm diameter is thus obtained.

Example 2

Methacrylic acid / methyl methacrylate copolymer (1:2 molar ratio) (80 parts) is dissolved in ethanol (1000 parts). In the solution are suspended or dissolved indomethacin (5 parts) and triacetin (20 parts), and the mixture is cast into a sheet, which is then pulverized into particles having an average size of 80μm.

Hydroxypropyl cellulose (10 parts) is dissolved in water (1000 parts), and tetracycline (25 parts) is added to the resultant solution, after adjusting to pH 6.0 by addition of hydrochloric acid. The resultant mixture (80 parts) is uniformly admixed with the particles obtained above (20 parts) to yield the product in a gel form.

Example 3

The particles produced in Example 2 (20 parts), methyl cellulose (80 parts) and tetracycline hydrochloride (5 parts) are uniformly admixed, and the resulting mixture is pressed to a sheet having a 500μm thickness.

Experiment 1

The controlled release of an active ingredient was evaluated for a pharmaceutical composition of the invention which contains two kinds of active ingredients.

Method and materials

(1) Preparation of Sample

Methacrylic acid / methyl methacrylate copolymer (1:2 molar ratio) (80 parts) was dissolved in ethanol (1000 parts). Triacetin (20 parts) and tetracycline hydrochloride (6 parts) were then mixed with the resultant solution. The mixture was cast on a Teflon tray and dried at 40°C. The resultant sheet was pulverized into particles of 105μm to 177μm in size.

On the other hand, hydroxypropyl cellulose (viscosity of 2% aqueous solution is 1000 to 4000 cp at 20°C) (one part) was dissolved in water (99 parts). In the solution was dissolved tetracaine hydrochloride (0.03 part).

The hydroxypropyl cellulose solution and the particles are uniformly admixed at a weight ratio of 100:0.5, and the mixture is deaerated, cast on a Teflon tray with care to ensure the constant thickness, and air-dried to yield a film having 300μm thickness.

In a solution of hydroxypropyl cellulose (1 part) dissolved in water (100 parts) were dissolved tetracycline hydrochloride (0.02 part) and tetracaine hydrochloride (0.02 parts), and the mixture was adjusted to pH 6, deaerated, cast on a Teflon tray, air-dried to obtain a film having 300μm thickness, which was employed as a reference.

(2) Evaluation of Dissolution Rate

The dissolution rates of the active ingredients released from the films obtained above were measured using a phosphate buffer (500ml), pH 7.2, at 37°C, in accordance with the Rotating Basket Method (100 rpm) of Japanese Pharmacopoeia (X).

Results

The dissolution profiles of the film of the invention and that of the reference are respectively shown in Fig. 1 and Fig. 2 of the accompanying drawing. The abscissa indicates immersion time and the ordinate indicates the dissolution rate. Fig. 1 shows that two active ingredients were released from the film with different release patterns while Fig. 2 shows the same and identical release pattern of the two active ingredients. Thus, this experiment illustrates that the composition of the invention permits separate control of the release patterns of two active ingredients. It also teaches that the composition of the invention in the form of a sustained release formulation may be obtained where a single active ingredient is employed rather than two active ingredients as employed in this experiment.

Claims

1. A controlled-released pharmaceutical composition in the form of gel, sheet, film, or bar to be inserted or placed into a periodontal pocket for treating a periodontal disease, said composition comprising a therapeutically effective amount of at least one active ingredient effective for the treatment or the periodontal disease, said active ingredient being dispersed in a two-phase carrier consisting of
   (a) a continuous phase consisting of a water-soluble polymer capable of dissolving in water at a concentration of more than 1% by weight irrespective of pH, and
   (b) a discontinuous phase consisting of solid particles composed of a polymer capable of dissolving in water at a concentration of at least about 0.1% and not more than about 1.0% by weight; or solid particles composed of a polymer capable of dissolving in water at a concentration of more than 1% by weight only at a pH higher than 4 or lower than 6.

   said particles having an average size ranging from 1 μm to 500 μm and being dispersed in said water-soluble polymer, with the weight ratio of said particles to said water-soluble polymer ranging from 1:99 to 99:1 on a dry weight basis, said water-soluble polymer being selected from the
   methyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, sodium alginate, propylene glycol al-

ginate, pullulan, tragacanth, xanthan gum, chitosan, polyethylene oxide, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, and salts thereof, and said solid particles being selected from

poly(glycolic acid), poly(lactic acid), polytetramethylglycolide, polydiethylglycolide, poly-ε-caprolactone, poly(DL-decalactone), poly(alkyleneadipate), methylacrylate/ methacrylic acid copolymer, methylacrylate/ methacrylic acid/ octylacrylate copolymer, ethylacrylate/ methacrylic acid copolymer, methylacrylate/ methacrylic acid/ methylmethacrylate copolymer, methylmethacrylate/ methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate maleate, starch acetate phthalate, amylose acetate phthalate, methyl cellulose phthalate, hydroxypropylmethyl cellulose phthalate, hydroxyethyl ethylcellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylethyl cellulose, polyvinylalcohol phthalate, polyvinyl acetate phthalate, polyvinylacetal phthalate, polyvinylbutylate phthalate, methylmethacrylate/ dimethylaminoethyl methacrylate copolymer, and polyvinylacetal/ dimethylamino acetate.

2. The composition of claim 1 wherein two active ingredients are dispersed in said carrier.

3. The composition of claim 1 having at least two active ingredients whereof one is in the continuous phase and one is in the discontinuous phase, whereby they have different release profiles.

4. Use of the two-phase carrier according to Claim 1 as a carrier for preparing a controlled-release pharmaceutical composition in the form of gel, sheet, film or bar to be inserted or placed into a periodontal pocket for treating a periodontal disease, a therapeutically effective amount of at least one active ingredient effective for tile treatment of the periodontal disease being dispersed in said two-phase carrier.

5. Use according to claim 4 wherein two active ingredients are dispearsed in said carrier.

6. Use according to claim 5 wherein one active ingredient is dispersed in the continuous phase and the other active ingredient is dispersed in the discontinuouse phase.

7. A process for preparing the controlled-released pharmaceutical composition of Claim 1, 2 or 3 which comprises the following steps:

(1) preparing polymer particles using a polymer capable of dissolving in water at a concentration of at least about 0.1% and not more than about 1.0% by weight or a polymer capable of dissolving in water only at a pH higher than 4 or a pH lower than 6 at a concentration of more than 1% by weight, said polymer being specified in Claim 1.

(2) uniformly admixing the particles and a polymer capable of dissolving in water at a concentration of more than 1% by weight irrespective of pH, said polymer being specified in Claim 1.

(3) processing the mixture to form a pharmaceutical composition in the form of gel, sheet, film or bar, wherein at least one active ingredient effective for the treatment of the periodontal disease is added in Step (1) and/or Step (2).

8. The process of Claim 7, wherein one active ingredient is added in Step (1) and another ingredient is added in Step (2).

Revendications

1. Composition pharmaceutique à libération contrôlée sous la forme de gel, feuille, pellicule ou barre à insérer ou placer dans une poche parodontale pour le traitement d'une parodontopathie, ladite composition comprenant une quantité thérapeutique efficace d'au moins un ingrédient actif efficace pour le traitement de la parodontopathie, ledit ingrédient actif étant dispersé dans un support à deux phases constitué de

(a) une phase continue formée d'un polymère hydrosoluble capable de se dissoudre dans l'eau à une concentration de plus de 1 % en poids quel que soit le pH, et

(b) une phase discontinue formée de particules solides constituées d'un polymère capable de se dissoudre dans l'eau à une concentration d'au moins environ 0,1 % et d'au plus environ 1,0 % en poids ; ou de particules solides constituées d'un polymère capable de se dissoudre dans l'eau à une concentration de plus de 1 % en poids uniquement à un pH supérieur à 4 ou inférieur à 6,

lesdites particules ayant une taille moyenne comprise entre 1 µm et 500 µm et étant dispersées dans ledit polymère hydrosoluble, le rapport en poids desdites particules audit polymère hydrosoluble étant compris entre 1:99 et 99:1 en poids sec, ledit polymère hydrosoluble étant choisi parmi ceux qui suivent : méthylcellulose, hydroxypropylcellulose, car-

boxyméthylcellulose sodique, hydroxypropylméthylcellulose, hydroxyéthylcellulose, alginate de sodium, alginate de propylène-glycol, pullulane, gomme adragante, gomme de xanthane, chitosane, poly(oxyde d'éthylène), alcool polyvinylique, acide polyacrylique, acide polyméthacrylique et leurs sels, et lesdites particules solides étant choisies parmi ceux qui suivent : poly(acide glycolique), poly(acide lactique), polytétraméthylglycolide, polydiéthylglycolide, poly-ε-caprolactone, poly(DL-décalactone), poly(adipate d'alkylène), copolymère acrylate de méthyle/acide méthacrylique, copolymère acrylate de méthyle/acide méthacrylique/acrylate d'octyle, copolymère acrylate d'éthyle/acide méthacrylique, copolymère acrylate de méthyle/acide méthacrylique/méthacrylate de méthyle, copolymère méthacrylate de méthyle/acide méthacrylique, acétophtalate de cellulose, acétosuccinate de cellulose, acétomaléate de cellulose, acétophtalate d'amidon, acétophtalate d'amylose, phtalate de méthylcellulose, phtalate d'hydroxypropylméthylcellulose, phtalate d'hydroxyéthyléthylcellulose, acétosuccinate d'hydroxypropylméthylcellulose, carboxyméthyléthylcellulose, phtalate d'alcool polyvinylique, acétophtalate de polyvinyle, phtalate de polyvinylacétal, butyrophtalate de polyvinyle, copolymère méthacrylate de méthyle/méthacrylate de diméthylaminoéthyle et polyvinylacétal/diméthylaminoacétate.

2. Composition selon la revendication 1, dans laquelle deux ingrédients actifs sont dispersés dans ledit support.

3. Composition selon la revendication 1, contenant au moins deux ingrédients actifs dont l'un se trouve dans la phase continue et l'autre dans la phase discontinue, de sorte qu'ils aient des profils de libération différents.

4. Utilisation du support à deux phases selon la revendication 1 comme support pour préparer une composition pharmaceutique à libération contrôlée sous la forme de gel, feuille, pellicule ou barre à insérer ou placer dans une poche parodontale pour le traitement de parodontopathies, une quantité thérapeutique efficace d'au moins un ingrédient actif, efficace pour le traitement de la parodontopathie, étant dispersée dans ledit support à deux phases.

5. Utilisation selon la revendication 4, dans laquelle deux ingrédients actifs sont dispersés dans ledit support.

6. Utilisation selon la revendication 5, dans laquelle un ingrédient actif est dispersé dans la phase continue et l'autre ingrédient actif est dispersé dans la phase discontinue.

7. Procédé pour préparer la composition pharmaceutique à libération contrôlée de la revendication 1, 2 ou 3, qui comprend les étapes suivantes :
   (1) préparer des particules de polymère en utilisant un polymère capable de se dissoudre dans l'eau à une concentration d'au moins environ 0,1 % et d'au plus environ 1,0 % en poids ou un polymère capable de se dissoudre dans l'eau a une concentration de plus de 1 % en poids uniquement à un pH supérieur à 4 ou un pH inférieur à 6 ledit polymère étant spécifié dans la revendication 1 ;
   (2) mélanger uniformément les particules et un polymère capable de se dissoudre dans l'eau à une concentration de plus de 1 % en poids quel que soit le pH, ledit polymère étant spécifié dans la revendication 1 ;
   (3) transformer le mélange pour former une composition pharmaceutique sous la forme de gel, feuille, pellicule ou barre,
   dans lequel au moins un ingrédient actif, efficace pour le traitement de parodontopathies, est ajouté dans l'Etape (1) et/ou l'Etape (2).

8. Procédé selon la revendication 7, dans lequel un ingrédient actif est ajouté dans l'Etape (1) et un autre ingrédient est ajouté dans l'Etape (2).

Patentansprüche

1. Pharmazeutisches Präparat mit kontrollierter, verzögerter Freigabe in Form eines Gels, einer Folie bzw. Platte, eines Films oder eines Stabes, das in eine periodontale Tasche eingesetzt oder eingesetzt wird, für die Behandlung einer periodontalen Krankheit, dadurch **gekennzeichnet,** daß das Präparat eine therapeutisch wirksame Menge von mindestens einem aktiven Bestandteil, der für die Behandlung der periodontalen Krankheit wirksam ist, enthält, wobei der aktive Bestandteil in einem Zweiphasen-Träger dispergiert ist, der aus
   (a) einer kontinuierlichen Phase, die aus einem wasserlöslichen Polymeren, welches sich in Wasser in einer Konzentration von über 1 Gew.-%, unabhängig vom pH-Wert, lösen kann, besteht, und
   (b) einer diskontinuierlichen Phase, die aus festen Teilchen, die aus einem Polymeren,

das sich in Wasser in einer Konzentration von mindestens etwa 0,1 Gew.-% und nicht mehr als etwa 1,0 Gew.-% lösen kann, bestehen, oder aus festen Teilchen, die aus einem Polymeren, das sich in Wasser in einer Konzentration von über 1 Gew.-% nur bei einem pH-Wert über 4 oder niedriger als 6 lösen kann, besteht,

besteht, wobei die Teilchen eine durchschnittliche Teilchengröße im Bereich von 1 µm bis 500 µm aufweisen und in dem genannten wasserlöslichen Polymeren dispergiert sind, das Gewichtsverhältnis der Teilchen zu dem wasserlöslichen Polymeren im Bereich von 1:99 bis 99:1 auf Trockengewichtsbasis liegt, das wasserlösliche Polymere ausgewählt wird aus der Gruppe:

Methylcellulose, Hydroxypropylcellulose, Natriumcarboxymethylcellulose, Hydroxypropylmethylcellulose, Hydroxyethylcellulose, Natriumalginat, Propylenglykolalginat, Pullulan, Traganthgummi, Xanthangummi, Chitosan, Polyethylenoxid, Polyvinylalkohol, Polyacrylsäure, Polymethacrylsäure und ihren Salzen, und daß die festen Teilchen ausgewählt werden aus:

Poly(glykolsäure), Poly(milchsäure), Polytetramethylglykolid, Polydiethylglykolid, Poly-ε-caprolacton, Poly-(DL-decalacton), Poly-(alkylenadipat), Methylacrylat/Methacrylsäure-Copolymeren, Methylacrylat/Methacrylsäure/Octylacrylat-Copolymeren, Ethylacrylat/Methacrylsäure-Copolymeren, Methylacrylat/Methacrylsäure/Methylmethacrylat-Copolymeren, Methylmethacrylat/Methacrylsäure-Copolymeren, Celluloseacetatphthalat, Celluloseacetatsuccinat, Celluloseacetatmaleat, Stärkeacetatphthalat, Amyloseacetatphthalat, Methyloellulosephthalat, Hydroxypropylmethylcellulosephthalat, Hydroxyethylethylcellulosephthalat, Hydroxypropylmethylcelluloseacetatsuccinat, Carboxymethylethylcellulose, Polyvinylalkoholphthalat, Polyvinylacetatphthalat, Polyvinylacetalphthalat, Polyvinylbutylatphthalat, Methylmethacrylat/Dimethylaminoethylmethacrylat-Copolymeren und Polyvinylacetal/Dimethylaminoacetat.

2. Präparat nach Anspruch 1, dadurch **gekennzeichnet,** daß zwei aktive Bestandteile in dem Träger dispergiert sind.

3. Präparat nach Anspruch 1, dadurch **gekennzeichnet,** daß es mindestens zwei aktive Bestandteile enthält, wovon einer in der kontinuierlichen Phase und einer in der diskontinuierlichen Phase vorliegt, wobei sie unterschiedliche Freigabeprofile aufweisen.

4. Verwendung eines Zweiphasen-Trägers nach Anspruch 1 als Träger für die Herstellung eines pharmazeutischen Präparats mit kontrollierter Freigabe in Form eines Gels, einer Folie bzw. Platte, eines Films oder eines Stabes, das in eine periodontale Tasche eingesetzt oder eingelegt wird, für die Behandlung einer periodontalen Krankheit, wobei das pharmazeutische Präpart eine therapeutisch wirksame Menge von mindestens einem aktiven Bestandteil, der für die Behandlung der periodontalen Krankheit wirksam ist und in dem Zweiphasen-Träger dispergiert ist, enthält.

5. Verwendung nach Anspruch 4, dadurch **gekennzeichnet,** daß zwei aktive Bestandteile in dem Träger dispergiert sind.

6. Verwendung nach Anspruch 5, dadurch **gekennzeichnet,** daß ein aktiver Bestandteil in der kontinuierlichen Phase dispergiert ist und der andere aktive Bestandteil in der diskontinuierlichen Phase dispergiert ist.

7. Verfahren zur Herstellung des pharmazeutischen Präparats mit kontrollierter Freigabe nach Anspruch 1, 2 oder 3, dadurch **gekennzeichnet,** daß die folgenden Stufen durchgeführt werden:

(1) Herstellung von Polymerteilchen unter Verwendung eines Polymeren, welches sich in Wasser in einer Konzentration von mindestens etwa 0,1 und nicht mehr als etwa 1,0 Gew.-% lösen kann, oder eines Polymeren, welches sich in Wasser nur bei einem pH-Wert über 4 oder einem pH-Wert unter 6 in einer Konzentration von nicht mehr als 1 Gew.-% lösen kann, wobei das Polymere das in Anspruch 1 definierte Polymere ist,

(2) einheitliches Vermischen der Teilchen und des Polymeren, welches sich in Wasser bei einer Konzentration von über 1 Gew.-%, unabhängig vom pH-Wert, lösen kann, wobei das Polymere in Anspruch 1 definiert wurde,

(3) Verarbeitung des Gemisches zu einem pharmazeutischen Präparat in Form eines Gels, einer Folie bzw. Platte, eines Films oder eines Stabes, wobei mindestens ein aktiver Bestandteil, der für die Behandlung der periodontalen Krankheit wirksam ist, bei der Stufe (1) und/oder der Stufe (2) zugegeben wird.

8. Verfahren nach Anspruch 7, dadurch **gekennzeichnet,** daß ein aktiver Bestandteil bei der

Stufe (1) und ein weiterer Bestandteil bei der Stufe (2) zugegeben werden.

Fig. 1

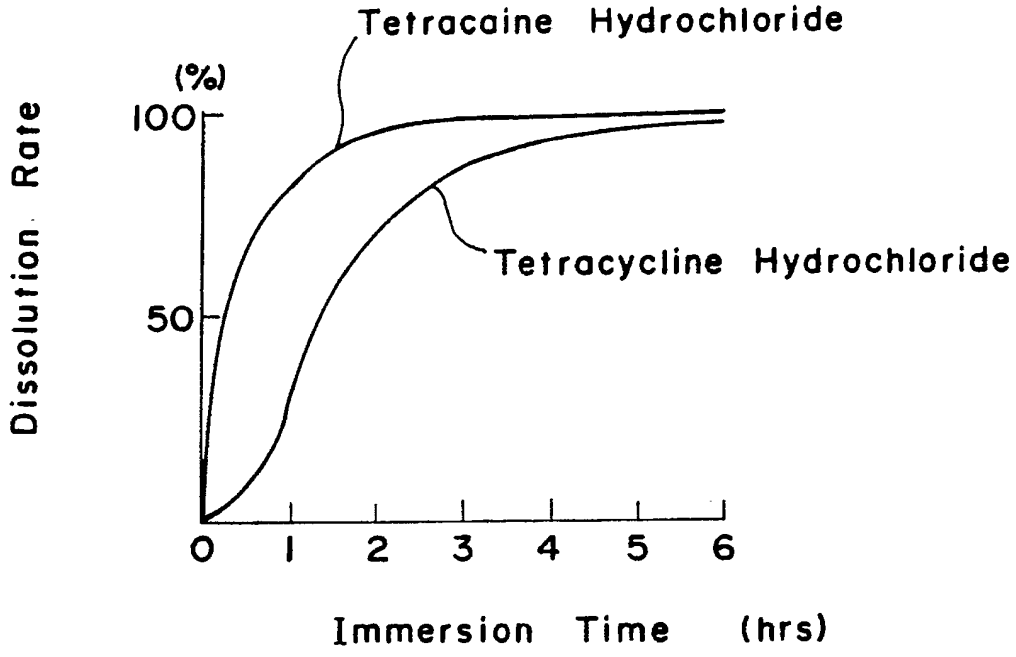
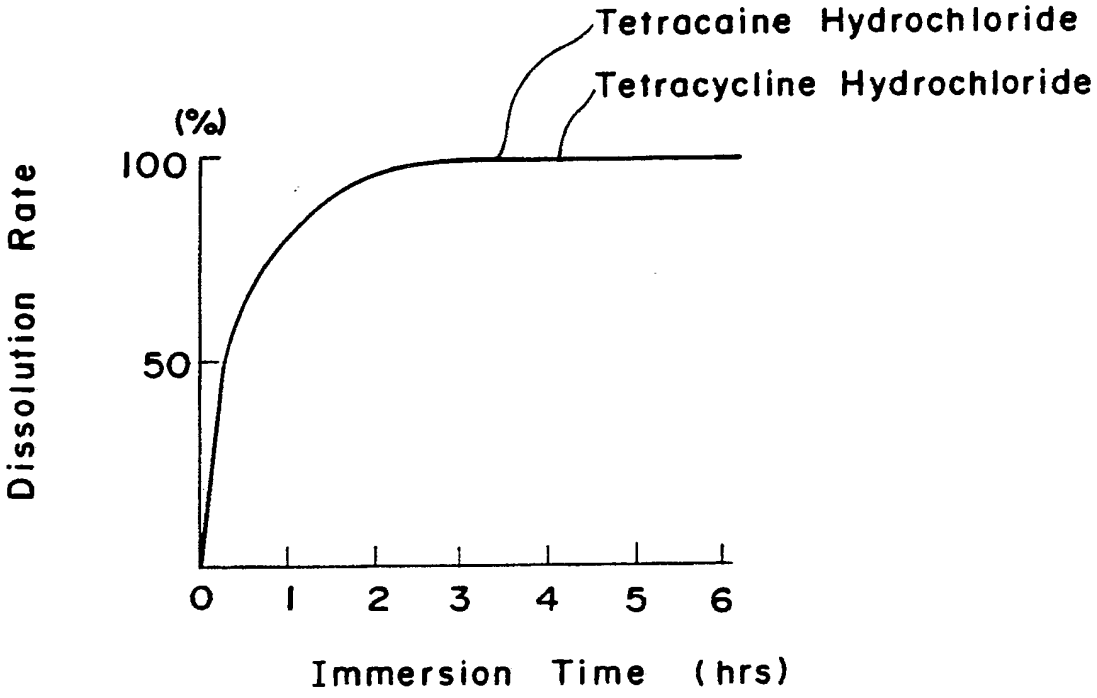


Fig. 2



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(54) **Bioadhesive extruded film for intra-oral drug delivery and process.**

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EP-A- 0 063 604
EP-A- 0 155 229
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PATENT ABSTRACTS OF JAPAN, vol. 7, no. 185 (C-181)[1330], 13th August 1983; & JP-A-58 90 507 (NIPPON SODA K.K.) 30-05-1983

CHEMICAL ABSTRACTS, vol. 102, no.24, June 1985, page 366, abstract no. 209484e, Columbus, Ohio, US; & JP-A-60 05 159 (LION CORP.) 11-01-1985

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Description

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a controlled-releasing medicament-containing preparation for intra-oral use. In particular it is more especially concerned with such a preparation (and the process of using it) in the form of a very thin extruded thermoplastic film (which can be in single layer or laminated multi-layer form) having at least one bioadhesive layer containing 22.4-68.3% by weight of a specified thermoplastic cellulose ether and 23.75-60% by weight of a specified homopolymer of ethylene oxide which can adhere to the mucosa of the oral cavity. The extruded film drug delivery system of the present invention, which has incorporated therein the medicament to be dispensed, is so thin and flexible when wet as to be unobtrusive to the patient after it has been properly positioned and placed in the mouth.

Description of the Prior Art

Several systems have previously been described which pertain to the delivery of drugs into the oral cavity. These include:

1. Treatment of periodontal disease with tetracycline. chlorhexidine or metronidazole loaded into hollow cellulose acetate fibers. These fibers are packed in the periodontal pockets and provide controlled release of the drug to the infected area.
2. Cast films containing ethyl cellulose/propylene glycol with chlorhexidine or metronidazole for treatment of periodontal disease.
3. An orthodontic appliance with a hydroxyethyl methacrylate/methyl methacrylate copolymer (HEMA/MMA) matrix. Sodium fluoride is incorporated into the HEMA/MMA matrix to provide sustained fluoride release and enhanced anticaries activity. HEMA/MMA with fluoride may also be attached to the tooth in the form of a wafer-like tablet.
4. Silicone/ethyl cellulose/polyethylene glycol films containing sodium fluoride are applied as coatings on orthodontic bands or in chewing gum. Controlled release of fluoride and anticaries activity is claimed.

The above systems are discussed in the "The Compendium of Continuing Education" Vol VI, No. 1, Jan.1985 p. 27-36 review article "Controlled Drug Delivery: A New Means of Treatment of Dental Disease", by J. Max Goodson, D.D.S., Ph.D. of the Forsyth Dental Center. Other systems, described in GB patent application 2,042,888 and U.S. Patents 4,292,299/4,226,848 (Teijin Ltd., Japan), use combinations of cellulosic and polyacrylate polymers. The preferred materials are hydroxypropyl cellulose ("Klucel") and a copolymer of acrylic acid ("Carbopol") that is administered in the form of thin tablets (discs), granules or powder. Other polymers that might be added are vinyl copolymers, polysaccharides, gelatin and collagen. U.S. patent 4,517,173 (Nippon Soda Co. Ltd, Japan) uses various celluloses in a multi-layered non-extruded cast film preparation.

Examples of prior art products currently on the market include ointments such as ORABASE* with Benzocaine (Squibb), Kenalog* (Triamcinolone Acetonide) in ORABASE* (Squibb) and Mycostatin* (Nystatin) ointment (Squibb).

The prior art products and delivery systems described above are useful but have the following disadvantages:

Tablets, appliances, hollow fibers are "bulky" in the mouth, are difficult to keep in place and inconvenient to apply.

Ethyl cellulose and/or silicone films do not adhere to mucosal tissue.

Ointments (i.e., ORABASE*) have an unpleasant feel and do not last very long.

Except for ORABASE*, all the foregoing systems require professional application to the tooth or periodontal pockets.

The bioadhesive film of the present invention alleviates many of the above problems. It may be applied easily by the consumer. It has very little or no mouthfeel, it has good adhesion to the mucosal tissues, and provides controlled release of the medicament.

Also EP-A-0 063 604 discloses a mucous membrane-adhering film preparation in which the one surface of water-soluble high polymer film containing pharmaceutical agents is treated to be made difficultly water-soluble. JP-A-5 890 507 discloses a film formed by an injection moulding machine or an extrusion moulding machine, the film comprising a mixture of a water-soluble polymer (water-soluble cellulose derivative), an active component (drug absorbable through the mucous membrane) arbitrary additives (diluent, taste or

scent improvers, colorants etc) and a plasticizer (polyethylene glycol).

Object of the Invention

It is an object of this invention to provide an extruded film that is an effective and convenient intra-oral drug delivery system and method for applying and delivering controlled dosages of therapeutic agents into the oral cavity. This technology may also be extended for controlled drug delivery in skin care, gynecological applications, wound care and like uses.

Summary of the Invention

The invention involves a pharmaceutically acceptable controlled-releasing medicament-containing extruded single or multi-layered thin film, capable of adhering to a wet mucous surface, comprising a water soluble or swellable polymer matrix bioadhesive layer which can adhere to a wet mucous surface and which bioadhesive layer consists essentially of 22.4-68.3% by weight of hydroxypropyl cellulose of molecular weight above 100,000 23.75-60% of a homopolymer of ethylene oxide of molecular weight above 100,000, 0-12.5%, of a water-insoluble polymer selected from ethyl cellulose, propyl cellulose, Carboxy methyl cellulose free acid, polyethylene and polypropylene, and 2.85-5% of a plasticizer, said film having incorporated therein a pharmaceutically effective amount of said medicament, the presence of medicament and optional components making the total 100%.

The present invention is directed to an extruded single or multi-layered laminated thin (1-10 mils or 0.025-0.25 mm) film, composed of selected water soluble and/or insoluble polymers. Various therapeutic agents are incorporated into the film during manufacture which are useful for treatment of oral disorders (i.e., denture discomfort, caries, periodontal disease, aphthous ulcers, etc.).

The extruded film of the present invention must have at least one bioadhesive layer, but may also have a reservoir layer and/or an outer protective barrier membrane layer. The therapeutic agent may be incorporated into any or all of the layers. When properly formulated and fabricated, these films will adhere to wet mucosal surfaces, provide a protective barrier for injured tissue and deliver controlled/sustained dosages of medication to the infected areas. The film may be designed for localized drug delivery (i.e., the periodontal pocket, an aphthous lesion), or may allow diffusion of the drug into the oral cavity.

An example of a non-localized system would be the delivery of sodium fluoride for caries prevention. A single or laminated film with good adhesion to the tooth or mucosal tissue may be employed in which the fluoride release rates may be controlled by varying film solubilities and/or concentration of fluoride in a multi-layered film.

An example of a localized application of medication would be in the treatment of aphthous lesions. A laminated two layer film with benzocaine incorporated into the adhesive layer would directly contact the injured mucosa. The outer layer would consist of non-soluble/non-adhesive polymers that provide durability, protection and directs the delivery of benzocaine toward the lesion.

The film forming polymers that are useful in this invention are selected from pharmaceutical grade materials, or those that are considered generally regarded as safe (GRAS) as food additives. They include, hydroxypropyl cellulose, and polyethylene oxide homopolymers. Small amounts of other polymers. e.g., polyvinyl ether-maleic acid copolymers and the like may be used in small amounts as well, replacing a small portion of the other polymers. The above materials are either water soluble or swellable and are most useful in the bioadhesive layer of the film. Various non-soluble polymers may also be incorporated for modification of the film's permeability properties, such as ethyl cellulose, propyl cellulose, polyethylene, polypropylene and carboxymethylcellulose (free acid) in an amount of up to 12.5% by weight. By varying the ratios of the above polymers both the solubility and the adhesive properties of each layer of film may be controlled. Therefore, depending on the desired delivery rate, the type of disorder to be treated, the area to be treated and the medication being administered it is possible to custom design the film by selecting and blending various polymers. The final film product may also be fabricated into flexible tapes of varied thickness and width, "spots" of different sizes and shapes or other pre-shaped forms.

The medicaments and pharmaceutical agents set forth in the prior art discussed above may generally be delivered by the drug delivery system of the present invention. Usable medicaments are those which are capable of withstanding the heats and pressures generated in the extrusion process involved in making the film of the present invention. Preferred medicaments include:

Anesthetics/Analgesics - benzocaine, dyclonine HCl, phenol, aspirin, phenacetin, acetaminophen, potassium nitrate, etc.

Anticaries Agents - sodium fluoride, sodium monofluorophosphate, stannous fluoride, etc.

Anti-inflammatories - hydrocortisone acetate, triamcinolone acetonide, dipotassium, glycyrrhizinate, etc.
Antihistamines - chlorpheniramine maleate, ephedrine HCL, diphenhydramine HCL, etc.
Antibiotics - i.e., tetracycline, doxycycline hyclate, meclocycline, minocycline, etc.
Antibacterials - chlorhexidine, cetyl pyridinium chloride, benzethonium chloride, dequalinium chloride, silver sulfadiazene, phenol, thymol, hexedine, hexetidine, alexidine, etc.
Fungistats - nystatin, miconazole, ketoconazole, etc.

The above are illustrative examples of therapeutic agents that are used to treat oral disorders. The present invention is not to be limited to these specific materials especially where it is intended to deliver drug outside of the oral cavity e.g. to skin where other drugs may be desirable.

The film of the present invention has the advantage of being an extruded film, rather than a cast film. When a multi-layered film is involved, the different layers can be coextruded and then laminated together, or else each layer can be separately extruded one on the other, and then laminated together, so that the final multi-layered film is still very thin. The films of the present invention can be made in thicknesses of only 1-10 mils or 0.025-0.25 mm. The films are so thin that when placed in the mouth after they become wet they soon become unobtrusive, and hardly noticeable by most patients.

The film must always have a bioadhesive layer, which enables it to adhere to wet mucosal surfaces. The bioadhesive layer has 22.4-68.3 wt % of hydroxpropyl cellulose, 23.75-60 wt % of a homopolymer of ethylene oxide and 2.85-5 wt % of a glycol plasticizer (all percents are % by weight).

The Hydroxypropyl cellulose (HPC), useful for purposes of the present invention is commercially available from Hercules, Inc. (Wilmington, DE) under the tradename KLUCEL*. Preferred grades include Klucel MF, with a molecular weight around 600,000 and having a viscosity of 4,000-6,000 cps (Brookfield) in 2 percent water solutions, or Klucel HP, having a molecular weight around 1,000,000 and viscosity of 1500-2500 cps in 1 percent water solution. Any HPC having a Molecular Weight above about 100,000 is useful for purposes of this invention.

The homopolymer of ethylene oxide useful for purposes of the present invention has a relatively high molecular weight, i.e., above 100,000 and preferably above 3,000,000. Such polymers are commercially available from various sources. The Union Carbide Corporation material, "Polyox WSR-301", which has a molecular weight of approximately 4,000,000 - 5,000,000 is most preferred for purposes of the present invention.

The "plasticizer" useful for purposes of the present invention are selected from glycols such as propylene glycol and polyethylene glycol; polyhydric alcohols such as glycerin and sorbitol; glycerol esters such as glycerol triacetate; fatty acid triglycerides such as NEOBEE* M-5 and MYVEROLS*; mineral oil; vegetable oils such as castor oil, etc.

For the uses for the present invention contemplated here, the plasticizer should be non-toxic. The purpose of the plasticizer is to improve polymer melt processing by reducing the polymer melt viscosity and to impart flexibility to the final product.

The preferred plasticizer for use in the present invention is either propylene glycol or polyethylene glycol (such as is available from Union Carbide Corporation as their series of Carbowaxes which runs from 200 to 600 molecular weight, of which we prefer to use Carbowax 400, which has a molecular weight of 400, average.

In addition to the polymers and plasticizer which are required ingredients of the films of the present invention, minor amounts of other non-essential but customary ingredients will often be used if desired, e.g., antioxidants, preservatives, flavors, colorants.

Detailed Description

The following examples will serve to illustrate the present invention in greater detail. The units shown in the examples are parts by weight. The thickness of the layers is expressed in either mils (.001 inches) or millimeters. For easy conversion, 4 mils is approximately equal to 0.1 mm.

EXAMPLE 1 - TRIPLE LAYERED LAMINATE CONTAINING SODIUM FLUORIDE FOR ANTICARIES PROTECTION:

This three layered film laminate is comprised of a "bioadhesive" layer, a sodium fluoride "reservoir" layer and, an "outer protective barrier membrane" layer, in which the composition and thickness of each layer are as shown below:

Ingredients	Bioadhesive Layer (4 mils) (0.1 mm)	% w/w Reservoir Layer (1 mil) (0.025 mm)	Outer Protective Barrier Membrane Layer (1 mil) (0.025 mm)
Polyethylene oxide homopolymer (Union Carbide-Polyox* WSR-301)	60.0	-	-
Hydroxypropyl Cellulose (Hercules, Inc.-Klucel* MF)	30.0	20.0	24.0
Polyethylene (Allied Chemical-6A) (Low Density)	5.0	-	-
Propylene Glycol, U.S.P.	3.0	-	-
Polyethylene Glycol 400 (Union Carbide)	2.0	-	-
Ethyl Cellulose (Hercules, Inc.-N100F)	-	59.0	69.6
Caprylic/Capric Triglyceride (PVO Incorporated-Neobee M-5)	-	5.0	6.0
Sodium Fluoride, U.S.P.	-	16.0	0.4
	100.0	100.0	100.0

The process used to make the above laminate was :

a) Powder Blending - Each layer is made separately and all ingredients used therein except propylene glycol and Neobee M-5 (liquid plasticizers) are placed in a Patterson Kelley (PK) V-blender equipped with liquid addition capabilities. The ingredients which are all powders are blended for approximately 10-15 minutes while the liquid plasticizer is slowly added to the mix. Three separate powder blends are made, one for each layer.

b) Extrusion Process - A standard Johnson 2-1/2 inch (0,0635 m) vinyl/polyolefin extruder equipped with a single three stage screw was used to extrude the "powder blend". The temperature conditions for the water soluble powders are however quite different from those used for vinyls and polyolefins. The

temperature (°C) profile for the "reservoir" and "membrane layers" of the triple laminate was as follows:

Barrel Zone 1	100
Barrel Zone 2	125
Barrel Zone 3	135
Barrel Zone 4	145
Barrel Zone 5	160
Barrel Zone 6	170
Adapter -	180
Die Zone 1	180
Die Zone 2	180
Die Zone 3	180

The films which had a width of 18 inches (0,45 m), were extruded at approximately 20 feet/minute (6 m/min) through a flat lipped die. The temperature profile for the "bioadhesive layer" was:

Barrel Zone 1	125
Barrel Zone 2	140
Barrel Zone 3	165
Barrel Zone 4	170
Barrel Zone 5	185
Barrel Zone 6	185
Adapter -	185
Die Zone 1	185
Die Zone 2	185
Die Zone 3	185

Each layer is extruded separately with the first layer extruded as a "free film". Successive layers are extruded onto each other and laminated by passing them through heated stainless steel rollers.

Test Results:

In vitro fluoride ion release studies were conducted on samples of the above described triple laminate film measuring 0.5 cm x 1.25cm (0.625 cm^2) according to the following procedures:
The test sample is adhered to a glass slide by prewetting the film and placing the bioadhesive layer on the glass surface. The slide is then immersed in a beaker containing 100 ml of distilled water with continuous stirring. Five milliliter aliquots are withdrawn from the solution, at prescribed time intervals, and analyzed for fluoride content with an Orion Ionanlyzer equipped with a fluoride specific electrode. Release rates are then calculated from the data.

The results obtained indicated fluoride release rates in the order of 0.05-0.2 mgs/cm^2/hr for 24 hours. This falls within the desirable range for maintaining constant low levels of fluoride in the mouth and enhanced anticaries activity. Release rates may be tailored to desired use levels by modification of the film composition and construction.

EXAMPLE 2 - SINGLE LAYER ADHESIVE FILM CONTAINING HYDROCORTISON ACETATE (0.5%) AS AN ANTI-INFLAMMATORY AGENT:

The composition of the film, which was 0.1 mm. thick, was as follows:

Ingredients	% w/w
Ethylene Oxide Homopolymer (Polyox* WSR-301)	59.4
Hydroxypropyl Cellulose (Klucel* MF)	30.0
Polyethylene (AC-6A)	5.0
Propylene Glycol	3.0
Polyethylene Glycol 400	2.0
Butylated Hydroxy Toluene (BHT) FCC (preservative)	0.1
Hydrocortisone Acetate	0.5
	100.0

The powder blending process and extruder conditions used were the same as those described in Example I for the "bioadhesive layer" of the sodium fluoride trilaminate. In vitro tests were performed on the above film and demonstrated a prolonged drug release pattern.

EXAMPLE 3 - SINGLE LAYER ADHESIVE FILM CONTAINING TRIAMCINOLONE ACETONIDE (0.1%) AS AN ANTI-INFLAMMATORY:

The composition of the film, which was 0.1 mm. thick, was as follows:

Ingredients	% w/w
Ethylene Oxide Homopolymer (Polyox WSR-301)	59.9
Hydroxypropyl Cellulose (Klucel MF)	29.9
Polyethylene (AC-6A)	5.0
Propylene Glycol	3.0
Polyethylene Glycol 400	2.0
BHT	0.1
Triamcinolone Acetonide	0.1
	100.0

The powder blending process and extruder conditions used to make the film of this Example 3 were the same as those of the "bioadhesive layer" of Example I.

Other desired active medicament ingredients may be incorporated into the adhesive films of any of Examples 1-3 in place of the particular medicament used in said examples. These include Benzocaine (analgesic), Potassium nitrate (analgesic), Silver sulfadiazene (antimicrobial).

Chlorhexidine (antimicrobial), miconazole nitrate (antifungal), Benzethonium chloride (antimicrobial), Tetracycline (antibiotic) and other similar therapeutic compounds.

EXAMPLE 4 - ANALGESIC FILMS WITH POTASSIUM NITRATE

This example shows 5 variations of the film having different solubilities, resulting in different release rates.

Ingredients	% w/w 1	2	3	4	5
Polyethylene oxide homopolymer (Polyox* WSR-301)	23.75	57.00	55.00	55.00	57.00
Hydroxypropyl Cellulose, N.F. (Klucel* HF)	68.30	-	-	-	-
Hydroxypropyl Cellulose, N.F. (Klucel* MF)	-	28.40	29.90	22.40	22.40
Ethyl Cellulose	-	4.75	5.00	12.50	12.50
Polyethylene Glycol 400	1.90	1.90	2.00	2.00	2.00
Polyethylene Glycol 8000	0.95	-	-	-	-
Propylene Glycol, U.S.P.	-	2.85	3.00	3.00	3.00
BHT, F.C.C.	0.10	0.10	0.10	0.10	0.10
Potassium Nitrate, F.C.C.	5.00	5.00	5.00	5.00	3.00

The above ingredients are blended in a Patterson-Kelly powder blender equipped with liquid addition capabilities. The resulting powder blend is then extruded into film on a Killion or Johnson vinyl extruder using processing procedures similar to those of the bioadhesive layer of Example I.

EXAMPLE 5 - ANESTHETIC FILMS WITH BENZOCAINE (LAMINATE)

This is an example of a two-layer laminate. The processing conditions used were similar to those of the bioadhesive layer and outer protective barrier membrane layer of Example I.

A. Inner medicated bioadhesive layer	
Polyoxyethylene Homopolymer (Polyox* WSR-301)	57.00
Hydroxypropyl Cellulose, N.F. (Klucel* MF)	28.40
Polyethylene (AC-6A)	4.75
Propylene Glycol, U.S.P.	2.85
Polyethylene Glycol 400	1.90
BHT, F.C.C.	0.10
Benzocaine, U.S.P.	5.00
	100.00

B. Outer protective/barrier layer	
Hydroxypropyl Cellulose (Klucel* MF)	78.00
Ethyl Cellulose	20.00
Polyethylene Glycol 400	2.00
	100.00

Part A was extruded on a Johnson extruder followed by subsequent extrusion and lamination of Part B to A.

Samples were applied to oral lesions, and provided profound anesthetic effects (lasting several hours) within minutes of application.

The identical two-layer laminate may also be made by coextruding the inner medicated bioadhesive layer (Part A) and the outer protective barrier layer (Part B) through separate die slots within a coextruder and laminating the two layers together.

EXAMPLE 6 - ANESTHETIC FILMS WITH PHENOL AND DYCLONINE HCl

Four variations of a single layer bioadhesive film were made as shown below:

Ingredients	1	2	3	4
Polyethylene oxide homopolymer (Polyox* WSR-301)	59.10	54.00	59.70	58.20
Hydroxypropyl Cellulose (Klucel HF)	29.45	26.91	29.75	29.00
Ethyl Cellulose	4.93	4.50	4.98	4.85
Propylene Glycol, U.S.P.	2.96	2.70	2.99	2.91
Polyethylene Glycol 400	1.97	1.80	1.99	1.94
BHT, F.C.C.	0.09	0.09	0.09	0.10
Phenol, U.S.P.	1.50	-	-	-
Dyclonine HCl	-	10.00	0.50	3.00

Following the procedures for the bioadhesive layer of Example I, the powders were blended in P-K blender equipped with liquid addition capabilities. Resulting powders were extruded on a Killion laboratory-sized extruder.

EXAMPLE 7 - SILVER SULFADIAZENE FILMS - ANTIMICROBIAL

Three different single-layered bioadhesive films containing 1.0% 0.5% and 0.5% respectively of silver sulfadiazene (SSD) were prepared on a heated Carver laboratory press (designed to simulate extruded conditions) as shown below.

Ingredients	% w/w A	% w/w B
Polyethylene oxide homopolymer (Polyox* WSR-301)	60.00	60.00
Hydroxypropyl Cellulose (Klucel* HF)	28.9	29.4
Polyethylene (AC-6A)	5.0	5.0
Propylene Glycol, U.S.P.	3.0	3.0
Polyethylene Glycol 400	2.0	2.0
BHT, F.C.C.	0.1	0.1
Silver Sulfadiazine	1.0	0.5
	100.0	100.0

Effects on wound repair and activity against Staphylococcus aureus were evaluated in the guinea pig model. Full-thickness excisions were inoculated with 3.8 x 10^5 organisms, (Staph. aureus) and wound surface microbiology samples taken 10 minutes and 24 hours after treatment. Test films were placed on the wound and covered with BIOCLUSIVE* Transparent Dressings secured with elastic tape. Wound contraction was measured over an eight-day period using OPTOMAX* Computer-Assisted Image Analysis. The three films tested were the following:

A. 1.0% Silver Sulfadiazene, 125 ° C/2 minutes/4 tons
B. 0.5% Silver Sulfadiazene, 125 ° C/2 minutes/4 tons
C. 0.5% Silver Sulfadiazene, 150 ° C/3 minutes/4 tons

SILVADENE Cream and un untreated occluded control. The results indicated that:

1. SILVADENE* treated wounds significantly inhibited full-thickness wound contraction.
2. Film A, B and C inhibited wound contraction relative to that of BIOCLUSIVE* dressed wounds.
3. The three SSD films each permitted substantially faster wound contraction than that of wounds treated daily with SILVADENE* cream.
4. All films were very active against S. aureus 24 hours after inoculation.

The films may be scaled up by using an extruder. This example demonstrates the feasibility of such a film to perform its intended purpose. Use of a press for larger samples would result in a non-uniform and lower-quality film than an extruded film.

Based on the above findings, the films were very effective antibacterial agents, while mildly inhibiting wound contraction. They offer clinicians a convenient and more effective delivery system for antimicrobials which can be place in wounds beneath any dressing or can be laminated to any acceptable dressing face.

Claims

1. A pharmaceutically acceptable controlled-releasing medicament-containing extruded single or multilayered thin film, capable of adhering to a wet mucous surface, comprising a water soluble or swellable polymer matrix bioadhesive layer which can adhere to a wet mucous surface and which bioadhesive layer consists essentially of 22.4-68.3% by weight of a hydroxypropyl cellulose having a molecular weight above 100,000, 23.75-60% by weight of a homopolymer of ethylene oxide having a molecular weight above 100,000, 0-12.5% by weight of a water-insoluble polymer selected from ethyl cellulose, propyl cellulose, carboxymethyl cellulose free acid, polyethylene and polypropylene, and 2.85-5% of a plasticizer, said film having incorporated therein a pharmaceutically effective amount of said medicament, the presence of medicament and optional components making the total 100%.

2. The extruded film of claim 1, made in a form which is so thin and flexible when wet as to be unobtrusive to the patient when properly positioned and placed in the patient's mouth.

3. The extruded film of claim 2 having a thickness no greater than 0.25 millimeters.

4. The extruded film of claim 3 wherein, in the bioadhesive layer the homopolymer of ethylene oxide has a molecular weight from 3,000,000 to 5,000,000.

5. The extruded film of Claim 3, in multi-layer laminated form, which in addition to the bioadhesive layer also contains a reservoir layer in which at least a major portion of the medicament is contained.

6. The extruded multi-layer film of Claim 5 in which the reservoir layer consists essentially of a polymer matrix comprised of both a water soluble or swellable polymer and a non-water soluble polymer selected from ethyl cellulose, propyl cellulose, polyethylene and polypropylene, and also hydroxypropyl cellulose.

7. The extruded film of Claim 4 in multi-layer laminated form, which in addition to the bioadhesive layer also contains an outer protective-barrier membrane layer.

8. The extruded multi-layer film of Claim 7 in which the outer protective-barrier membrane layer is thinner than the bioadhesive layer, and said outer protective barrier layer consists essentially of a polymer matrix of a major proportion of a non-water-soluble polymer selected from ethyl cellulose, propyl cellulose, polyethylene and polypropylene, and a minor proportion of hydroxypropyl cellulose.

9. The extruded multi-layer film of Claim 1 in the form of a triple layered laminate containing sodium fluoride for anticaries protection having the following composition:

Ingredients	% w/w Bioadhesive Layer (0.1 mm)	Reservoir Layer (0.025 mm)	Outer Protective Barrier Membrane Layer (0.025 mm)
Polyethylene oxide homopolymer (MW 3,000,000 minimum)	60.0	-	-
Hydroxypropyl Cellulose (MW 1,000,000)	30.0	20.0	24.0
Polyethylene (Low Density)	5.0	-	-
Propylene Glycol, U.S.P.	3.0	-	-
Polyethylene Glycol (MW 400)	2.0	-	-
Ethyl Cellulose	-	59.0	69.6
Caprylic/Capric Triglyceride	-	5.0	6.0
Sodium Fluoride	-	16.0	0.4
	100.0	100.0	100.0

Patentansprüche

1. Ein pharmazeutisch verträglicher, dünner extrudierter Film, der ein Medikament enthält und kontrolliert freisetzt, mit einer einzigen oder mit mehreren Schichten, der die Fähigkeit aufweist, daß er auf der nassen Schleimhautoberfläche festkleben kann, umfassend eine wasserlösliche oder quellbare Polymermatrix einer bioadhäsiven Schicht, die auf der nassen Oberfläche der Schleimhaut kleben kann, wobei die bioadhäsive Schicht im wesentlichen aus 22,4 - 68,3 Gew.-% Hydroxypropyl-Cellulose mit einem Molekulargewicht von oberhalb 100 000, 23,75 - 60 Gew.-% eines Homopolymers von Ethylenoxid mit einem Molekulargewicht von oberhalb 100 000, 0 - 12,5 Gew.-% eines wasserunlöslichen Polymers, ausgewählt aus Ethyl-Cellulose, Propyl-Cellulose, Carboxymethyl-Cellulose in Form der freien Säure, Polyethylen und Polypropylen und 2,85 - 5 % eines Weichmachers besteht, wobei der Film eine pharmazeutisch wirksame Menge des Medikamentes inkorporiert enthält und das Medikament und die wahlweise enthaltenen Komponenten insgesamt 100 % ergeben.

2. Extrudierter Film nach Anspruch 1, der in einer Form hergestellt ist, die so dünn und flexibel ist, daß er, wenn er naß ist, den Patienten nicht stört, wenn er im Mund des Patienten an die richtige Stelle gelegt und eingebracht worden ist.

3. Extrudierter Film nach Anspruch 2 mit einer Dicke, die nicht größer als 0,25 mm ist.

4. Extrudierter Film nach Anspruch 3, bei dem die bioadhäsive Schicht des Homopolymers von Ethylenoxid ein Molekulargewicht von 3 000 000 bis 5 000 000 aufweist.

5. Extrudierter Film nach Anspruch 3 in einer mehrschichtigen laminierten Form, die zusätzlich zur bioadhäsiven Schicht noch eine Reservoir-Schicht enthält, in der zumindest ein Hauptanteil des Medikamentes enthalten ist.

6. Extrudierter mehrschichtiger Film nach Anspruch 5, in dem die Reservoir-Schicht im wesentlichen aus einer polymeren Matrix besteht, die sowohl aus einem wasserlöslichen und quellbaren Polymer und einem nichtwasserlöslichen Polymer besteht, das ausgewählt ist aus Ethyl-Cellulose, Propyl-Cellulose, Polyethylen und Polypropylen und auch Hydroxypropyl-Cellulose.

7. Extrudierter Film nach Anspruch 4 in Form eines mehrschichtigen Laminates, das zusätzlich zur bioadhäsiven Schicht auch eine äußere Schicht aus einer protektiven Membranbarriere enthält.

8. Extrudierter mehrschichtiger Film nach Anspruch 7, bei dem die äußere Schicht mit einer protektiven Membranbarriere dünner ist als die bioadhäsive Schicht und in dem die protektive Barriereschicht im wesentlichen aus einer Polymermatrix aus einem Hauptanteil eines nichtwasserlöslichen Polymers, das ausgewählt ist aus Ethyl-Cellulose, Propyl-Cellulose, Polyethylen und Polypropylen und einem geringeren Anteil von Hydroxypropyl-Cellulose, besteht.

9. Extrudierter mehrschichtiger Film nach Anspruch 1 in Form eines dreischichtigen Laminats, das Natriumfluorid zum Antikariesschutz enthält und das die folgende Zusammensetzung aufweist:

Bestandteile	bioadhäsive Schicht (0,1 mm)	% Gew./Gew. Reservoirschicht (0,025 mm)	äußere protektive Schicht der Membranbarriere (0,025 mm)
Homopolymer des Polyethylenoxids (MG mindestens 3 000 000)	60,0	-	-
Hydroxypropyl-Cellulose (MG 1 000 000)	30,0	20,0	24,0
Polyethylen (geringe Dichte)	5,0	-	-
Propylen-Glycol, U.S.P.	3,0	-	-
Polyethylen-Glycol (MG 400)	2,0	-	-
Ethyl-Cellulose	-	59,0	69,6
Capryl/Caprinsäure-Triglycerid	-	5,0	6,0
Natriumfluorid	-	16,0	0,4
	100,0	100,0	100,0

Revendications

1. Film mince extrudé mono- ou multicouche pharmaceutiquement acceptable contenant un médicament à libération contrôlée pouvant adhérer sur une surface de muqueuse humide, comprenant une couche bioadhésive de matrice de polymère gonflable ou soluble dans l'eau qui peut adhérer sur une surface de muqueuse humide et cette couche bioadhésive est constituée essentiellement de 22,4-68,3 % d'hydroxypropylcellulose ayant un poids moléculaire supérieur à 100 000, de 23,75-60% en poids d'un homopolymère d'oxyde d'éthylène ayant un poids moléculaire supérieur à 100 000, 0-12,5 % en poids d'un polymère insoluble dans l'eau choisi parmi l'éthylcellulose, la propylcellulose, la carboxyméthylcellulose exempte d'acide, le polyéthylène et le polypropylène, et 2,85-5 % d'un plastifiant, ledit film

contient une quantité pharmaceutiquement efficace du médicament qui y est incorporée, la présence du médicament et de composants éventuels faisant le complément du total de 100 %.

2. Film extrudé de la revendication 1, d'une forme suffisamment fine et souple quand il est humide de façon à ne pas gêner le patient quand il est placé et positionné correctement dans la bouche du patient.

3. Film extrudé de la revendication 2 ayant une épaisseur non supérieure à 0,25 millimètre.

4. Film extrudé de la revendication 3 dans lequel, dans la couche bioadhésive l'homopolymère d'oxyde d'éthylène a un poids moléculaire de 3 000 000 à 5 000 000.

5. Film extrudé de la revendication 3 sous forme feuilletée multicouche, qui contient aussi en plus de la couche bioadhésive une couche réservoir dans laquelle se trouve au moins une portion majeure du médicament.

6. Film multicouche extrudé de la revendication 5 dans lequel la couche réservoir est constituée essentiellement d'une matrice polymère contenant à la fois un polymère gonflable ou soluble dans l'eau et un polymère non soluble dans l'eau choisi parmi l'ethylcellulose, la propylcellulose, le polyéthylène et le polypropylène, et aussi de l'hydroxypropylcellulose.

7. Film extrudé de la revendication 4 sous forme feuilletée multicouche, qui contient en plus de la couche bioadhésive une couche membrane barrière de protection externe.

8. Film extrudé multicouche de la revendication 7 dans lequel la membrane barrière protectrice externe est plus mince que la couche bioadhésive, et ladite couche barrière protectrice externe est constituée essentiellement d'une matrice polymère composée en proportion majoritaire d'un polymère non soluble dans l'eau choisi dans le groupe de l'éthylcellulose, de la propylcellulose, du polyéthylène et du polypropylène, et d'une proportion mineure d'hydroxypropylcellulose.

9. Film multicouche extrudé de la revendication 1 sous forme d'un lamifié à triple couche contenant du fluorure de sodium pour la protection anticaries qui a la composition suivante :

Ingrédients	couche Bioadhésive 0,1 mm	% pds/pds Couche Réservoir (0,025 mm)	couche Membrane Barrière Protectrice Externe (0,025 mm)
Oxyde de Polyéthylène homopolymère (PM 3 000 000 minimum)	60,0	-	-
Hydroxypropylcellulose (PM 1 000 000)	30,0	20,0	24,0
Polyéthylène (basse densité)	5,0	-	-
Propylèneglycol, U.S.P.	3,0	-	-
Polyéthylèneglycol (PM 400)	2,0	-	-
Ethylcellulose	-	59,0	69,6
Triglycéride caprylique/caprique	-	5,0	6,0
Fluorure de sodium	-	16,0	0,4
	100,0	100,0	100,0

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(54) **Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder dergleichen sowie Verfahren zu deren Herstellung.**

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Beschreibung

Arzneimittel können in Form von Pulvern, Tropflösungen oder Säften oral verabreicht werden. Da bei diesen Abgabeformen eine genaue Dosierung jedoch schwierig ist, werden vom Hersteller dosierte Applikationsformen wie Tabletten, Dragees oder Kapseln generell bevorzugt. Auch Reagentien und andere Wirkstoffe, z.B. Süßstoffe, werden für eine genaue dosierte Anwendung häufig tablettiert. Die Herstellungstechnik für Tabletten, Dragees, Kapseln und dergleichen ist zwar weitgehend ausgereift, doch sind eine Reihe von systembedingten Nachteilen nicht zu übersehen.

Für niedrig dosierte Wirkstoffe muß ein großer Anteil an Hilfsstoffen zugesetzt werden, um zu einer handhabbaren Größe der Einzeldosis zu gelangen. Weiterhin ist eine genaue Kennzeichnung einzelner Tabletten oder Dragees praktisch nicht möglich. Es haben sich deshalb Durchdrückpackungen durchgesetzt, welche eine Mehrzahl von Tabletten, Dragees oder auch Kapseln enthalten und welche mit den notwendigen Informationen, insbesondere dem Namen des Präparates bedruckt sind. Die Herstellung solcher Verpackungen erfordert naturgemäß einen zusätzlichen Arbeitsgang und es werden Umverpackungen in Form von Faltschachteln benötigt, welche ein beträchtliches Leervolumen aufweisen und dadurch zusätzlich Lagerraum beanspruchen. Ein besonders gravierender Nachteil von Dragees und Kapseln besteht darin, daß eine Zerteilung praktisch unmöglich ist, die kleinste Dosis somit vorgegeben ist. Auch bei Tabletten ist eine genaue Zerteilung schwierig, lediglich größere Tabletten mit einer Kerbe als Sollbruchstelle lassen sich allenfalls teilen, wobei häufig ungleichgroße Bruchstücke entstehen.

Es sind bereits Versuche zur Schaffung einer neuen Darreichungsform für die orale Verabreichung von Arzneimitteln bekannt geworden, welche aus wirkstoffhaltigen Folien bestehen. Gemäß der BE-PS 637 363 wird ein papierartiges Trägermaterial aus unlöslichen Zellulosefasern mit einer Wirkstofflösung getränkt bzw. beschichtet und eine Dosierung durch Perforation der Trägerfolie nach Art eines Briefmarkenbogens erreicht. Aus den DE-OS 24 32 925 und 24 49 865 ist es bekannt, Arzneimittelwirkstoffe in Folienbildner einzuarbeiten, bei denen es sich vorzugsweise um wasserlösliche Verbindungen wie Methyl- und Ethylzellulose, insbesondere aber Hydroxypropylzellulose, Hydroxyethylzellulose oder Methylhydroxypropylzellulose handelt. Auch die so erhaltenen wirkstoffhaltigen Folien lassen sich zur Dosierung durch Perforation in einzelne Abschnitte aufteilen. Aus DE-A-2746414 ist es ferner bekannt, derartige Dosierfolien mit weiteren Wirkstoffhaltigen oder- freien folien zu Dosierlaminaten zu vereinigen. Dadurch lassen sich inkompatible Wirkstoffe verarbeiten oder die Lösungsgeschwindigkeit bereinflussen. Diese Laminate insgesamt werden in form von Dosiereinheiten verwendet. Diese Vorschläge haben keinen Eingang in die Praxis gefunden und in dem neuesten Lehrbuch der "Arzneiformenlehre" von P.H. List, 4. Auflage, Stuttgart, 1985, finden sie keine Erwähnung. Dies beruht ersichtlich darauf, daß die bislang bekanntgewordenen Vorschläge es nicht ermöglichen, die geforderte Gewichtskonstanz und gleichmäßige Wirkstoffverteilung zu erreichen, welche heute gefordert werden. Die Ph. Eur. setzt zum Beispiel Maßstäbe für die Gleichförmigkeit des Gewichtes einzeldosierter Arzneiformen, wobei diese dem jeweiligen Durchschnittsgewicht entsprechend nach höchstzulässigen Abweichungen in % gestaffelt sind. Die Forderung liegt im allgemeinen bei +/- 5 bis max. 10%. Entsprechende Werte für feste Arzneiformen bestehen auch hinsichtlich anderer Parameter wie Zerfallzeit und Lösungsgeschwindigkeit.

Die oben erwähnten Vorschläge des Standes der Technik führen zu Produkten ungenügender Akzeptanz durch die Patienten (Papierabschnitte lassen sich nur schlecht einnehmen) und erlauben keine exakte Dosierung pro Flächeneinheit, wie sie unbedingt gefordert werden muß. Bei Inkorporieren des Wirkstoffes in eine Folie bereitet nicht nur die genaue Dosierung Schwierigkeiten, sondern ein wesentlicher weiterer Nachteil besteht darin, daß für jeden Wirkstoff eine entsprechende Folie gesondert hergestellt werden muß, so daß die Wirtschaftlichkeit des Herstellungsverfahrens nicht gegeben ist.

Der Erfindung liegt demgegenüber die Aufgabe zugrunde, eine "zweidimensionale" Darreichungs- und Dosierungsform zu schaffen, welche die genannten Nachteile nicht aufweist, sich leicht herstellen läßt und mit großer Flexibilität an die Anforderungen des Marktes und verschiedener Wirkstoffe angepaßt werden kann.

Gegenstand der Erfindung ist eine Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder dergleichen in Form eines folienförmigen Trägermaterials mit einer wirkstoffhaltigen Beschichtung, wobei diese Darreichungsform dadurch gekennzeichnet ist, daß das Trägermaterial ein Release-Papier, ein Release-Film oder eine Release-Folie ist und daß das Trägermaterial einseitig mit der wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

Die erfindungsgemäße Darreichungsform weist mehrere wesentliche Vorteile auf:

- Da der Träger im Gegensatz zu den vorbekannten Ausführungsformen keinen Teil der Darreichungsform bildet, kann er die erforderliche Festigkeit aufweisen, ohne die Akzeptanz des Arzneimittels

durch Patienten zu beeinträchtigen,

- die wirkstoffhaltige Schicht kann bei hochwirksamen Arzneimitteln sehr dünn sein, da das Trägermaterial die mechanische Festigkeit gewährleistet,
- mit Hilfe moderner Auftragverfahren läßt sich die wirkstoffhaltige Beschichtung mit konstanter Schichtdicke aufbringen, so daß die erforderlichen Toleranzen eingehalten werden können,
- falls eine Sterilisierung erforderlich ist, kann diese wegen der geringen Schichtdicke problemlos mittels Strahlenbehandlung erreicht werden,
- der Träger läßt sich auf der Vorder- und insbesondere der Rückseite mit verschiedenen Informationen bedrucken,
- aufgrund der relativ großen Fläche von beispielsweise 4 bis 10 cm^2 lassen sich ausführliche Informationen für den Benutzer auf das unbeschichtete Trägermaterial oder auch nachträglich aufdrucken,
- die Dosiseinheiten lassen sich durch entsprechende Vorzerteilung flexibel gestalten, so daß für verschiedene Dosierungen (z.B. für Erwachsene und Kinder) nur ein Produkt hergestellt werden muß; die Vorzerteilung kann ggf. auch erst in der Apotheke oder im Krankenhaus nach ärztlichen Angaben vorgenommen werden.

Mit den vorbekannten Darreichungsformen in Folienform hat die erfindungsgemäße Darreichungsform darüberhinaus den Vorteil des äußerst geringen Platzbedarfes gemeinsam. Statt Faltschachteln können daher beispielsweise Taschen oder Beutel aus Kunststoffolie oder kunststoffbeschichtetem Papier verwendet werden, in welche das Produkt eingesiegelt wird, ähnlich wie feuchte Erfrischungstücher.

Als Trägermaterialien eignen sich die verschiedensten Materialien, beispielsweise Papiere mit einem Gewicht von etwa 80 bis 120, vorzugsweise 100 g/m^2, Kunststoffilme bzw. -folien auf Basis von Polyethylen, Polyvinylchlorid, Polyvinylidenchlorid, Polyester und anderen indifferenten Polymeren oder dünne Metallfolien, beispielsweise solche aus Aluminium. Bevorzugt werden siliconisierte Papiere, welche in unterschiedlichen Qualitäten im Handel erhältlich sind, und welche insbesondere zur Abdeckung von selbstklebenden Produkten wie Pflastern, Klebebändern oder Haftetiketten Verwendung finden. Die an sich auch geeigneten mit Wachs oder Paraffin beschichten Release-Papiere sind dagegen in der Praxis weitgehend durch die mit inerten Siliconen beschichteten Papiere ersetzt worden. Bei einem Auftrag der wirkstoffhaltigen Beschichtung auf nur eine Seite der Trägerfolie reicht es aus, wenn nur diese mit einer nicht haftenden Beschichtung versehen ist. Die Rückseite sollte dagegen vorzugsweise so beschaffen sein, daß sie mit Informationen unterschiedlicher Art gut und dauerhaft bedruckbar ist.

Die Möglichkeit der vorder- und rückseitigen Bedruckung ist ein besonderer Vorteil der erfindungsgemäßen Darreichungsform. Beispielsweise können die Kennzeichnung, Angaben über die Inhaltsstoffe sowie Dosierungsangaben aufgedruckt werden. Gegebenenfalls läßt sich sogar der ganze Inhalt eines Beipackzettels rückseitig aufdrucken mit der Folge, daß ein separater Beipackzettel, der auch häufig verlorengeht, überflüssig wird. Bei Arzneimitteln, welche regelmäßig genommen werden müssen, beispielsweise bei hormonalen Contrazeptiva, kann der gesamte Verabreichungsplan so angebracht werden, daß eine einfache Einnahmekontrolle gewährleistet ist. Da die einzelnen Dosiseinheiten von dem Träger abgezogen werden, bleibt dieser bis zum vollständigen Aufbrauch des Arzneimittels erhalten und es gehen keine der aufgedruckten Informationen verloren.

Für die wirkstoffhaltige Beschichtung findet vorzugsweise eine wässrige Beschichtungsmasse Verwendung, die physiologisch inert ist und deren Einzelkomponenten für Arzneimittel bzw. Lebensmittel geeignet sind. Dabei handelt es sich zum einen um wasserlösliche Quellstoffe in der Art polymerer Filmbildner, vorzugsweise Gelatine, Zellulosen oder Hemizellulosen, quellende oder lösliche Stärken. Vorzugsweise werden ferner Weichmacher zugesetzt, insbesondere mehrwertige Alkohole wie Glycerin oder Sorbitol. Zur Einstellung der erwünschten Viskosität der Beschichtungsmasse, welche etwa die Konsistenz eines Schleimes aufweist, finden polymere Quellstoffe Verwendung, vorzugsweise Alginate, Pectine, Chitine, Lecithine oder Polyethylenglykole. Diese letzteren Stoffe können gleichzeitig als Haftvermittler dienen. Andererseits können auch wasserlösliche Gumme oder Gummi arabicum zugesetzt werden, um die Haftung der Beschichtung auf dem Trägermaterial zu verbessern. Schließlich können noch Konservierungsmittel wie z.B. p-Hydroxybenzoesäureester, Farbstoffe (Lebensmittelfarbstoffe), Pigmente wie Titandioxid oder Aroma- und Süßstoffe zugesetzt werden.

Coatingmassen mit einem Wassergehalt von ungefähr 50% und einer Viskosität von etwa 30 bis zu 10000 cPs haben sich als besonders geeignet erwiesen. Die Rezeptur und Herstellung ähnelt derjenigen eines Arzneimittelsaftes, in welchem der Wirkstoff bzw. die Wirkstoffkombination gelöst oder gleichmäßig dispergiert wird. Die Beschichtungsmasse muß ausreichende Homogenität und galenische Stabilität aufweisen, damit ein gleichmäßiger Wirkstoffgehalt der fertigen Beschichtung sichergestellt ist.

Folgende Rahmenrezeptur hat sich bewährt:

Gelatine	8 bis 10 g
Stärke	3 bis 8 g
Glycerin	1 bis 2 g
Wasser	30 bis 50 g

In dieser Grundmasse wird der Wirkstoff gelöst bzw. dispergiert. Im Fall der Verwendung einer Dispersion muß der Wirkstoff für eine gleichmäßige Verteilung äußerst feinteilig sein. Vorzugsweise liegt die mittlere Teilchengröße im Bereich von etwa 1 bis 20 µm.

Die gewünschte Dosis des Wirkstoffes und die angestrebte Fläche der Dosiseinheiten bestimmen letztlich die Dicke der Schicht, wobei der Feuchtigkeitsgehalt der Beschichtungsmasse und der fertigen Beschichtung zu berücksichtigen sind.

Im Rahmen der Erfindung ist es auch möglich, die Beshichtungsmasse zu einer wirkstoffhaltigen Folie zu verarbeiten und diese anschließend, gegebenenfalls unter Verwendung eines physiologisch einsetzbaren inerten Klebstoffes, auf das Trägermaterial aufzukaschieren. Diese Ausführungsform kommt insbesondere dann in Betracht, wenn die wirkstoffhaltige Beschichtung eine größere Dicke aufweisen soll, so daß die Verarbeitung zu einer Folie möglich und sinnvoll ist.

Die erfindungsgemäße Darreichungsform ist besonders geeignet für Arzneimittel, welche niedrig dosiert verabreicht werden, d.h. bei welchen die Einzeldosis für die orale Applikation zwischen 0 mg (Placebo) und etwa 20 mg liegt. Geeignete Arzneimittelwirkstoffe finden sich in allen Bereichen der oralen Therapie; hervorzuheben sind u.a. Analeptika, Antibiotika, Antidiabetika, Antiemetika, Antiepileptika, Antihypertonika, Cortikoide, Geriatrika, Hypnotika, Cardiaka, Hypostatika und Biowirkstoffe.

Die Beschichtung kann einen oder mehrere Arzneimittelwirkstoffe enthalten. Falls bei Verwendung mehrerer Wirkstoffe diese nicht ohne weiteres miteinander verträglich sind, ist es bei der erfindungsgemäßen Darreichungsform möglich, die Beschichtung in mehreren Schichten unterschiedlicher Zusammensetzung aufzubringen und die Wirkstoffe dadurch voneinander zu trennen, wobei erforderlichenfalls eine wirkstofffreie Zwischenschicht vorgesehen werden kann. Weiterhin ist es möglich, über der wirkstoffhaltigen Schicht noch eine weitere Schutzschicht vorzusehen, welche den/die Wirkstoff(e) gegen eine Berührung mit der Atmosphäre und/oder gegen Licht schützt. In diesen Fällen muß die Schutzschicht demgemäß luft- und feuchtigkeitsundurchlässig und/oder durch Zusatz entsprechender Farbstoffe bzw. Pigmente lichtundurchlässig sein.

Weiterhin kann durch entsprechenden Aufbau der Beschichtung die Wirkstoffabgabe nach Verabreichung des Arzneimittels gesteuert werden. Beispielsweise ist es möglich, eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten anzuordnen, welche die Wirkstoffresorption im Magen/Darmtrakt in an sich bekannter Weise steuern. Dabei kann die Wirkstoffschicht z.B. zwischen zwei säureunlöslichen Schichten angeordnet werden, so daß bei Verabreichung der Magen passiert wird und die Resorption erst im Darmtrakt erfolgt. In ähnlicher Weise können unterschiedliche Wirkstoffe in verschiedenen Schichten übereinander auf die Trägerfolie aufgebracht werden, damit die Resorption nacheinander und/oder verzögert erfolgt. Ähnliche pharmakokinetische Effekte lassen sich durch das Einarbeiten (z.B. Suspendieren) von unterschiedlich vorbehandelten mikroverkapselten Wirkstoffen erzielen.

Die Aufbringung der wirkstoffhaltigen Beschichtungen auf den Träger, z.B. ein Release-Papier oder eine Release-Kunststoffolie, erfolgt vorzugsweise mit Hilfe eines Glattwalzen-Beschichtungsverfahrens. Die vorzugsweise auf ca. 60 bis 80 °C erwärmte Beschichtunsmasse wird dabei au einem geschlossenen Auftragsystem auf eine beheizte Walze in dünner Schicht übertragen. Mit verzögertem Gleichlauf in bestimmten wählbaren Verhältnissen wird die Masse auf eine parallel angeordnete Walze übertragen, wobei eine Reduzierung der Schichtdicke im Verhältnis 1:2 bis 1:10 erfolgen kann, wodurch gleichzeitig die Toleranzen bei der Auftragung um diese Faktoren verringert werden. Im Gleichlauf erfolgt dann über ein weiteres Walzensystem die Beschichtung des Trägermaterials. Bei einer Anpassung der Wirkstoffbeschichtungsmasse an den Release-Wert des Trägermaterials kann auf den Zusatz eines Klebemittels völlig verzichtet werden. Gegebenenfalls können jedoch auch geeignete Haftvermittler zugesetzt werden.

Bei Aufbringung mehrerer Schichten, wie dies oben bereits beschrieben wurde, werden diese nacheinander aufgebracht, wobei ggf. jede Beschichtung zuvor eine Trocknungsstation durchläuft. Diese kann beispielsweise aus einem temperierten Walzenpaar und einem in Sektionen steuerbaren Trockentunnel bestehen. Nach dem letzten Beschichtungsvorgang wird das beschichte Material auf Rollen aufgewickelt.

Die wirkstoffhaltige Beschichtung wird anschließend in Dosiseinheiten vorzerteilt, welche ähnlich wie Haftetiketten vom Trägermaterial abziehbar sind. Normalerweise wird diese Vorzerteilung beim Arzneimittelhersteller erfolgen, es ist jedoch auch denkbar, das beschichtete Material beispielsweise an Krankenhäuser oder Apotheken auszuliefern, wo dann die Vorzerteilung dosisabhängig oder auch individuell nach ärztlicher Vorgabe durchgeführt werden kann.

Die Vorzerteilung erfolgt in besonders einfacher Weise durch Stanzung, wobei es möglich ist, diesen

Schritt mit der Bedruckung des Trägermaterials zu kombinieren. In vielen Fällen wird es allerdings günstiger sein, die Bedruckung des Trägermaterials vor der Beschichtung vorzunehmen.

Vor oder besser nach Vorzerteilung der wirkstoffhaltigen Beschichtung in Dosiseinheiten wird das beschichtete Trägermaterial zu gebrauchsfertigen Abschnitten zerschnitten, welche eine bestimmte Anzahl von Dosiseinheiten enthalten. Es ist auch denkbar, das Material auf Rollen zu schmalen Bändern zu zerschneiden. Von einer solchen Einzelrolle können dann die einzelnen Dosiseinheiten ähnlich wie einzelne Haftetiketten abgezogen werden.

Vorstehend wurde die Erfindung im wesentlichen im Zusammenhang mit Arzneimitteln beschrieben, worauf sie jedoch keineswegs beschränkt ist. Beispielsweise lassen sich in derselben Weise auch Dosierungsformen für chemische Reagentien, Aromastoffe und dergleichen herstellen.

Zur näheren Erläuterung der Erfindung sollen die nachfolgenden Ausführungsbeispiele dienen.

Beispiel 1
Herstellung eines Cardiakum

Zum Naßauftrag auf ein Releasepapier (Silikonpapier mit einem Flächengewicht von 100 g/m^2) wurde eine Beschichtungsmasse gemäß folgender Rezeptur hergestellt:

Gelatine	10,0	Gew.-Teile	= 22,22%
Kartoffelstärke	3,0	-"-	= 6,67%
Glycerin	1,5	-"-	= 3,33%
Titandioxid	0,3	-"-	= 0,67%
α-Acetyldigoxin	0,2	-"-	= 0,44%
Wasser	30,0	-"-	= 66,67%

Diese Beschichtungsmasse wurde in einer Schichtdicke von 90 g/m^2 mittels Walzen auf das Releasepapier aufgebracht. Nach dem Trocknen wies die Beschichtung einen Restwassergehalt von 11,76% auf. Das Beschichtungsgewicht lag bei 34 g/m^2, was einem Arzneimittelanteil von 0,4 g/m^{2}entspricht. Ein Abschnitt von 2 × 2,5 cm = 5 cm^2 (entsprechend den Abmessungen einer üblichen Briefmarke) enthält 0,2 mg α-Acetyldigoxin, was mit dem Gehalt der handelsüblichen Tabletten übereinstimmt.

Beispiel 2
Herstellung eines Contrazeptivum

Zum Naßauftrag auf ein Releasepapier (einseitig siliconisiertes Papier von 110 g/m^2) wurde eine Beschichtungsmasse von schleimartiger Konsistenz nach folgender Rezeptur hergestellt:

Gelatine	10,00	Gew.-Teile	= 22,222%
Maisstärke	3,17	-"-	= 7,044%
Glycerin	1,50	-"-	= 3,333%
Titandioxid	0,30	-"-	= 0,667%
Levonorgestrel	0,03	-"-	= 0,067%
Wasser	30,00	-"-	= 66,663%

Die Beschichtungsmasse wurde mittels eines Walzenübertragungsverfahrens mit einem Beschichtungsgewicht von 45 g/m^2 auf das Releasepapier aufgebracht. Nach dem Trocknen wies die Beschichtung einen Restwassergehalt von 11,76% auf. Bei einem Beschichtungsgewicht von 17 g/m^2 betrug der Arzneimittelanteil 0,03 g/m^2.

Ein Abschnitt von 2,5 × 4 cm bzw. zwei Abschnitte von 2,5 × 2 cm = 10 cm^2 enthalten somit 0,03 mg Levonorgestrel, was dem Gehalt der handelsüblichen Dragees entspricht.

Patentansprüche

1. Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien, Aromastoffe oder dergleichen in Form eines folienförmigen Trägermaterials mit einer wirkstoffhaltigen Beschichtung, dadurch gekennzeichnet, daß das Trägermaterial ein Releasepapier, ein Releasefilm oder eine Releasefolie ist und daß das Trägermaterial einseitig mit der wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

2. Darreichungsform nach Anspruch 1, dadurch gekennzeichnet, daß das Trägermaterial ein silicon- oder wachsbeschichtetes Releasepapier ist.

3. Darreichungsform nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die wirkstoffhaltige Beschichtung durch Stanzung in Dosiseinheiten vorzerteilt ist.

4. Darreichungsform nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß die Beschichtung einen oder mehrere Arzneimittelwirkstoffe enthält.

5. Darreichungsform nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß die Beschichtung wasserlösliche Quellstoffe als polymere Filmbildner und gegebenenfalls Weichmacher enthält.

6. Darreichungsform nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß sie zur Viskositätseinstellung polymere Quellstoffe enthält, welche gleichzeitig als Haftvermittler dienen können.

7. Darreichungsform nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß die Beschichtung in mehreren Schichten unterschiedlicher Zusammensetzung aufgebracht ist.

8. Darreichungsform nach Anspruch 7, dadurch gekennzeichnet, daß miteinander inkompatible Wirkstoffe in getrennten Schichten nacheinander auf das Trägermaterial aufgebracht sind.

9. Darreichungsform nach Anspruch 7, dadurch gekennzeichnet, daß eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten angeordnet ist, welche die Wirkstoff-Resorption im Magen/Darmtrakt in an sich bekannter Weise steuern.

10. Darreichungsform nach Anspruch 7, dadurch gekennzeichnet, daß über der Wirkstoffschicht eine weitere Schicht aufgebracht ist, die den Wirkstoff gegen Berührung mit der Atmosphäre und/oder gegen Licht schützt.

11. Darreichungsform nach einem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß die Rückseite des Trägermaterials mit die Wirkstoffzusammensetzung und/oder deren Einnahme betreffenden Informationen bedruckbar ist.

12. Verfahren zur Herstellung der Arzneimitteldarreichungsform der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß man eine wirkstoffhaltige Zusammensetzung mit Hilfe von Walzen auf die nichthaftend ausgerüstete Seite eines Releasepapiers, eines Releasefilms oder einer Releasefolie aufbringt.

Claims

1. Presentation and dosage form for pharmaceutical active substances, reagents, aromas or the like in the form of a foil-like carrier material with an active-substance-containing coating, characterized in that the carrier material is a release paper, a release film or a release foil and that the carrier material is provided on one side with the active-substance-containing coating, which can be removed dosewise from the carrier material following prior division into dosage units.

2. Presentation form according to claim 1, characterized in that the carrier material is a silicone or wax-coated release paper.

3. Presentation form according to claims 1 or 2, characterized in that the active-substance-containing coating substance is pre-divided into dosage units by punching.

4. Presentation form according to one of claims 1 to 3, characterized in that the coating contains one or more pharmaceutical active substances.

5. Presentation form according to one of claims 1 to 4, characterized in that the coating contains water-soluble swelling substances as polymeric foil formers and optionally softeners.

6. Presentation form according to one of claims 1 to 5, characterized in that it contains, to set the viscosity, polymeric swelling substances, which can simultaneously serve as adhesion promoters.

7. Presentation form according to one of claims 1 to 6, characterized in that the coating is applied in the form of several layers having differing composition.

8. Presentation form according to claim 7, characterized in that incompatible active substances are applied one after the other as separate layers to the carrier material.

9. Presentation form according to claim 7, characterized in that an active substance layer is arranged between at least two other layers which control the absorption of the active substance in the gastro-intestinal tract in a manner known per se.

10. Presentation form according to claim 7, characterized in that a further layer is applied onto the active substance layer, said layer protecting the active substance against contact with the atmosphere and/or against light.

11. Presentation form according to one of claims 1 to 10, characterized in that the back of the carrier material can be printed with the active substance composition and/or information concerning the intake thereof.

12. Process for preparing the pharmaceutical presentation form according to claims 1 to 11, characterized in that an active-substance-containingcomposition is applied with the aid of rollers to the non-adhesively finished side of a release paper, a release film or a release foil.

Revendications

1. Forme de présentation ou de dosage de principes actifs médicamenteux, réactifs, substances aromatisantes ou similaires, sous la forme d'un matériau support en forme de feuille muni d'un revêtement contenant le principe actif, caractérisée en ce que le matériau support est un papier détachable, un film détachable ou une feuille détachable et, le matériau support est muni d'un côté du revêtement contenant le principe actif, que l'on peut détacher par doses du matériau support après l'avoir préalablement divisé en doses unitaires.

2. Forme de présentation selon la revendication 1, caractérisée en ce que le matériau support est un papier détachable revêtu de silicone ou de cire.

3. Forme de présentation selon la revendication 1 ou 2, caractérisée en ce que le revêtement contenant le principe actif est préalablement divisé en doses unitaires par poinçonnage.

4. Forme de présentation selon l'une quelconque des revendications 1 à 3, caractérisée en ce que le revêtement contient un ou plusieurs principe(s) actif(s) médicamenteux.

5. Forme de présentation selon l'une quelconque des revendications 1 à 4, caractérisée en ce que le revêtement contient des substances épaississantes, comme des agents filmogènes polymères et, le cas échéant, des plastifiants.

6. Forme de présentation selon l'une quelconque des revendications 1 à 5, caractérisée en ce qu'elle contient des substances épaississantes polymères pour ajustement de la viscosité, celles-ci pouvant servir en même temps d'agents adhésifs.

7. Forme de présentation selon l'une quelconque des revendications 1 à 6, caractérisée en ce que le