administering the unit dose into the oral cavity of a patient or(b) dispensing the unit dose into an intermediate receptacle and thereafter administering the unit dose into the oral cavity of the patient.

[0038] In certain embodiments, the invention provides a drug formulation for gastrointestinal deposition comprising a non-compressed free flowing plurality of particles comprising a drug and a pharmaceutically acceptable excipient, the particles having a mean diameter of greater than 10 μm to about 1 mm.

[0039] In certain embodiments, the particles of the invention comprise at least about 40% drug; at least about 50% drug; at least about 60% drug; at least about 80% drug; or at least about 90% drug.

[0040] In certain embodiments, the invention provides a method for delivery of a drug comprising delivering the multiparticulates disclosed herein comprising drug particles via the use of a multiple unit dosing device comprising a housing and an actuator, the device upon actuation delivering a unit dose of the multiparticulates disclosed herein, and thereafter re-using said device to deliver additional unit doses of the multiparticulates at appropriate dosing intervals.

[0041] In certain embodiments of the invention, greater than about 80% of the unit dose is deposited in the gastrointestinal tract, preferably greater than about 90% or greater than about 95%,or greater than about 99% and most preferably, about 100% of the unit dose is deposited in the gastrointestinal tract.

[0042] In preferred embodiments of the invention, the unit dose comprises a discreet collection of multiparticulates. For purposes of the invention, a "discreet collection" means that the multiparticulates are in the form of a non-compressed free flowing unit and not dispersed in a cloud or mist, which effectively minimizes inhalation of the active agent into the lungs of the patient. The unit dose can be, e.g., from about 0.01 mg to about 1.5 g,

depending on the dose of the active agent being delivered. For example, the unit dose can be from about 1 mg to about 100 mg or from about 10 mg to about 50 mg. Preferably, the unit dose is administered to the tongue, most preferably towards the front of the tongue behind the teeth, where it can be easily swallowed with or without the need for an additional fluid. However the invention does contemplate delivery to any portion of the tongue, taking into account, e.g., the taste sensations of different sections of the tongue and/or individual patient preference associated with comfort, e.g. mouth position.

[0043] In certain embodiments of the invention, the mean diameter of the drug particles is of a size which minimizes their capacity to be inhaled into the lower lung. Typically, the mean particle size of the drug particles (or agglomerates) is greater than 10 μm, preferably greater than about 50 μm or greater than about 75 μm. In certain embodiments of the invention, the mean particle size range of the drug particles is from about 100 μm to about 1 mm, preferably from about 50 μm to about 500 μm . In preferred embodiments, greater than 80% of the drug particles have the above disclosed diameter (not mean diameter), e.g. 80% of the drug particles have a diameter of greater than 10 μm, or a diameter of from about 100 μm to about 1 mm. In other embodiments, greater than about 90% of the drug particles have the above disclosed diameter.

[0044] In certain embodiments of the invention, the mean diameter of the drug particles does not vary by greater than about 20%, preferably not greater than about 15% and most preferably not greater than about 10%.

[0045] In certain embodiments of the invention, the multiparticulates comprise a pharmaceutically acceptable excipient. The excipient preferably does not comprise more than about 60% by weight of the formulation; more preferably not more than about 50%; more preferably not more than about 40% by weight by weight; more preferably not more than about 20% by weight multiparticulates by weight, and most preferably not more than about 10% by weight of the formulation.

[0046] In certain embodiments of the invention, the multiple doses of the drug formulation disclosed herein are contained in a reservoir. The reservoir can contain an amount of multiparticulates to provide any number of unit doses, e.g. from about 2 doses to about 400 doses. For ease in patient compliance, the reservoir has a sufficient quantity of to provide e.g. a days supply, a months supply or a years supply of doses, e.g. 30 or 365 for once daily dosing for a month or year, respectively.

[0047] In order to aid in patient compliance, certain embodiments of the invention include a counter or indicator to display the number of doses remaining in the system or the number of doses actuated.

[0048] In certain embodiments of the invention, the unit doses are individually metered prior to actuation, e.g., in the form of capsules or blisters, wherein each blister contains one individual unit dose. The system can be capable of containing any multiple of pre-metered unit doses, e.g. from about 2 to about 400 blisters.

[0049] The invention is also directed to methods of delivery (e.g., in vivo administration and ex vivo dispensing) and methods of treatment utilizing any of the disclosed embodiments directed to compositions of matter. The invention is also directed to methods of preparation of all of the disclosed embodiments.

[0050] The invention is also directed to methods of providing a therapeutic effect to a patient comprising administering to the patient a unit dose of a drug utilizing the systems and formulations disclosed herein. The invention is also directed to methods of preparing the systems and devices.

[0051] For purposes of the present invention, the term "device" refers to an apparatus capable of delivering a unit dose of drug.

[0052] The term "system" refers to a drug delivery device in combination with the disclosed multiparticulate drug having the specifications disclosed herein, e.g. drug particle size, excipient type, etc.

[0053] The term "discreet collection" refers to a non-compressed free flowing unit of multiparticulates with minimal particulate matter being dispersed in the surrounding environment (e.g., as a cloud or mist).

[0054] The term "drug" refers to any agent which is capable of providing a therapeutic effect to a patient upon gastrointestinal deposition. This encompasses all drugs which are intended for absorption for a systemic effect (regardless of their actual bioavailability) as well as drugs intended for a local effect in the gut and /or oral cavity, e.g. nystatin, antibiotics or local anesthetics.

[0055] The term "particle size" refers to the diameter of the particle.

[0056] The term "deposition" means the deposit of the unit dose at the intended point of absorption and/or action. For example, gastro-intestinal deposition means the intended deposit of the unit dose in the gastrointestinal system for e.g., absorption for a systemic effect or to exert a local effect. Pulmonary deposition means the intended deposit of drug into the lungs in order to provide a pharmaceutical effect, regardless that the unit dose may enter the oral cavity prior to pulmonary deposition.

[0057] The term "dispense", when used in connection with the devices and systems of the present invention, means that the device or system delivers the unit dose *ex vivo* with the intent of subsequent administration to a mammal. For example, the device or system can dispense the unit dose into a food, a liquid, a spoon, or another intermediate receptacle.

[0058] The term "administer", when used in connection with the devices and systems of the present invention, means that the device or system delivers the unit dose *in vivo*, i.e., directly

into the gastrointestinal tract of a mammal.

[0059] The term "deliver" is meant to cover all *ex vivo* and *in vivo* delivery, i.e., dispensing and administering, respectively.

[0060] The term "patient" refers to humans as well as other mammals in need of a therapeutic agent, e.g., household pets or livestock. This term also refers to humans or mammals in need of or receiving prophylactic treatment.

[0061] The term "functional coat" means a coating on a drug particle which provides a controlled release of the drug (e.g., a sustained release), a delayed release of the drug (e.g., via an enteric coating), taste masking, salivary stimulation, a moisture barrier, texture modification, minimization of surface asperities, chip resistance, pliability or any combination of any of the foregoing.

[0062] In certain embodiments, the particulates are defined functionally with respect to the fact that they are of a size such that an effective dose cannot be delivered into the lower lung of a human patient. However, this definition should be understood to mean that a small percentage of drug (but not an amount effective to render a therapeutic effect) may in fact be inadvertently delivered to the lungs of the patient. Also, this definition is meant to define the particles, but not to limit the use of the invention to the treatments of humans only. The invention may be used for delivering doses of drugs to other mammals as well.

BRIEF DESCRIPTION OF THE DRAWINGS

[0063] Fig.1 is a graph of adhesion vs. humidity for standard powders.

[0064] Fig. 2 is a graph of adhesion vs. humidity for powders of the present invention.

[0065] Fig. 3 is a dissolution profile of Indomethacin & 4% PVP K-30 wet granulation in a pH 6.8 phosphate buffer made in accordance with an embodiment of the present invention.

[0066] Fig. 4 is a pH 6.8 phosphate buffer dissolution profile of Indomethacin & 10% PEG6000 melt granulation made in accordance with an embodiment of the present invention.

[0067] Fig. 5 is a .1 N Hydrochloric Acid dissolution profile of Indomethacin & 10% PEG6000 & 15% Acryl-eze melt granulation made in accordance with an embodiment of the present invention.

[0068] Fig. 6 is a pH 6.8 phosphate buffer dissolution profile of Indomethacin & 10% PEG6000 & 15% Acryl-eze melt granulation made in accordance with an embodiment of the present invention.

[0069] Fig. 7 is a .1 N Hydrochloric Acid dissolution profile of Indomethacin & 15% Sureteric & 10% PEG6000 melt granulation made in accordance with an embodiment of the present invention.

[0070] Fig. 8 is a 6.8 pH phosphate buffer dissolution profile of Indomethacin & 15% Sureteric & 10% PEG6000 melt granulation made in accordance with an embodiment of the present invention.

[0071] Fig. 9 is a .1 N Hydrochloric Acid dissolution profile of Indomethacin & 15% Sureteric melt granulation made in accordance with an embodiment of the present invention.

[0072] Fig. 10 is a 6.8 pH phosphate buffer dissolution profile of Indomethacin & 15% Sureteric melt granulation made in accordance with an embodiment of the present invention.

[0073] Fig. 11 is a .1 N Hydrochloric Acid dissolution profile of Indomethacin & 15% Sureteric & 10% Lustre Clear melt granulation made in accordance with an embodiment of the present invention.

[0074] Fig. 12 is a 6.8 pH phosphate buffer dissolution profile of Indomethacin & 15%

Sureteric & 10% Lustre Clear melt granulation made in accordance with an embodiment of the present invention.

[0075] Fig. 13 depicts the particle size distribution for the formulations made in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION

[0076] In general, it has been recognized in the art that dry powder inhalation or insufflation formulations must consist of particles of a size of about 2 microns in diameter in order for the particles, when inhaled, to reach the peripheral or "deep" lung, including alveoli. Particles larger than 10 microns in diameter are not able to reach the deep lung when inhaled because they are collected on the back of the throat and upper airways in humans. Therefore, known powder delivery systems have been formulated with particle sizes of less than 10 microns in order for the particles to reach the intended site of action, the pulmonary system. Known powder delivery devices have not contemplated delivery of particles from a multi-dose delivery device to achieve gastrointestinal deposition, and therefore have avoided the use of drug particles having a large size, e.g. greater than 10 microns. By virtue of the invention disclosed in Applicants copending application, PCT/IB01/00251, it has been a surprising discovery that drug particles greater than 10 microns can be delivered from a multi-use drug delivery device for gastrointestinal deposition in a patient in order to minimize the inhalation of the drug particles into the lungs, in order to have substantially all of the dose deposited in the gastrointestinal system. By virtue of the present invention, it has been surprisingly discovered that powders that can be used in such devices can be functionally coated in order to provide desired characteristics with respect to their use in the device, e.g., increased flowability and decreased bridging (disclosed in more detail below) as well as characteristics of the powder itself, e.g. an acceptable weight variability. The powders can be used in the device or can be administered without the use of the device, e.g., by using a sachet.

[0077] In preferred embodiments, the drug formulation for gastrointestinal deposition of the invention comprising a non-compressed free flowing plurality of particles comprising a core

comprising a drug and a pharmaceutically acceptable excipient, with the core overcoated with a functional coating.

[0078] In preferred embodiments, the core of the invention comprises drug coated with the excipient and a functional coat overcoating the excipient coat, thus providing a dual coated powder. The dual coated powder has improved functionality as a multiparticulate dosage form.

[0079] In other preferred embodiments, the core of the invention comprises drug interdispersed with the excipient and a functional coat overcoating the core. In these embodiments, the core can be prepared by wet granulation or by melt granulation. It has been surprisingly found that preparing the core by wet granulation or melt granulation results in a decreased fraction of fine particles in the resultant dosage form.

[0080] Depending on the choice of the initial excipient overcoat, single coated particles can have a surface area which is not smooth, with a significant degree of rugosity and surface asperities. Such particles have significant associated problems which decrease the usefulness and benefits of multiparticulate dosage forms.

[0081] For example, the presence of surface asperities on the surface of the particles provides gaps and cavernous areas which promote the coalescence of water onto the surface of the particles. The accumulation of water onto the surface of the particles promoted cohesiveness of the particles which is undesirous in the multiparticulate dosage form of the present invention, e.g., due to decreased flowability. Accordingly, the use of the present invention may not be able to be used to full benefit in areas which have increased humidity. This is relevant not only by the geographic location of use, e.g., a tropical area, but also relevant by the workplace, e.g. air conditioned buildings which may result in increased humidity. The functional overcoat can be provided in order to provide a relatively smooth surface area with minimal rugosity and surface asperities. The overcoated particles can then be resistant to the deleterious effects of moisture and humidity of the functionality of the

multiparticulate dosage form. The moisture resistant overcoat may have the added benefit of protecting the stability of the drug contained therein.

[0082] Another functional problem associated with particles with increased rugosity and surface asperities is the presence of points or protrusions which rise from the surface of the particle and increase cohesiveness by multiple pathways.

[0083] One reason for increased adhesion between particles due to surface points or protrusions is due to physical interlocking between adjacent particles in the formulation. The protrusions of one particles can interlock between a "valley" in another particle. Alternatively, protrusions can actually interlock due to "jigsaw" type characteristics of the protrusions. The resultant is agglomeration of particles and decreased flowability of the formulation. An overcoat which smooths the surface can minimize asperities and rugosity and increase the functionality of the formulation.

[0084] Another reason for increased adhesion between particles due to surface points or protrusions is due to the fact that charge tends to gather at these points and protrusions. Thus, the existence of localized charge can increase electrostatic forces between the particles and promote agglomeration and adhesion. An overcoat which smooths the surface of the underlying particle and decreases asperities and rugosity can decrease accumulation and adhesion due to electrostatic forces. Electrostatic forces can also be minimized by coating a substrate with a conductive polymer, disclosed in more detail below.

[0085] The concept of rugosity of particles can be quantified by a rugosity index. The calculation of the rugosity index involves the concept of a "convex hull". A convex hull is a minimum enveloping boundary fitted to an outline of the measured particle that is nowhere concave. The rugosity index is defined as the perimeter of the particles outline divided by the perimeter of the convex hull. According to this index, certain embodiments of the multiparticulates of the present invention can have a mean rugosity index of between 1.0 and 1.5, more preferably from about 1.0 to about 1.2. In other embodiments, greater than 80% of

the particles of the invention have a rugosity index within the disclosed mean range. In other embodiments, greater than 90% of the particles of the invention have a rugosity index within the disclosed mean range.

[0086] Another calculation index which can be used in the present invention is a roundness index. When the particles of the present invention are coated as disclosed herein, certain embodiments will exhibit a roundness of the particles. The roundness index can be calculated as the square of the perimeter of the particles outline divided by 4π(cross-sectional or projection area of particle outline). According to this index, certain embodiments of the multiparticulates of the present invention can have a mean roundness index of between .70 and 1.0, more preferably from about .85 to about 1.0. In other embodiments, greater than 80% of the particles of the invention have a roundness index within the disclosed mean range. In other embodiments, greater than 90% of the particles of the invention have a roundness index within the disclosed mean range.

[0087] In certain embodiments of the invention, flowability is improved by virtue of the functional coatings, without the need for certain flow aids known in the art such as the inclusion of silicone dioxide. The use of silicone dioxide is not preferred in the present invention because this compound is not suited for inhalation, should a patient accidentally or inadvertently have aspiration into the lungs of a fraction of the unit dose.

[0088] Adhesion and agglomeration also leads to the concept of bridging which is particularly problematic with respect to the use of the multiparticulate formulation disclosed herein in multiple unit dosing devices. When multiple unit doses of the multiparticulates of the present invention are stored in containers, e.g., reservoirs, and unloaded therefrom through an opening or openings in the bottom of the container, the containers are often designed to have very steep walls adjacent the opening to aid the outward flow of the multiparticulates. Nevertheless the multiparticulates can become clogged and will have reduced or no flow out of the container. This phenomenon is generally termed "bridging" since the bulk material tends to assume a curved or cupola-like shape. It is known that sometimes vibrating or knocking the container walls from outside is sufficient to break the

integrity of the bridge enable the flow to return to normal. Sometimes, however, such vibrating or knocking results in container wall vibrations which further compact the material resulting in an even more rigid and indestructible bridge being formed, or the shaking and vibrating of the container can break or damage the dosing device.

[0089] One aspect of the present invention is formulating the mean particles size of the particulates to have a diameter which can minimize or possibly eliminate bridging when the formulation is included in a system in a multiple unit dosing device (e.g., a hopper base device). The multiple unit dosing devices as disclosed herein and in PCT/IB01/00251 may be susceptible to bridging which could result in reduced flow and inaccurate dosing. It has been discovered that bridging can be significantly reduced if the particles size of the multiparticulates are no greater than 1/14th or 1/15th the diameter of the exit opening in the reservoir or container of the bulk formulation. The typical opening of a multiple unit dosing device is about 7 mm, thus, a preferred particle size of the present invention is a mean particles size of less than about 500 micrometers. If the mean particle size of the multiparticulates are significantly greater than 1/14th the size of the diameter of the exit opening, the resultant bridging and reduced flow will increase. For example, bridging may be more problematic if the mean particle size of the formulation is 1.5 mm in a dosing device with a 7 mm exit. Bridging is also increased if the particulates have asperities and protrusions due to interlocking as discussed above. With interlocking, the particles cannot move relative to each other in the direction of an applied driving force component, such as gravity, due to the presence of a force such as a frictional force component which is larger than the driving force component and normal thereto and which urges the particles against each other. The frictional force component that holds the particles together is proportional to the coefficient of friction of the particular bulk material. Thus, materials having relatively large coefficients of friction have a relatively large tendency to bridge. The inclusion of a coating or overcoating which smooths the surface of the multiparticulates will result in decreased bridging due to decreased interlocking.

[0090] The multiparticulates of the present formulation, when in motion are known to have a relatively smaller coefficient of friction than at rest. The present invention is therefore directed to devices which reduce the coefficient of friction between multiparticulates by producing relative motion therebetween in order to reduce bridging effects. This can be accomplished, for example, by the inclusion of a internal rake or lever which agitates and

moves the particles within the device upon actuation, or by a vibrating mechanism which is preferably activated upon actuation.

[0091] The present invention is therefore directed to particles having a novel size range, which are dependent on a number of factors. In order to reduce pulmonary inhalation, the mean diameter of the particles are preferably greater than about 10 micrometers and preferably greater than about 50 micrometers and the mean diameter of the multiparticulates are preferably less than about 500 micrometers as a typical dosing device will have an exit opening of about 7 mm. However, this range is not meant to be limiting as the dosing devices (e.g., hopper base devices) can have different size openings and the formulations of the present invention may be used without the device.

[0092] As bridging and aspiration will depend on the actual size of the particles in proximity to each other, mean particles size is only one factor to consider, as the actual particles in proximity to each other may wind up being very large or very small, despite the mean particles size of the entire batch.

[0093] Accordingly, with respect to aspiration, it is preferred that greater than 90% of said particles have a diameter of greater than about 10 μm. Preferably, greater than 95% of said particles have a diameter of great than about 10 μm. More preferably, greater than 99% of said particles have a diameter of greater than about 10 μm.

[0094] In other embodiments, greater than 90% of said particles have a diameter of greater than about 50 μm. Preferably, greater than 95% of said particles have a diameter of great than about 50 μm. More preferably, greater than 99% of said particles have a diameter of greater than about 50 μm.

[0095] In other embodiments, greater than 90% of said particles have a diameter of less than about 500 μm. Preferably, greater than 95% of said particles have a diameter of less than about 500 μm. More preferably, greater than 99% of said particles have a diameter of greater than about 500 μm.

[0096] In other embodiments, greater than 90% of said particles have a diameter of greater than about 50 μm and greater than 90% of said particles have a diameter of less than about 500 μm.. Preferably, greater than 95% of said particles have a diameter of great than about 50 μm and greater than 95% of said particles have a diameter of less than about 500 μm. More preferably, greater than 99% of said particles have a diameter of greater than about 50 μm and greater than 99% of said particles have a diameter of greater than about 500 μm..

[0097] In order to achieve the desired lower limit of the particles size of the present invention the invention, in certain embodiments is directed to a method of preparation comprising air jet sieving particles to remove fine particles. In particular embodiments, the invention is directed to a method of preparing a multiparticulate drug formulation for gastrointestinal deposition comprising preparing a non-compressed free flowing plurality of particles comprising a core comprising a drug and a pharmaceutically acceptable excipient as disclosed herein and air jet sieving the particles to separate the cores from fine particles; and thereafter overcoating said core with a functional coating as disclosed herein. The invention is also directed to compositions obtained using these methods.

[0098] The compositions of multiparticulates obtained using air jet sieving and methods thereof are not limited to the particular embodiments disclosed herein. Air jet sieving can be used for any composition of multiparticulates intended for oral use in order to remove fine particles (e.g., particles which may be aspirated into the lungs). Accordingly, the present invention is directed to compositions and methods of preparing a multiparticulate formulations for oral delivery comprising preparing a multiparticulate composition and air jet sieving the composition to remove particles of less than about 10 μm, less than about 50 μm or less than about 100 μm. In preferred embodiments, particles larger than about 500 μm or larger than about 1 mm are also removed from the composition. Preferably, multiple unit doses of the composition are then placed in an oral delivery device capable of metering a unit dose of the composition for oral delivery. These compositions can be coated (e.g. for sustained release or tastemasking) before air jet sieving, after air jet sieving or not coated at

all. The coated embodiments can be single or multiple coated (e.g., as disclosed herein).

[0099] The use of an air jet sieve is beneficial as the standard sieving techniques used with screens and meshes may not separate all of the desired fine particles as the fine particles may adhere to the surface of larger particles and thus not separate during the sieving process. The air jet sieving process utilizes a negative pressure to draw particles below a particular size range down through an appropriate screen or mesh. In another embodiment, there is a combination of a downward negative pressure and an upward positive pressure which facilitates the de-agglomeration of the different particle sizes. In other embodiments, the upward pressure can be introduced upwards from a rotating wand. An apparatus utilizing a negative downward pressure and an upward positive pressure through a rotating wand is a Micron Air Jet Sieve MAJS I/II manufactured by Hosakawa.

[0100] In order to facilitate swallowing of a unit dose of the present formulation, excipient should be kept to a minimum in order to reduce the mass of the dose. Therefore, in preferred embodiments of the present invention, the drug particles comprise at least about 40% drug, at least about 50% drug, at least about 60% drug, at least about 80% drug, or at least about 90% drug.

[0101] In preferred embodiments, the core comprises drug coated with excipient; drug interdispersed in excipient; a combination thereof or drug coated onto excipient, e.g., drug coated inert beads. The core of drug and excipient is then overcoated with a functional coating. This is not limiting however, as it is contemplated that single coated particles and cores containing only drug (with at least one coating) are contemplated by the invention, as long as the desired functional characteristics are met. In preferred embodiments, the core is formed by mixing drug with excipient (e.g. a binder such as polyvinylpyrrolidone) to form a granulate which is then sieved and coated with further excipient (e.g. ethylcellulose). These cores can then be coated with a functional coating (e.g. microcrystalline cellulose).

[0102] In certain embodiments, wet granulation techniques can be used to prepare cores

with the drug interdispersed in excipient. Utilizing wet granulation in preparing the core reduces any resultant fine particles in the final formulation. Reducing the fine particles results in an oral formulation which has decreased potential for pulmonary deposition due to the presence of respirable fine particles. The application of the functional coat of the invention results in a further decrease in respirable fine particles.

[0103] In certain embodiments, melt granulation techniques can be used to prepare the cores with the drug interdispersed in excipient. In certain embodiments, melt granulation of the drug with excipient results in a smaller fraction of respirable fine materials as compared to wet granulation techniques. In certain embodiments, in order to provide an equivalent reduction of respirable fines with wet granulation techniques as compared to melt granulation techniques, it is necessary to increase the amount of functional coat. An increase in functional coat can result in a delayed drug release with variable batch to batch dissolution rates. In certain embodiments, final products prepared with a melt granulation step has minimal batch to batch variability and an acceptable drug release profile, e.g., without an unwanted delay. As with wet granulation embodiments, the application of the functional coat of the invention results in a further decrease in respirable fine particles.

[0104] In certain embodiments, melt granulation can be used in preparing the core in addition to wet granulation. For example, a fine material with a large surface area would require an increased amount of melt granulation excipient. In such embodiments, the fine particles can be wet granulated in order to provide large particles with a decreased surface area, while at the same time, reducing respirable particles. The resultant wet granulated particles can then be melt granulated with a suitable excipient, which can result in a further reduction of respirable particles.

[0105] In certain embodiments, melt granulation can be used prior to, or after the application of the functional coat. For example, if the functional coat is an enteric coating, the melt granulation can be performed before application of the enteric coat, or enteric coated drug particles can be melt granulated with the melt granulation excipient. Both alternatives

would result in a reduction of respirable particles as compared to the formulations without the melt granulation before or after the application of the enteric coat. In certain embodiments, performing the melt granulation prior to application of the functional coat results in a less variable batch to batch ratio as compared to performing the melt granulation after the application of the functional coat. In certain embodiments, performing the melt granulation prior to the application of the functional coat results in a more acceptable particle size distribution for applying the functional coat, due to the increased reduction of fine particles.

[0106] When applying the functional coat, e.g., an enteric coat to the melt granulated core, it is preferable to have a difference between the melting point of the melt granulation excipient and the film forming temperature of the coating agent of 20 degrees C or more, in order to reduce interdispersion of the melt granulated material and the functional coat.

[0107] Suitable melt granulations excipients for the present invention include, e.g., wax materials such as beeswax, white wax, emulsifying wax, hydrogenated vegetable oil, cetyl alcohol, stearyl alcohol, free wax acids such as stearic acid; esters of wax acids; propylene glycol monostearate, glyceryl monostearate; and carnauba wax. The wax material can be a water insoluble wax material or a non-polymeric wax material. In certain preferred embodiments, the melt granulation excipient is glyceryl monostearate, a glyceryl stearate, glyceryl palmitostearate, glyceryl behenate, stearyl alcohol, stearic acid, or a combination thereof.

[0108] Other suitable melt granulation excipients include polyethylene glycols which can have a weight average molecular weight of from about 100 to about 10,000, from about 200 to about 1000, or from about 200 to about 400. Preferably, the polyethylene gycol has a molecular weight of from about 4,000 to about 8,000 and most preferably a molecular weight of about 6,000.

[0109] In certain embodiments, the melt granulation is transferred to a tray for cooling, rather than cooling the granulation while mixing as cooling the granulation while mixing may

result in fragmentation of the granules. Such fragmentation can result in an increased percentage of unwanted respirable fines.

[0110] In certain embodiments, the excipient of the core provides a controlled release (e.g., a sustained release) of the drug upon gastrointestinal deposition. For example, the excipient can provide a controlled release of the drug upon gastrointestinal deposition to provide a therapeutic effect for at least 12 hours after oral administration. In other embodiments, the excipient can provide a controlled release of the drug upon gastrointestinal deposition to provide a therapeutic effect for at least 24 hours after oral administration.

[0111] In other embodiments, the excipient can provide a delayed release (e.g., via an enteric coating) of the drug upon gastrointestinal deposition, such as delaying release of the drug to effect intestinal absorption for drugs irritating to the gastric mucosa.

[0112] In other embodiments, the excipient can provide tastemasking. This is especially beneficial for bitter tasting drugs, especially when administered to small children. If a dose of drug intended for a child has a bad taste, the child may spit out the dose resulting in waste and a possible reduction in the amount administered. An overdose is also possible as if the dose is administered again, it is possible that the child already ingested a portion of the previous dose.

[0113] In other embodiments, the excipient can include a salivary stimulant to promote the production of saliva to facilitate the swallowing of the unit dose. This is especially useful in patients with xerostomia.

[0114] In other embodiments, the excipient can provide a moisture barrier in order to reduce the coalescence of water on the surface of the particles and reduce undesirable cohesiveness over a wide range of humidities. In certain embodiments, the cohesiveness of the particles does not substantially change over a humidity gradient from about 20% relative humidity to about 80% relative humidity. In other embodiments, the cohesiveness of the

particles does not substantially change over a humidity gradient from about 40% relative humidity to about 60% relative humidity.

[0115] The effect of humidity can have a negative impact of the flowability of particles (e.g., due to cohesiveness). Flowability of the particles can be measured by such tests as the Carr consolidation index, the uniaxial compression test and the Jenike shear test. The tests can be performed over a range of relative humidities in order to evaluate the moisture resistance of the present invention.

[0116] The Carr consolidation index is measured as Tapped Density - Bulk Density x 100
Tapped Density

The relation between Carr's index and powder flowability is expressed in the table below:

Carr's Index	State of Flowability
5-15	Excellent
12-16	Good
18-21	Fair
23-35	Poor
33-38	Very Poor
>40	Very, Very Poor

[0117] In certain embodiments of the invention, the flowability according to Carr's index over a humidity gradient from about 20% relative humidity to about 80% relative humidity is preferably 21 or less, preferably 16 or less and most preferably 12 or less. In other embodiments, the Carr's index does not change by more than about 20%, preferably does not change by more than 10%, most preferably does not change by more than 5%, over a humidity from about 20% relative humidity to about 80%. In other embodiments, the composition has the above characteristics over a humidity gradient from about 40% relative humidity to about 60% relative humidity or 10% to about 90% relative humidity.

[0118] In the uniaxial compression test, a hollow split cylinder is filled with the test powder. A force transducer is used to apply force or a weight from the top of the cylinder onto the powder to consolidate it in a vertical direction for a short known time. The applied consolidation force (σ_1) is then recorded. Then the hollow split cylinder is removed from around the consolidated powder. Thereafter increasing vertical load is applied onto the powder until the consolidated powder collapses or crackers. This new weight force (σ_c) is noted. The smaller this value is the better the flowability of the powder. The value (ffc) usually known as the quotient of consolidation stress and the unconfined yield strength is then calculated by σ_1 divided by σ_c

[0119] The larger this value, the better the flowability of the powder. If the value is >10, the powder is free flowing. If it is between 4-10, the powder shows adequate flow.

[0120] In certain embodiments of the invention, the flowability according to the uniaxial compression test over a humidity gradient from about 20% relative humidity to about 80% relative humidity is preferably greater than about 4, preferably greater than about 10 and most preferably greater than about 12. In other embodiments, the uniaxial compression test does not change by more than about 20%, preferably does not change by more than 10%, most preferably does not change by more than 5%, over a humidity from about 20% relative humidity to about 80%, more preferably. In other embodiments, the composition has the above characteristics over a humidity gradient from about 40% relative humidity to about 60% relative humidity or 10% to about 90% relative humidity.

[0121] The Jenike shear test involves the use of a cell consisting of a base, a ring that rests on the base, a mold ring, a preconsolidation lid and shearing lid. The cell is first filled with the test powder using a spoon. The preconsolidation lid is then placed on the powder and a pre-shear stress is applied on it. The sample is then consolidated by applying a number of 90° twists to the lid. A horizontal shearing force is then applied to the ring at a rate of 2 mm per minute until the consolidated powder collapses. The ffc can then be calculated as above.

Preferably, the flowability of the powder over a humidity range according to the Jenike shear test is the same as with respect to the uniaxial test as disclosed above.

[0122] In other embodiments, the excipient provides a texture modifier in order to improve mouthfeel of the unit dose in the mouth. An increase in palatability would be expected to increase compliance as patients may be unwilling to take multiple or chronic dosing of a formulation which they perceived to be objectionable.

[0123] In other embodiments, the functional coating can have the same affect as disclosed above with respect to the excipient coating.

[0124] For example, the functional coating can provide a controlled or delayed release of the drug upon gastrointestinal deposition; the functional coating can provide tastemasking; the functional coating can comprise a salivary stimulant; the functional coating can provide a moisture barrier; or the functional coating can be a texture modifier. The present invention is contemplated to encompass all combinations of functional coating with particular characteristics of core excipient. It is also understood that one or more of the functions and characteristics of the excipient and overcoating can be achieved with a single coating. For example, an overcoat which provides a moisture barrier, may also provide texture modification. The same is true in the core, for example, when the core is coated with an excipient that provides controlled release and tastemasking of the underlying drug.

[0125] In a preferred embodiment, the functional coating minimizes asperities on the surface of the particles to provide the beneficial characteristics disclosed above, e.g. reduced static and reduced interlocking.

[0126] The desired flow characteristics and reduced adhesion and agglomeration of the multiparticulates of the present invention are better achieved when the coating or coatings of the particles have pliability and are not brittle, with a resistant to chipping. Brittleness can increase surface asperities and reduce the smoothness of the outer coating. Further, chipping

can result in the presence of small particles which can aspirated into the lungs. Thus, it is desirous to have a pliable tough film which is deformable (pliable) and resistant to chipping (tough).

[0127] The pliable tough film of the present invention can be achieve by the manipulation of the process and materials of the coating. In certain embodiments, a plasticizer can be used in the functional coating in order to make the particles pliable.

[0128] Also, the desired pliable tough film can be obtained by minimally including or not including ingredients which can promote brittleness of the coating. In certain embodiments of the invention, the use of lakes and opacifiers are minimally used or not used at all as the increased use of such ingredients can promote brittleness. In certain embodiments, a colorant which is not a lake or an opacifier can be used and the lake or opacifier is not used at all in order to maintain the integrity of the coating. Other embodiments are directed to including plasticizer and coloring agents in a ratio which results in a coating having a desired pliability and non-brittleness.

[0129] In certain preferred embodiments of the invention, the multiparticulate dosage form has minimal adhesion and non-agglomeration over a broad range of humidity. A low humidity dry environment tends to promote adhesion and agglomeration of particles due to electrostatic forces. The functional coating of the present invention can provide a smooth surface to the particles in order to reduce the accumulation of charge in protrusions and to keep the dosage form from having increased particle to particle interaction.

[0130] Likewise, an environment of increased humidity can promote adhesion of particles due to surface tension of water accumulating of the surface of the particles. The functional coating of the present invention can also provide a surface to the particles in order to reduce the coalescence of water on the surface and thus reducing surface tension and particle to particle interaction. This concept of decreased coalescence of water can be in addition to, or separate from the embodiment which reduces the accumulation of charge on the particles.

Figure 1 is a representative graph of typical powders plotting stickiness versus humidity. Figure 2 is a representative graph of particles of the present invention, graphing stickiness versus humidity.

[0131] As previously discussed, the functional coating and the core excipient can provide overlapping characteristics. The following representative materials are meant to be used (i) in the functional overcoat of the core; (ii) the core excipient coat over the drug; (iii) interdispersed with then drug or (iv) any combination of (i), (ii) and (iii).

[0132] Controlled release materials useful in the present invention are preferably hydrophobic materials. The hydrophobic materials can be selected from the group consisting of an acrylic polymer, a cellulosic material, shellac, zein and mixtures thereof.

[0133] Preferably the hydrophobic material is an acrylic polymer. The acrylic polymer can be, e.g., selected from, the group consisting of acrylic acid and methacrylic acid copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, methyl methacrylate, copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, methyl methacrylate copolymers, methyl methacrylate copolymers, methacrylic acid copolymer, aminoalkyl methacrylate copolymer, methacrylic acid copolymers, methyl methacrylate copolymers, poly(acrylic acid), poly(methacrylic acid, methacrylic acid alkylamide copolymer, poly(methyl methacrylate), poly(methacrylic acid) (anhydride), methyl methacrylate, polymethacrylate, methyl methacrylate copolymer, poly(methyl methacrylate), poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), glycidyl methacrylate copolymers and mixtures thereof.

[0134] When the controlled release material is a cellulosic material, the cellulosic material is, e.g., selected from the group consisting of cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate

propionate, cellulose acetate butyrate and mixtures thereof.

[0135] Particularly preferred controlled release materials are ethylcellulose, polymethacrylates,e.g. Eudragit RL and RS, glyceryl behenate, methylcellulose and sodium carboxymethylcellulose.

[0136] In other embodiments of the invention, the controlled release material comprises a lacquer material. The lacquer material can be selected, e.g., from the group consisting of corn oil, cottonseed oil, menhaden oil, pine oil, peanut oil, safflower oil, sesame oil, soybean oil, linseed oil and mixtures thereof. Other suitable oils useful as lacquer materials include fatty acids of C8-C20 oils which can be saturated, unsaturated, glycerides thereof, and combination thereof. Preferably a salt such as magnesium stearate is included. Other suitable oils useful as lacquer materials include branched or polycarboxylated oils such as linoleic acid, linolenic acid, oleic acid and combinations thereof. Saturated oils from the following table are also useful as lacquer agents:

Systematic name	Trivial name	Shorthand designation	Molecular wt.	Melting point (°C)
Octanoic	Caprylic	8:0	144.2	16.7
Decanoic	Capric	10:0	172.3	31.6
Dodecanoic	Lauric	12:0	200.3	44.2
Tetradecanoic	Myristic	14:0	228.4	53.9
Hexadecanoic	Palmitic	16:0	256.4	63.1
Heptadecanoic	Margaric	17:0	270.4	61.3
Octadecanoic	Stearic	18:0	284.4	69.6
Eicosanoic	Arachidic	20:0	412.5	75.3
Docosanoic	Behenic	22:0	340.5	79.9
Tetracosanoic	Lignoceric	24:0	368.6	84.2

[0137] The use of lacquer agents may not release the drug of the multiparticulates. Therefore it may be necessary to include a channeling agent in an amount sufficient to

provide the desired release of the drug, e.g., over 12 or 24 hours. Suitable channeling agents include polyvinylpyrrolidone, polyethyleneglycols, dextrose, sucrose, mannitol, xylitol and lactose. Antioxidants can also be added in order to reduce polymerization which leads to increased hardness.

[0138] The use of lacquer agents is beneficial as it reduces the amount of excipient needed to provide a controlled release of the drug from the particles of the present invention. In certain embodiments, less than about 1% lacquer is needed in the formulation (w/w) to provide the desired effect. Accordingly, as only a small amount of lacquer material is needed, it is preferably mixed with a dispersing agent. Suitable dispersing agents include colloidal silicone dioxide, talc, kaolin, silicone dioxide, colloidal calcium carbonate, bentonite, Fuller's earth, magnesium aluminum silicate and mixtures thereof. A preferred lacquer material is linseed oil with kaolin as a dispersing agent.

[0139] The lacquer material can be granulated with the drug in order to provide controlled release matrices or can coat the drug particulates. The use of lacquer materials is disclosed as providing controlled release in multiparticulate dosage forms. However, it also contemplated by the present invention that the use of lacquer agents with optional channeling agents and dispersing agents can also be used in solid dosage forms such as tablets. For example, an immediate release tablet core can be coated with sustained release coating comprising a lacquer agent as disclosed above with an optional channeling agent and dispersing agent. In these embodiments as well, a preferred lacquer material is linseed oil with kaolin as a dispersing agent.

[0140] Preferably, the delayed release material used in the present invention are enteric polymers. The enteric polymers can be selected from, e.g., the group consisting of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethyl-cellulose and mixtures thereof. Particularly preferred enteric polymers are polymethacrylates such as Eudragit L/S polymers, cellulose

acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl- methylcellulose phthalate and shellac. Sureteric™ is an example of a polyvinyl acetate phthalate based entereic coating. Acryl-eze™ is an example of a methacrylic acid copolymer based enteric coating.

[0141] The tastemasking material of the present material can be selected from, e.g., the group consisting of water-soluble sweetening agents, water-soluble artificial sweeteners, dipeptide based sweeteners and mixtures thereof. The water-soluble sweetening agent can be selected from, e.g., the group consisting of monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, sugar, maltose, partially hydrolyzed starch, or corn syrup solids and sugar alcohols such as sorbitol, xylitol, or mannitol and mixtures thereof. The water-soluble artificial sweetener material of the present invention is selected from, e.g., the group consisting of soluble saccharin salts, such as sodium or calcium saccharin salts, cyclamate salts, acesulfam-K, the free acid form of saccharin and mixtures thereof. The dipeptide based sweetener is preferably L-aspartyl L-phenylalanine methyl ester. Particularly preferred taste masking agents are glyceryl behenate, glyceryl palmitostearate, ethylcellulose and polymethacrylates such as Eudragit E, EPO and RD.

[0142] In other embodiments of the invention, the multiparticulates can comprise an effervescent compound or composition which provides a pleasing organoleptic effect which can substantially mask the taste of unpalatable active ingredients in the powder. The effervescent action also acts as a stimulant to saliva production. Effervescent agents include compounds which evolve gas. The preferred effervescent agents evolve gas by means of chemical reactions which take place upon exposure to a liquid such as saliva in the mouth. This bubble or gas generating chemical reaction is most often the result of the reaction of an acid (e.g. the saliva stimulant acids listed above) and an alkali metal carbonate/dicarbonate or base. The reaction of these two general classes of compounds produces carbon dioxide gas upon contact with saliva.

[0143] Other salivary stimulant of the present invention can be selected from, e.g., food

acids, acid anhydrides and acid salts. Food acids include tartaric acid, malic acid, fumaric acid, adipic acid, and succinic acids and fruit acids, e.g., citric acid. Acid anhydrides of the above described acids may also be used. Acid salts may include sodium, dihydrogen phosphate, disodium dihydrogen pyrophosphate, acid citrate salts and sodium acid sulfite.

[0144] The moisture barrier material of the present invention can be, e.g., selected from the group consisting of acacia gum, acrylic acid polymers and copolymers (polyacrylamides, polyacryldextrans, polyalkyl cyanoacrylates, polymethyl methacrylates), agar--agar, agarose, albumin, alginic acid and alginates, carboxyvinyl polymers, cellulose derivatives such as cellulose acetate, polyamides (nylon 6-10, poly (adipyl-L-lysines, polyterephthalamides and poly-(terephthaloyl-L-lysines)), poly-.epsilon.-caprolactam, polydimethylsiloxane, polyesters, poly (ethylene-vinyl acetate), polyglycolic acid, polyactic acid and its copolymers, polyglutamic acid, polylysine, polystyrene, shellac, xanthan gum, anionic polymers of methacrylic acid and methacrylic acid esters, hydroxyalkylcelluloses and mixtures thereof. In certain embodiments, the moisture barrier material is a hydroxyalkylcellulose such as hydroxypropylmethylcellulose; a cellulosic material such as microcrystalline cellulose; carrageenan; or mixtures thereof. Particularly preferred moisture barrier materials are microcrystalline cellulose/carrageenan-based coating systems, such as LustreClear, ethylcellulose; such as Aquacoat ECD (formulated as a 50:50 mixture with hydroxypropylmethylcellulose) and polyvinyl alcohol based systems such as Opadry AMB. The above disclosed lacquer agents can also be used as moisture barriers.

[0145] The texture modifier material of the present invention can be, e.g., selected from the group consisting of acacia gum, acrylic acid polymers and copolymers (polyacrylamides, polyacryldextrans, polyalkyl cyanoacrylates, polymethyl methacrylates), agar--agar, agarose, albumin, alginic acid and alginates, carboxyvinyl polymers, cellulose derivatives such as cellulose acetate, polyamides (nylon 6-10, poly (adipyl-L-lysines, polyterephthalamides and poly-(terephthaloyl-L-lysines)), poly-epsilon.-caprolactam, polydimethylsiloxane, polyesters, poly (ethylene-vinyl acetate), polyglycolic acid, polyactic acid and its copolymers, polyglutamic acid, polylysine, polystyrene, shellac, xanthan gum, anionic polymers of

methacrylic acid and methacrylic acid esters, hydroxyalkylcelluloses and mixtures thereof. Particularly preferred texture modifiers are cellulose, e.g., carboxymethyl cellulose and microcrystalline cellulose; polydextrose; modified starch; dextrins; gums, e.g. xanthan, guar, locust-bean, carrageenan and alginates; pectins; maltodexrins and carbomers.

[0146] Materials which can be used to obtain a pliable and/or chip resistant coating of the present invention can be selected, e.g., from the group consisting of acacia gum, alginic acid and alginates, carboxymethylcellulose, ethylcellulose, gelatine, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, xanthan gum, pectin, tragacanth, microcrystalline cellulose, hydroxyethylcellulose, ethylhydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycols, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid, gum arabic, lactose, starch (wheat, maize, potato and rice starch), sucrose, glucose, mannitol, sorbitol, xylitol, stearic acid, hydrogenated cottonseed oil, hydrogenated castor oil, vinylpyrrolidone-vinyl acetate copolymers, fructose, methylhydroxyethylcellulose, agar-agar, carrageenan, karaya gum, chitosan, starch hydrolysates and mixtures thereof. Especially preferred materials are plasticizers which can be selected from, e.g., the group consisting of dibutyl sebacate, diethyl phthalate, triethyl citrate, tibutyl citrate, triacetin, benzyl benzoate, chlorobutanol, sorbitol, glycerol, polyethyleneglycol and mixtures thereof.

[0147] With respect to decreasing static in the particles, it was disclosed above that a smooth surface can be provided to the surface of the particles in order to avoid charge gathering and decrease adhesion and agglomeration of particles. Decreasing charge can also be effected on the particles of the present invention by including a conductive polymer into the functional coat. Examples of conductive polymers are polypyrroles, polythiophene, poly(p-phenylene), poly(phenylene vinylene) and trans-polyacetylene. These are rigid polymers and may require the addition of a plasticizer in order to provide a more flexible coating. A less rigid conductive polymer is polyanilene, although inclusion of a plasticizer is still preferable.

[0148] A preferred method to decrease charge on the multiparticulates is by the

electrohydrodynamic spraying of a viscous and highly conductive polyvinyl alcohol aqueous solution, as described in Electrospraying of a highly conductive and viscous liquid, Speranza et al. Journal of Electrostatics, (51) p494, hereby incorporated by reference.

[0149] Conductive polymers are further discussed in U.S. Patent Numbers 6,060,116 and 5,268,407, hereby incorporated by reference with respect to their combination with the multiparticulate formulations of the present invention..

[0150] Another method of reducing charge in the present invention is to include in the multiparticulates, or provide a final coat of compounds selected from magnesium stearate and the like, surfactants such as sodium lauryl sulphate and combinations thereof. In order for these materials to be most effective, they would be included as a final coat with robust mixing in order to provide an even coat on the particles.

[0151] Classes of drugs which are suitable in the present invention include antacids, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, anti-infectives, psychotropics, anti-manics, stimulants, anti-histamines, laxatives, decongestants, vitamins, gastro-intestinal sedatives, anti-diarrheal preparations, anti-anginal drugs, vasodilators, anti-arrhythmics, anti-hypertensive drugs, vasoconstrictors and migraine treatments, anti-coagulants and anti-thrombotic drugs, analgesics, anti-pyretics, hypnotics, sedatives, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypoglycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, mineral and nutritional additives, anti-obesity drugs, anabolic drugs, erythropoietic drugs, anti-asthmatics, bronchodilators, expectorants, cough suppressants, mucolytics, drugs affecting calcification and bone turnover and anti-uricemic drugs.

[0152] Specific drugs include gastro-intestinal sedatives such as metoclopramide and propantheline bromide; antacids such as aluminum trisilicate, aluminum hydroxide, ranitidine and cimetidine; anti-inflammatory drugs such as phenylbutazone, indomethacin, naproxen, ibuprofen, flurbiprofen, diclofenac, dexamethasone, prednisone and prednisolone; coronary

vasodilator drugs such as glyceryl trinitrate, isosorbide dinitrate and pentaerythritol tetranitrate; peripheral and cerebral vasodilators such as soloctidilum, vincamine, naftidrofuryl oxalate, co-dergocrine mesylate, cyclandelate, papaverine and nicotinic acid; anti-infective substances such as erythromycin stearate, cephalexin, nalidixic acid, tetracycline hydrochloride, ampicillin, flucloxacillin sodium, hexamine mandelate and hexamine hippurate; neuroleptic drugs such as flurazepam, diazepam, temazepam, amitryptyline, doxepin, lithium carbonate, lithium sulfate, chlorpromazine, thioridazine, trifluperazine, fluphenazine, piperothiazine, haloperidol, maprotiline hydrochloride, imipramine and desmethylimipramine; central nervous stimulants such as methylphenidate, ephedrine, epinephrine, isoproterenol, amphetamine sulfate and amphetamine hydrochloride; antihistamic drugs such as diphenhydramine, diphenylpyraline, chlorpheniramine and brompheniramine; anti-diarrheal drugs such as bisacodyl and magnesium hydroxide; the laxative drug, dioctyl sodium sulfosuccinate; nutritional supplements such as ascorbic acid, alpha tocopherol, thiamine and pyridoxine; anti-spasmodic drugs such as dicyclomine and diphenoxylate; drugs affecting the rhythm of the heart such as verapamil, nifedipine, diltiazem, procainamide, disopyramide, bretylium tosylate, quinidine sulfate and quinidine gluconate; drugs used in the treatment of hypertension such as propranolol hydrochloride, guanethidine monosulphate, methyldopa, oxprenolol hydrochloride, captopril and hydralazine; drugs used in the treatment of migraine such as ergotamine; drugs affecting coagulability of blood such as epsilon aminocaproic acid and protamine sulfate; analgesic drugs such as acetylsalicylic acid, acetaminophen, codeine phosphate, codeine sulfate, oxycodone, dihydrocodeine tartrate, oxycodeinone, morphine, heroin, nalbuphine, butorphanol tartrate, pentazocine hydrochloride, cyclazacine, pethidine, buprenorphine, scopolamine and mefenamic acid; anti-epileptic drugs such as phenytoin sodium and sodium valproate; neuromuscular drugs such as dantrolene sodium; substances used in the treatment of diabetes such as tolbutamide, disbenase glucagon and insulin; proteins and peptides such as heparin and calcitonin, drugs used in the treatment of thyroid gland dysfunction such as triiodothyronine, thyroxine and propylthiouracil, diuretic drugs such as furosemide, chlorthalidone, hydrochlorthiazide, spironolactone and triamterene; the uterine relaxant drug ritodrine; appetite suppressants such as fenfluramine hydrochloride, phentermine and

diethylproprion hydrochloride; anti-asthmatic and bronchodilator drugs such as aminophylline, theophylline, salbutamol, orciprenaline sulphate and terbutaline sulphate; expectorant drugs such as guaiphenesin; cough suppressants such as dextromethorphan and noscapine; mucolytic drugs such as carbocisteine; anti-septics such as cetylpyridinium chloride, tyrothricin and chlorhexidine; decongestant drugs such as phenylpropanolamine and pseudoephedrine; hypnotic drugs such as dichloralphenazone and nitrazepam; anti-nauseant drugs such as promethazine theoclate; haemopoietic drugs such as ferrous sulphate, folic acid and calcium gluconate; uricosuric drugs such as sulphinpyrazone, allopurinol and probenecid; and calcification affecting agents such as biphosphonates, e.g., etidronate, pamidronate, alendronate, residronate, teludronate, clodronate and alondronate.

[0153] Drugs which possess taste and/or odor characteristics which, when administered orally without any excipients, render the drug or therapeutic agent unpalatable to a subject and would be candidates for taste masking in the present invention include, but are not limited to, H_2 receptor antagonists, antibiotics, analgesics, cardiovascular agents, peptides or proteins, hormones, anti-migraine agents, anti-coagulant agents, anti-emetic agents, anti-hypertensive agents, narcotic antagonists, chelating agents, anti-anginal agents, chemotherapy agents, sedatives, anti-neoplastics, prostaglandins, antidiuretic agents and the like. Typical drugs include but are not limited to nizatidine, cimetidine, ranitidine, famotidine, roxatidine, etinidine, lupitidine, nifentidine, niperitone, sulfotidine, tuvatidine, zaltidine, erythomycin, penicillin, ampicillin, roxithromycin, clarithromycin, psylium, ciprofloxacin, theophylline, nifedipine, prednisone, prednisolone, ketoprofen, acetaminophen, ibuprofen, dexibuprofen lysinate, flurbiprofen, naproxen, codeine, morphine, sodium diclofenac, acetylsalicylic acid, caffeine, pseudoephedrine, phenylpropanolamine, diphenhydramine, chlorpheniramine, dextromethorphan, berberine, loperamide, mefenamic acid, flufenamic acid, astemizole, terfenadine, certirizine, phenytoin, guafenesin, N-acetylprocainamide HCl, pharmaceutically acceptable salts thereof and derivatives thereof.

[0154] Particularly preferred agents include antibiotics such as clarithromycin, amoxicillin erythromycin, ampicillin, penicillin, cephalosporins, e.g., cephalexin, pharmaceutically acceptable salts thereof and derivatives thereof.

[0155] Other preferred agents are acetaminophen and NSAIDS such as ibuprofen, indomethacin, aspirin, diclofenac and pharmaceutically acceptable salts thereof.

[0156] The size of the unit dose is dependent on the amount of drug needed to provide the intended therapeutic effect and the amount of any pharmaceutically acceptable excipient which may be necessary. Typically, a unit dose of from about .01 mg to about 1.5 g would be sufficient to contain a therapeutically effective amount of the drug to be delivered, however, this range is not limiting and can be smaller or higher, depending on the amount of drug and excipient that is necessary.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

Example 1

Controlled-release Propranolol HCl

Step 1: Granulation of Propranolol HCl

[0157] Prior to commencing granulation of the Propranolol HCl, the vessel of the MP Micro is pre-warmed by heating at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 76g of Propranolol HCl and 4g of PVP K-30 is added to the vessel and the process temperature set to 70°C. The airflow is then increased until the product is fluidised. Once a constant temperature is achieved within the powder bed, spray granulation of the product is commenced by the introduction of distilled water as the granulation fluid. An atomising pressure of 2 bar is used.

[0158] Once the material is granulated the addition of the granulation fluid is stopped and the powder bulk is dried. The end point of the drying process is indicated by a constant temperature within the powder bed. At this point the temperature of the inlet air is reduced to 25°C and the bulk material removed. Once cooled the material is screened through a 250

micron sieve then air jet sieved to remove particles below 100 microns.

Step 2: Spray coating with Surelease

[0159] An aqueous dispersion of Surelease is prepared by diluting to 15%w/w solids (i.e. 60% Surelease dispersion and 40% distilled or deionised water) and stirred using a low shear mixer for approximately 15 minutes. With the precision coater module attached the vessel is preheated at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 60g of the granulated Propranolol HCl is returned to the MP Micro and the process temperature set at 70°C to achieve a product temperature of 40-45°C. The airflow is increased until the product is fluidised. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. The material is then sprayed with the Surelease dispersion to achieve a 10 – 30% wt. gain depending on the desired release profile at a spraying rate of 1.0g/min with an atomising air pressure of 2 bar. Once the desired weight of Surelease coating are added to the granules the pump and the atomising air are stopped and the material dried until the powder bed reaches a constant temperature. At this point the inlet air temperature is reduced to 25°C and the operation stopped.

Step 3: Overcoating with LustreClear

[0160] A 9% w/w dispersion of LustreClear is prepared as follows:

- The necessary quantity of LustreClear film coating system is accurately weighed out.
- The necessary quantity of water is accurately weighed into the mixing vessel.
- With the propeller in the centre and as close to the bottom of the vessel as possible, the water is stirred to form a vortex without drawing air into the liquid.
- The LustreClear powder is steadily added to the vortex, avoiding powder flotation on the liquid surface.
- The stirrer speed is increased in order to maintain the vortex as required.
- After all the LustreClear is added, the dispersion is then mixed for a further 3 hours.
- The dispersion is then left for a further 2 hours before use.

[0161] Residual Surelease is removed from the spray nozzle by rapidly flushing through with the 9%w/w dispersion LustreClear. The precision coater module is washed and then dried by heating at 85°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. The Surelease coated granules are placed into the precision coater and are fluidised using the same conditions as for the addition of Surelease. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. At this point the granules are coated with the 9%w/w dispersion of LustreClear at a rate of 1.0g/min. Once a coating of 4 – 30%wt. gain is applied, spraying of the LustreClear dispersion is stopped and the material dried until a constant temperature is observed within the powder bed. At this point the airflow temperature is reduced to 25°C and the bulk material removed, allowing it to cool.

Example 2

Enteric Coated Indomethacin

Step 1: Granulation of Indomethacin

[0162] Before commencing the granulation of the Indomethacin, the vessel of the MP Micro is pre-warmed by heating at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 76g of Indomethacin and 4g of PVP K-30 is added to the vessel and the process temperature set to 70°C. The airflow is then increased until the product is fluidised. Once a constant temperature is achieved within the powder bed, spray granulation of the product is commenced by the introduction of distilled water as the granulation fluid. An atomising pressure of 2 bar is used.

[0163] Once the material is granulated, the addition of the granulation fluid is stopped and the powder bulk is dried. The end point of the drying process is indicated by a constant temperature within the powder bed. At this point the temperature of the inlet air is reduced to 25°C and the bulk material removed. Once cooled the material is screened through a 250 microns sieve and air jet sieved to remove particles below 100 microns. 156

Step 2: Spray coating with Sureteric

[0164] Before applying the Sureteric coat, a 10% w/w dispersion of Opadry II (white) is applied to the granulated Indomethacin to a 2% wt. gain. The 10% w/w dispersion of Opadry II is prepared as follows:

[0165] The necessary quantity of Opadry II film coating system is accurately weighed out.

[0166] The necessary quantity of water is accurately weighed into the mixing vessel.

[0167] With the propeller in the centre and as close to the bottom of the vessel as possible, the water is stirred to form a vortex without drawing air into the liquid.

[0168] The Opadry II powder is steadily added to the vortex, avoiding powder flotation on the liquid surface.

[0169] The stirrer speed is increased in order to maintain the vortex as required.

[0170] After all the Opadry II system is added, the mixer speed is reduced to nearly eliminate the vortex. The dispersion is then mixed for a further 45 minutes.

[0171] With the precision coater module attached the vessel is preheated at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 60g of the granulated Indomethacin is returned to the MP Micro and the process temperature set at 75°C to achieve a product temperature of 40-45°C. The airflow is increased until the product is fluidised. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. The 10%w/w dispersion is then sprayed onto the Indomethacin granules at a rate of 0.2 g/min with an atomising air pressure of 2 bar. Once the desired weight of Opadry II is applied to the granules the pump and the atomising air are stopped and the material is dried until the powder bed reaches a constant temperature. At this point the inlet air temperature is reduced to 25°C and the operation stopped.

[0172] A15%w/w Sureteric dispersion (containing 0.33%w/w simethicone, as an anti-foaming agent) is prepared as follows:

[0173] The necessary quantity of Sureteric powder is accurately weighed out.

[0174] The necessary quantity of water is accurately weighed into the mixing vessel.

[0175] With the propeller in the centre and as close to the bottom of the vessel as possible, the water is stirred to form a vortex without drawing air into the liquid.

[0176] The necessary quantity of anti-foaming emulsion is weighed out and added to the water.

[0177] The Sureteric powder is steadily added to the vortex, whilst maintaining a vigorous vortex.

[0178] The mixer speed is reduced to nearly eliminate the vortex and the dispersion mixed for a further 45 minutes.

[0179] Prior to coating, the dispersion is passed through a 250 micron sieve.

[0180] Residual Opadry II dispersion is removed from the spray nozzle by rapidly flushing through with the 10%w/w dispersion of Sureteric. The precision coater module is washed and then dried by heating at 85°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. The Opadry II coated granules are placed into the precision coater and are fluidised using the same conditions as for the addition of Opadry II. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. At this point the granules are coated with the 10%w/w dispersion of Sureteric at a rate of 1.0g/min. Once a 10 - 20%wt. gain coating is applied, spraying of the Sureteric dispersion is stopped and the material dried until a constant temperature is observed within the powder bed. At this point the airflow temperature is reduced to 25°C and the bulk material removed, allowing it to cool.

Step 3: Overcoating with LustreClear

[0181] A 9% w/w dispersion of LustreClear is prepared as follows:

[0182] The necessary quantity of LustreClear film coating system is accurately weighed out.

[0183] The necessary quantity of water is accurately weighed into the mixing vessel.

[0184] With the propeller in the centre and as close to the bottom of the vessel as possible, the water is stirred to form a vortex without drawing air into the liquid.

[0185] The LustreClear powder is steadily added to the vortex, avoiding powder flotation on the liquid surface.

[0186] The stirrer speed is increased in order to maintain the vortex as required.

[0187] After all the LustreClear is added, the dispersion is then mixed for a further 3 hours.

[0188] The dispersion is then left for a further 2 hours before use.

[0189] Residual Sureteric is removed from the spray nozzle by rapidly flushing through with the 9%w/w dispersion of LustreClear. The precision coater module is washed and then dried by heating at 85°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. The enteric-coated granules are placed into the precision coater and are fluidised using the same conditions as for the addition of Sureteric. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. At this point the granules are coated with the 9%w/w dispersion of LustreClear at a rate of 1.0g/min. Once a coating of 4 – 30%wt. gain is applied, spraying of the LustreClear dispersion is stopped and the material dried until a constant temperature is observed within the powder bed. At this point the airflow temperature is reduced to 25°C and the bulk material removed, allowing it to cool.

Example 3

Controlled-release Clarithromycin

Step 1: Granulation of Clarithromycin

[0190] Prior to commencing granulation of the Clarithromycin, the vessel of the MP Micro is pre-warmed by heating at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 76g of Clarithromycin and 4g of PVP K-30 is added to the vessel and the process temperature set to 70°C. The airflow is then increased until the product is fluidised. Once a constant temperature is achieved within the powder bed, spray granulation of the product is commenced by the introduction of distilled water as the granulation fluid. An atomising pressure of 2 bar is used.

[0191] Once the material is granulated the addition of the granulation fluid is stopped and the powder bulk is dried. The end point of the drying process is indicated by a constant temperature within the powder bed. At this point the temperature of the inlet air is reduced to 25°C and the bulk material removed. Once cooled the material is screened through a 250 micron sieve then air jet sieved to remove particles below 100 microns.

Step 2: Spray coating with combined Eudragit RS/RL-100

[0192] An aqueous dispersion of Eudragit RS/RL-100 is prepared by reconstituting both materials separately as follows:

- The necessary quantity of Eudragit is accurately weighed out, necessary to prepare a 12.5%w/w aqueous dispersion.
- The necessary quantity of water is accurately weighed into the mixing vessel.
- With the propeller in the centre and as close to the bottom of the vessel as possible, the water is stirred to form a vortex without drawing air into the liquid.
- The Eudragit powder is steadily added to the vortex, avoiding powder floatation on the liquid surface.
- The stirrer speed is increased in order to maintain the vortex as required.

- Once all of the Eudragit is added, the mixer speed is reduced to nearly eliminate the vortex. The dispersion is then mixed for a further 120 minutes.
- The dispersion is then diluted further by the addition of 10-25% of a suitable plasticiser (in this case Triethyl Citrate)

[0193] Once the Eudragit RS-100 and RL-100 is prepared, they are mixed at varying ratios (e.g. 1:3, 1:1 and 3:1) to produce the required release profile. With the precision coater module attached the vessel is preheated at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 60g of the granulated Clarithromycin is returned to the MP Micro and the process temperature set at 95°C. The airflow is increased until the product is fluidised. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. The material is then sprayed with the Eudragit RS/RL-100 dispersion to achieve a 6 – 30% wt. gain depending on the desired release profile at a spraying rate of 1.0g/min with an atomising air pressure of 2 bar.

[0194] Once the desired weight of Eudragit coating is added to the granules, the pump and the atomising air are stopped and the material dried until the powder bed reaches a constant temperature. At this point the inlet air temperature is reduced to 25°C and the operation stopped.

Step 3: Overcoating with LustreClear

[0195] A 9% w/w dispersion of LustreClear is prepared as follows:

- The necessary quantity of LustreClear film coating system is accurately weighed out.
- The necessary quantity of water is accurately weighed into the mixing vessel.
- With the propeller in the centre and as close to the bottom of the vessel as possible, the water is stirred to form a vortex without drawing air into the liquid.
- The LustreClear powder is steadily added to the vortex, avoiding powder flotation on the liquid surface.
- The stirrer speed is increased in order to maintain the vortex as required.
- After all the LustreClear is added, the dispersion is then mixed for a further 3 hours.

– The dispersion is then left for a further 2 hours before use.

[0196] Residual Eudragit is removed from the spray nozzle by rapidly flushing through with the 9%w/w dispersion LustreClear. The precision coater module is washed and then dried by heating at 85°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. The Eudragit coated granules are placed into the precision coater and are fluidised using the same conditions as for the addition of Eudragit. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. At this point the granules are coated with the 9%w/w dispersion of LustreClear at a rate of 1.0g/min. Once a coating of 4 – 30%wt. gain is applied spraying of the LustreClear dispersion is stopped and the material dried until a constant temperature is observed within the powder bed. At this point the airflow temperature is reduced to 25°C and the bulk material removed, allowing it to cool.

Example 4

Controlled-release enteric-coated Clarithromycin

Step 1: Granulation of Clarithromycin

[0197] Prior to commencing granulation of the Clarithromycin, the vessel of the MP Micro is pre-warmed by heating at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 76g of Clarithromycin and 4g of PVP K-30 is added to the vessel and the process temperature set to 70°C. The airflow is then increased until the product is fluidised. Once a constant temperature is achieved within the powder bed, spray granulation of the product is commenced by the introduction of distilled water as the granulation fluid. An atomising pressure of 2 bar is used.

[0198] Once the material is granulated the addition of the granulation fluid is stopped and the powder bulk is dried. The end point of the drying process is indicated by a constant temperature within the powder bed. At this point the temperature of the inlet air is reduced to

25°C and the bulk material removed. Once cooled the material is screened through a 250 micron sieve then air jet sieved to remove particles below 100 microns.

Step 2: Spray coating with combined Eudragit RS/RL-100

[0199] An aqueous dispersion of Eudragit RS/RL-100 is prepared by reconstituting both materials separately as follows:

- The necessary quantity of Eudragit is accurately weighed out, necessary to prepare a 12.5%w/w aqueous dispersion.
- The necessary quantity of water is accurately weighed into the mixing vessel.
- With the propeller in the centre and as close to the bottom of the vessel as possible, the water is stirred to form a vortex without drawing air into the liquid.
- The Eudragit powder is steadily added to the vortex, avoiding powder floatation on the liquid surface.
- The stirrer speed is increased in order to maintain the vortex as required.
- Once all of the Eudragit is added, the mixer speed is reduced to nearly eliminate the vortex. The dispersion is then mixed for a further 120 minutes.
- The dispersion is then diluted further by the addition of 10-25% of a suitable plasticiser (in this case Triethyl Citrate)

[0200] Once the Eudragit RS-100 and RL-100 is prepared, they are mixed at varying ratios (e.g. 1:3, 1:1 and 3:1) to produce the required release profile. With the precision coater module attached, the vessel is preheated at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 60g of the granulated Clarithromycin is returned to the MP Micro and the process temperature set at 70°C to achieve a product temperature of 40-45°C. The airflow is increased until the product is fluidised. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. The material is then sprayed with the Eudragit RS/RL-100 dispersion to achieve a 6 – 30% wt. gain depending on the desired release profile at a spraying rate of 1.0g/min with an atomising air pressure of 2 bar.

[0201] Once the desired weight of Eudragit coating is added to the granules the pump and the atomising air are stopped and the material dried until the powder bed reached a constant temperature. At this point the inlet air temperature is reduced to 25°C and the operation stopped.

Step 3: Spray coating with Sureteric

[0202] Before applying the Sureteric coat, a 10% w/w dispersion of Opadry II (white) is applied to the granulated Clarithromycin to a 2% wt. gain. The 10% w/w dispersion of Opadry II is prepared as follows:

- The necessary quantity of Opadry II film coating system is accurately weighed out.
- The necessary quantity of water is accurately weighed into the mixing vessel.
- With the propeller in the centre and as close to the bottom of the vessel as possible, the water is stirred to form a vortex without drawing air into the liquid.
- The Opadry II powder is steadily added to the vortex, avoiding powder flotation on the liquid surface.
- The stirrer speed is increased in order to maintain the vortex as required.
- After all the Opadry II system is added, the mixer speed is reduced to nearly eliminate the vortex. The dispersion is then mixed for a further 45 minutes.

[0203] With the precision coater module attached the vessel is preheated at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 60g of the granulated Clarithromycin is returned to the MP Micro and the process temperature set at 70°C to achieve a product temperature of 40-45°C. The airflow is increased until the product is fluidised. Once the material equilibrated within the vessel, a constant temperature is reached within the powder bed. The 10%w/w dispersion is then sprayed onto the Clrithromycin granules at a rate of 1.0g/min with an atomising air pressure of 2 bar. Once the desired weight of Opadry II is applied to the granules, the pump and the atomising air are stopped and the material dried until the powder bed reached a constant temperature. At this point the inlet air temperature is reduced to 25°C and the operation stopped.

[0204] A 15%w/w Sureteric dispersion (containing 0.33%w/w simethicone, as an anti-foaming agent) is prepared as follows:

- The necessary quantity of Sureteric powder is accurately weighed out.
- The necessary quantity of water is accurately weighed into the mixing vessel.
- With the propeller in the centre and as close to the bottom of the vessel as possible, the water is stirred to form a vortex without drawing air into the liquid.
- The necessary quantity of anti-foaming emulsion is weighed out and added to the water.
- The Sureteric powder is steadily added to the vortex, whilst maintaining a vigorous vortex.
- The mixer speed is reduced to nearly eliminate the vortex and the dispersion is mixed for a further 45 minutes.
- Prior to coating, the dispersion is passed through a 250 micron sieve.

[0205] Residual Opadry II dispersion is removed from the spray nozzle by rapidly flushing through with the 10%w/w dispersion of Sureteric. The precision coater module is washed and then dried by heating at 85°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. The Opadry II coated granules are placed into the precision coater and are fluidised using the same conditions as for the addition of Opadry II. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. At this point the granules are coated with the 10%w/w dispersion of Sureteric at a rate of 1.0g/min. Once a 10 - 20%wt. gain coating is applied, spraying of the Sureteric dispersion is stopped and the material dried until a constant temperature is observed within the powder bed. At this point the airflow temperature is reduced to 25°C and the bulk material removed, allowing it to cool.

Step 4: Overcoating with Aquacoat CPD

[0206] A 20% w/w dispersion of Aquacoat CPD is prepared as follows:

- The necessary quantities of water, Aquacoat CPD and plasticiser (in this case 24%w/w diethyl phthalate) are accurately weighed out.
- With the propeller in the centre and as close to the bottom of the vessel as possible, the diethyl phthalate is steadily added to the Aquacoat CPD and mixed for 30 minutes.

– The water is then slowly added to the mixture and stirred for a further 10 minutes.

[0207] Residual Sureteric dispersion is removed from the spray nozzle by rapidly flushing through with the 20%w/w dispersion of Aquacoat CPD. The precision coater module is washed and then dried by heating at 85°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. The enteric-coated granules are placed into the precision coater and are fluidised using the same conditions as for the addition of Eudragit. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. At this point the granules are coated with the 20%w/w dispersion of Aquacoat CPD at a rate of 1.5g/min. Once a coating of 4 – 30%wt. gain is applied spraying of the Aquacoat CPD dispersion is stopped and the material dried until a constant temperature is observed within the powder bed. At this point the airflow temperature is reduced to 25°C and the bulk material removed, allowing it to cool.

Example 5

Taste-masked Acetaminophen

Step 1: Granulation of Acetaminophen

[0208] Prior to commencing granulation of the Acetaminophen, the vessel of the MP Micro is pre-warmed by heating at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 76g of Acetaminophen and 4g of PVP K-30 is added to the vessel and the process temperature set to 70°C. The airflow is then increased until the product is fluidised. Once a constant temperature is achieved within the powder bed, spray granulation of the product is commenced by the introduction of distilled water as the granulation fluid. An atomising pressure of 2 bar is used.

[0209] Once the material is granulated the addition of the granulation fluid is stopped and the powder bulk is dried. The end point of the drying process is indicated by a constant temperature within the powder bed. At this point the temperature of the inlet air is reduced to 25°C and the bulk material removed. Once cooled the material is screened through a 250 micron sieve and then air jet sieved to remove particles below 100 microns.

Step 2: Spray coating with Surelease

[0210] An aqueous dispersion of Surelease is prepared by diluting to 15%w/w solids (i.e. 60% Surelease dispersion and 40% distilled or deionised water) and stirred using a low shear mixer for approximately 15 minutes. With the precision coater module attached the vessel is preheated at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 60g of the granulated Acetaminophen is returned to the MP Micro and the process temperature set at 70°C to achieve a product temperature of 40-45°C. The airflow is increased until the product is fluidised. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. The material is then sprayed with the Surelease dispersion to achieve approximately a 15 to 30% wt. gain depending on the degree of tastemasking which is required at a spraying rate of 1.0g/min with an atomising air pressure of 2 bar.

[0211] Once the desired weight of Surelease coating is added to the granules, the pump and the atomising air are stopped and the material is dried until the powder bed reaches a constant temperature. At this point the inlet air temperature is reduced to 25°C and the operation stopped.

Step 3: Overcoating with a Polyvinylalcohol (PVA) based coating system

[0212] A 10% w/w dispersion of the PVA based coating system is prepared as follows:

- The necessary quantity of the PVA film coating system is accurately weighed out.
- The necessary quantity of water is accurately weighed into the mixing vessel.
- With the propeller in the centre and as close to the bottom of the vessel as possible, the water is stirred to form a vortex without drawing air into the liquid.
- The PVA film coating system is steadily added to the vortex, avoiding powder flotation on the liquid surface.
- The stirrer speed is increased in order to maintain the vortex as required.
- After all the PVA film coating system is added, the mixer speed is reduced to nearly eliminate the vortex. The dispersion is then mixed for a further 45 minutes.

[0213] Residual Surelease is removed from the spray nozzle by rapidly flushing through with the 10%w/w dispersion of the PVA film coating system. The precision coater module is washed and then dried by heating at 85°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. The Surelease coated granules are placed into the precision coater and are fluidised using the same conditions as for the addition of Surelease. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. At this point the granules are coated with the 10%w/w dispersion of the PVA film coating system at a rate of 1.0g/min. Once a coating of 4 – 30%wt. gain is applied spraying of the PVA film coating system is stopped and the material dried until a constant temperature is observed within the powder bed. At this point the airflow temperature is reduced to 25°C and the bulk material removed, allowing it to cool.

Example 6

Taste-masked Verapamil Hydrochloride

Step 1: Granulation of Verapamil

[0214] Prior to commencing granulation of the Verapamil, the vessel of the MP Micro is pre-warmed by heating at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 76g of Verapamil and 4g of PVP K-30 is added to the vessel and the process temperature set to 70°C. The airflow is then increased until the product is fluidised. Once a constant temperature is achieved within the powder bed, spray granulation of the product is commenced by the introduction of distilled water as the granulation fluid. An atomising pressure of 2 bar is used.

[0215] Once the material is granulated, the addition of the granulation fluid is stopped and the powder bulk is dried. The end point of the drying process is indicated by a constant temperature within the powder bed. At this point the temperature of the inlet air is reduced to 25°C and the bulk material removed. Once cooled the material is screened through a 250 micron sieve then air jet sieved to remove particles below 100 microns.

Step 2: Spray coating with Eudragit RD-100

[0216] An aqueous dispersion of Eudragit RD-100 is prepared as follows:

- The necessary quantity of Eudragit RD-100 to prepare a 13%w/w dispersion is accurately weighed out.
- The necessary quantity of water is accurately weighed into the mixing vessel and 0.003%w/w polysorbate 80 added to it as a plasticiser.
- With the propeller in the centre and as close to the bottom of the vessel as possible, the water is stirred to form a vortex without drawing air into the liquid.
- The Eudragit RD-100 powder is steadily added to the vortex, avoiding powder flotation on the liquid surface.
- The stirrer speed is increased in order to maintain the vortex as required.
- Once all of the Eudragit is added, the mixer speed is reduced to nearly eliminate the vortex. The dispersion is then mixed for a further 30 minutes.
- The dispersion is then screened through a 0.4mm mesh prior to use.

[0217] With the precision coater module attached the vessel is preheated at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 60g of the granulated Verapamil is returned to the MP Micro and the process temperature set at 95°C. The airflow is increased until the product is fluidised. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. The material is then sprayed with the Eudragit RD-100 dispersion to achieve approximately a 10 - 15% wt. gain depending on the degree of tastemasking which is required at a spraying rate of 1.0g/min with an atomising air pressure of 2 bar.

[0218] Once the desired weight of Eudragit RD-100 is added to the granules, the pump and the atomising air are stopped and the material dried until the powder bed reaches a constant temperature. At this point the inlet air temperature is reduced to 25°C and the operation stopped.

Step 3: Overcoating with neutralised Carbopol 971

[0219] A 0.5%w/w aqueous dispersion of neutralised Carbopol 971 is prepared as follows

- The necessary quantity of Carbopol 971 to prepare a 0.5% aqueous dispersion is accurately weighed out.
- A 0.0025M dispersion of hydrochloric acid is prepared and the necessary quantity weighed into the mixing vessel.
- With the propeller in the centre and as close to the bottom of the vessel as possible, the 0.0025M dispersion of hydrochloric acid is stirred to form a vortex without drawing air into the liquid.
- The Carbopol 971 powder is steadily added to the vortex, avoiding powder flotation on the liquid surface.
- The stirrer speed is increased in order to maintain the vortex as required.
- Once all of the Carbopol 971 is added dispersion is mixed for a further 15-20 minutes or until the polymer is swelled to produce a smooth product.

[0220] Residual Eudragit RD-100 is removed from the spray nozzle by rapidly flushing through with the dispersion of neutralised Carbopol 971. The precision coater module is washed and then dried by heating at 85°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. The tastemasked granules are placed into the precision coater and are fluidised using the same conditions as for the addition of Eudragit RD-100. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. At this point the granules are coated with the 0.5%w/w dispersion of neutralised Carbopol 971 at a rate of 1.0g/min. Once a coating of 5-30 %wt. gain is applied, spraying of the neutralised Carbopol 971 dispersion is stopped and the material dried until a constant temperature is observed within the powder bed. At this point the airflow temperature is reduced to 25°C and the bulk material removed, allowing it to cool.

Example 7

Taste-masked Amoxycillin

Step 1: Granulation of Amoxycillin

[0221] Prior to commencing granulation of the Amoxycillin, the vessel of the MP Micro is pre-warmed by heating at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 76g of Amoxycillin and 4g of PVP K-30 is added to the vessel and the process temperature set to 50°C. The airflow is then increased until the product is fluidised. Once a constant temperature is achieved within the powder bed, spray granulation of the product is commenced by the introduction of 96% ethanol as the granulation fluid. An atomising pressure of 2 bar is used.

[0222] Once the material is granulated the addition of the granulation fluid is stopped and the powder bulk is dried. The end point of the drying process is indicated by a constant temperature within the powder bed. At this point the temperature of the inlet air is reduced to 25°C and the bulk material removed. Once cooled, the material is screened through a 250 micron sieve and air jet sieved to remove particles below 100 microns.

Step 2: Spray coating with Opadry AMB

[0223] Due to the moisture sensitivity of the Amoxycillin granulation, a moisture barrier film is applied to the material to a 5-30% wt. gain with a 20% w/w dispersion of Opadry AMB, which is prepared as follows:

- The necessary quantity of Opadry AMB is accurately weighed out.
- The necessary quantity of water is accurately weighed into the mixing vessel.
- With the propeller in the centre and as close to the bottom of the vessel as possible, the water is stirred to form a vortex without drawing air into the liquid.
- The Opadry AMB powder is steadily added to the vortex, avoiding powder flotation on the liquid surface.
- The stirrer speed is increased in order to maintain the vortex as required.
- After all the Opadry AMB system is added, the mixer speed is reduced to nearly eliminate the vortex. The dispersion is then mixed for a further 45 minutes.

[0224] With the precision coater module attached the vessel is preheated at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 60g of the granulated Amoxycillin is returned to the MP Micro and the process temperature set at 70°C to achieve a product temperature of 40-45°C. The airflow is increased until the product is fluidised. Once the material equilibrated within the vessel, a constant temperature is reached within the powder bed. The 20%w/w dispersion is then sprayed onto the Amoxycillin granules at a rate of 1.0g/min with an atomising air pressure of 2.5 bar. Once the desired weight of Opadry AMB is applied to the granules, the pump and the atomising air are stopped and the material dried until the powder bed reaches a constant temperature. At this point the inlet air temperature is reduced to 25°C and the operation stopped. Once the moisture barrier coating is applied to the granules it is possible to add the functional tastemasking coat to the Amoxycillin.

Step 2: Overcoating with Surelease

[0225] An aqueous dispersion of Surelease is prepared by diluting to 15%w/w solids (i.e. 60% Surelease dispersion and 40% distilled or deionised water) and stirred using a low shear mixer for approximately 15 minutes. With the precision coater module attached the vessel is preheated at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 60g of the granulated Amoxycillin is returned to the MP Micro and the process temperature set at 70°C to achieve a product temperature of 40-45°C. The airflow is increased until the product is fluidised. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. The material is then sprayed with the Surelease dispersion to achieve approximately a 15-30% wt. gain depending on the degree of tastemasking which is required at a spraying rate of 1.0g/min with an atomising air pressure of 2 bar.

[0226] Once the desired weight of Surelease coating is added to the granules the pump and the atomising air are stopped and the material dried until the powder bed reaches a constant temperature. At this point the inlet air temperature is reduced to 25°C and the operation stopped.

Example 8

Enteric-coated Mesalazine

Step 1: Granulation of Mesalazine

[0227] Prior to commencing granulation of the Mesalazine, the vessel of the MP Micro is pre-warmed by heating at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 76g of Mesalazine and 4g of PVP K-30 is added to the vessel and the process temperature set to 70°C. The airflow is then increased until the product is fluidised. Once a constant temperature is achieved within the powder bed, spray granulation of the product is commenced by the introduction of distilled water as the granulation fluid. An atomising pressure of 2 bar is used.

[0228] Once the material is granulated, the addition of the granulation fluid is stopped and the powder bulk is dried. The end point of the drying process is indicated by a constant temperature within the powder bed. At this point the temperature of the inlet air is reduced to 25°C and the bulk material removed. Once cooled the material is screened through a 250 micron sieve and air jet sieved to remove particles below 100 microns.

Step 2: Spray-coating with Aquacoat CPD

[0229] A 20% w/w dispersion of Aquacoat CPD is prepared as follows:

- The necessary quantities of water, Aquacoat CPD and plasticiser (in this case 24%w/w diethyl phthalate) are accurately weighed out.
- With the propeller in the centre and as close to the bottom of the vessel as possible, the diethyl phthalate is steadily added to the Aquacoat CPD and mixed for 30 minutes.
- The water is then slowly added to the mixture and stirred for a further 10 minutes.

[0230] With the precision coater module attached the vessel is preheated at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 60g of the granulated Mesalazine is returned to the MP Micro and the process temperature set at 70°C to achieve a product temperature of 40-45°C. The airflow is increased until the product is fluidised. Once the material equilibrated within the

vessel, a constant temperature is reached within the powder bed. The 20%w/w dispersion is then sprayed onto the Mesalazine granules at a rate of 1.0g/min with an atomising air pressure of 2.0 bar. Once the desired weight of Aquacoat CPD is applied to the granules, the pump and the atomising air are stopped and the material dried until the powder bed reaches a constant temperature. At this point the inlet air temperature is reduced to 25°C and the operation stopped.

Step 3: Overcoating with Xanthan Gum

[0231] A 5%w/w dispersion of Xanthan Gum is prepared as follows:

- The necessary quantity of Xanthan Gum is accurately weighed out.
- The necessary quantity of water is accurately weighed into the mixing vessel.
- With the propeller in the centre and as close to the bottom of the vessel as possible, the water is stirred to form a vortex without drawing air into the liquid.
- The Xanthan Gum powder is steadily added to the vortex, avoiding powder flotation on the liquid surface.
- The stirrer speed is increased in order to maintain the vortex as required.
- After all the Xanthan Gum system is added, the mixer speed is reduced to nearly eliminate the vortex. The dispersion is then mixed for a further 45 minutes.

[0232] Residual Aquacoat CPD is removed from the spray nozzle by rapidly flushing through with the 5%w/w dispersion of Xanthan Gum. The precision coater module is washed and then dried by heating at 85°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. The enteric coated granules are placed into the precision coater and are fluidised using the same conditions as for the addition of Aquacoat CPD dispersion. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. At this point the granules are coated with the 5%w/w dispersion of Xanthan Gum at a rate of 1.0g/min. Once a coating of 5-30%wt. gain is applied, spraying of the Xanthan gum dispersion is stopped and the material dried until a constant temperature is observed within the powder bed. At this point the airflow temperature is reduced to 25°C and the bulk material removed, allowing it to cool.

Example 9

Controlled-release Sodium Valproate

Step 1: Granulation of Sodium Valproate

[0233] Prior to commencing granulation of the Sodium Valproate, the vessel of the MP Micro is pre-warmed by heating at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 76g of Sodium Valproate and 4g of PVP K-30 is added to the vessel and the process temperature set to 70°C. The airflow is then increased until the product is fluidised. Once a constant temperature is achieved within the powder bed, spray granulation of the product is commenced by the introduction of distilled water as the granulation fluid. An atomising pressure of 2 bar is used. Once the material is granulated the addition of the granulation fluid is stopped and the powder bulk is dried. The end point of the drying process is indicated by a constant temperature within the powder bed. At this point the temperature of the inlet air is reduced to 25°C and the bulk material removed. Once cooled the material is screened through a 250 micron sieve and air jet sieved to remove particles below 100 microns.

Step 2: Spray coating with Surelease

[0234] An aqueous dispersion of Surelease is prepared by diluting to 15%w/w solids (i.e. 60% Surelease dispersion and 40% distilled or deionised water) and stirred using a low shear mixer for approximately 15 minutes. With the precision coater module attached the vessel is preheated at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 60g of the granulated Sodium Valproate is returned to the MP Micro and the process temperature set at 70°C to achieve a product temperature of 40-45°C. The airflow is increased until the product is fluidised. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. The material is then sprayed with the Surelease dispersion to achieve a 6 – 30% wt. gain depending on the desired release profile at a spraying rate of 1.0g/min with an atomising air pressure of 2 bar.

[0235] Once the desired weight of Surelease coating is added to the granules the pump and the atomising air are stopped and the material dried until the powder bed reached a constant temperature. At this point the inlet air temperature is reduced to 25°C and the operation stopped.

Stage 3: Overcoating with Eudragit L30 D-55

[0236] A plasticized 50%w/w dispersion of Eudragit L30 D-55 formulation for spray coating the Sodium Valproate granules is prepared by diluting to 25%w/w solids with between 5 and 15%w/w plasticizer, 0.2% antifoam agent in distilled or deionised water. The dispersion is then stirred using a low shear mixer for approximately 15 minutes. Prior to use, the plasticized dispersion is filtered through a 0.25mm sieve. With the precision coater module attached, the vessel is preheated at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 60g of the granulated Sodium Valproate is returned to the MP Micro and the process temperature set at 95°C. The airflow is increased until the product is fluidised. Once the material is equilibrated within the vessel, a constant temperature is reached within the powder bed. The material is then sprayed with the Eudragit dispersion (which is continuously stirred throughout the spraying procedure) to achieve a 8 – 25% wt. gain depending on the desired degree of mechanical protection which is required at a spraying rate of 1.0g/min with an atomising air pressure of 2 bar.

[0237] Once the desired weight of Eudragit L30 D-55 coating is added to the granules, the pump and the atomising air are stopped and the material dried until the powder bed reached a constant temperature. At this point the inlet air temperature is reduced to 25°C and the operation stopped.

Example 10

Wet-granulated Indomethacin

Step 1: Granulation of Indomethacin

[0238] Prior to commencing granulation of the Indomethacin (pulverized), the vessel of an MP Micro fluid bed dryer (available from Niro Pharma Systems of GEA Niro, Inc.) is pre-warmed by heating at 70°C for 15 minutes with a nominal airflow of 6.0m3/Hr. 96g of Indomethacin and

4g of PVP K-30 is added to the vessel and the process temperature set to 70°C. The airflow is then increased until the product is fluidised. Once a constant temperature is achieved within the powder bed, spray granulation of the product is commenced by the introduction of distilled water as the granulation fluid. An atomising pressure of 2 bar is used.

[0239] Once the material was granulated, the addition of the granulation fluid was stopped and the powder bulk was dried. The end point of the drying process is indicated by a constant temperature within the powder bed. At this point the temperature of the inlet air is reduced to 25°C and the bulk material removed. Once cooled, the material was screened through a 600 micron sieve.

[0241] Dissolution testing was then performed using a United States Pharmacopeia Type IV dissolution apparatus (hereinafter USP Type IV apparatus), configured to recirculate the dissolution media. More specifically, the apparatus was a Sotax CE 70. A flow rate of 32ml/min was used. The drug release was quantified by UV absorbance measured at 318nm. Dissolution studies were performed in a basic dissolution media (45 minutes pH 6.8 Phosphate Buffer (3:1 ratio of 0.1N HCl : 0.2M Na_3PO_4).

[0242] Figure 3 is a graph plotting the dissolution data for the wet-granulated Indomethacin and 4% PVP K-30 with the pH 6.8 phosphate buffer. The corresponding data plotted in this Figure is shown in the following table:

Table 1

% Dissolved			
Time (min)	Cell 1	Cell 2	Cell 3
0	0	0	0
1	34.46	42.04	41.12
3	61.21	64.43	64.7
5	75.16	76.27	77.04
10	89.9	90.23	90.04
15	95.55	96.55	95.01
20	98.62	100.27	97.6
25	100.45	102.71	99.28
30	101.84	104.47	100.46
35	102.86	105.95	101.44
40	103.65	106.94	102.22
45	104.36	107.73	102.97

Example 11

Enteric Coated Melt Granulated Indomethacin Formulation

Step 1: Melt Granulation of Indomethacin

[0243] Using a Mixer-Granulator P1-6 (available from Dionsa Dierks & Soehne GmbH) equipped with a 1 litre jacketed bowl, 180g of indomethacin (pulverized) was equilibrated at 70°C for 10 minutes at a mixer speed of 600rpm. 20g of powdered polyethylene glycol (PEG) 6000 was added to the bowl. The massing time, impeller and chopper speeds were varied to achieve to the required granule size distribution (in this case, 100-400 microns in diameter). Once granulated, the material was cooled by reducing the temperature of the bowl jacket to 25°C whilst mixing at a speed of 100rpm and a chopper speed of 50rpm. The mixing continued until the temperature of the powder bed stabilized to around the temperature of the jacketed bowl.

[0244] Dissolution testing was then performed using the USP Type IV apparatus described above in connection with Example 10. A flow rate of 32ml/min was used. The drug release was quantified by UV absorbance measured at 318nm. Dissolution studies were performed in basic dissolution media (45 minutes pH 6.8 Phosphate Buffer (3:1 ratio of 0.1N HCl : 0.2M Na_3PO_4).

[0245] Figure 4 depicts a graph plotting the dissolution data for the Indomethacin and 10% PEG6000 melt granulation with the pH 6.8 phosphate buffer medium. The corresponding data plotted in this Figure is shown in the following table:

Table 2

	% Dissolved		
Time (min)	Cell 1	Cell 2	Cell 3
0	0	0	0
1	55.91	65.8	63.39
3	77.02	83.75	80.46
5	87.97	92.47	89.44
10	100.51	101.72	99.24
15	106.07	105.08	103.08
20	108.96	106.8	104.98
25	110.37	107.91	106.28
30	112.07	108.71	107.53
35	113.14	109.35	108.32
40	113.96	109.96	108.91
45	114.64	110.39	109.44

[0246] It is evident from this data that melt granulating the Indomethacin with PEG 6000 aids the wetting, and hence, the dissolution of the Indomethacin. Specifically, the melt granulated formulation of Example 11 has consistently faster dissolution than the wet granulated formulation of Example 10.

Step 2: Acryl-eze Enteric Coating of Melt-Granulated Indomethacin and PEG 6000

[0247] An aqueous dispersion containing 20% (w/w) Acryl-eze (available from Colorcon) and 0.5% (w/w) simethicone was prepared in an amount sufficient to apply a 15% weight gain of Acryl-eze solids to the indomethacin melt granulation of step 1 . The MP-Micro fluid bed drier was used with a Precision Coater Module attached. The Precision Coater Module was preheated at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. Approximately 100g of the melt granulated indomethacin of step 1 was loaded into the Precision Coater Module and heated at 60°C at an airflow sufficient to fluidise the melt granulated indomethacin (hereinafter, the "product"). Once a product temperature of 20° – 35°C was achieved, the product was sprayed with the dispersion of Acryl-eze, until a 15% weight gain was achieved. At this point, the pump and atomising air was stopped, and the sprayed product was dried until the product temperature begins to increase. The inlet air temperature was then reduced to 25°C and the drying operation was stopped. Any material which had a diameter greater than 600 microns was removed by sieving.

[0248] Dissolution testing was then performed using the USP Type IV apparatus described above in connection with Example 10. A flow rate of 32ml/min was used. The drug release was quantified by UV absorbance measured at 318nm. Dissolution studies were performed in both acidic dissolution media (0.1N Hydrochloric Acid for 2 hours) and basic dissolution media (45 minutes pH 6.8 Phosphate Buffer (3:1 ratio of 0.1N HCl : 0.2M Na_3PO_4).

[0249] A concern before preparing an enteric coated, melt granulated formulation was that the acid phase drug release would be unacceptably high, due to a mixing of the enteric coating polymer with the PEG 6000 melt binder. It was postulated that if this occurred, there would be a high degree of drug release in the acid phase due to a dilution of the polymer coat. To prevent this, a melt binder was selected that showed an appreciable difference in melting point (which, for PEG 6000, is 60 – 65°C) from the film forming temperature (which, for Acryl-eze, is 25 – 35°C) of the enteric coat polymer. It was believed that the mixing of the two materials would thereby be minimized.

[0250] Figure 5 is a graph plotting the dissolution data for Indomethacin & 10% PEG6000 & 15% Acryl-eze melt granulation prepared in Step 2 with the .1N Hydrochloric Acid medium. The corresponding data plotted in this Figure is shown in the following table:

Table 3

	% Dissolved					
Time (min)	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6
0	0	0	0	0	0	0
30	0.9	0.31	0.39	0.47	0.17	0.36
60	1.04	0.35	0.45	0.54	0.2	0.43
90	1.31	0.39	0.49	0.57	0.25	0.49
120	1.49	0.41	0.53	0.62	0.29	0.53

[0251] It is evident from this data that the enteric coated melt granulated Indomethacin formulation of step 2 does not exhibit a high degree of drug release in the acid phase. To the contrary, less than 1.5 % of the formulation dissolved after 2 hours. As such, this formulation meets the U.S.P. acceptance criteria for "Acid Stage" release of "Delayed-release (Enteric-

coated) Articles" (less than 10% released in 2 hours in 0.1 N hydrochloric acid in each of 6 units (U.S.P. Level A1)).

[0252] Figure 6 is a plot of the dissolution data for the Indomethacin & 10% PEG6000 & 15% Acryleze melt granulation from Step 2 with a pH 6.8 phosphate buffer. The corresponding data plotted in this Figure is shown in the following table:

Table 4

% Dissolved						
Time (min)	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6
0	0	0	0	0	0	0
1	4.97	3.87	3.64	8	7.85	8.16
3	15.54	12.34	11.68	19.13	16.04	17.43
5	25.49	20.08	21.91	31.1	24.63	26.73
10	48.14	37.55	42.88	52.55	40.93	44.06
15	64.99	51.69	54.43	65.13	52.12	56.24
20	75.34	60.83	62.12	72.9	61.78	65.1
25	81.23	66.99	67.36	77.55	69.09	71.12
30	84.62	70.83	71.53	80.95	74.95	75.38
35	86.89	73.62	74.52	83.31	79.1	78.37
40	88.54	75.98	77.06	85.09	82.18	80.62
45	89.67	78.19	79.2	86.58	84.48	82.3

[0253] As illustrated in Figure 6 and Table 4, 78-90 % of the indomethacin was released within 45 minutes. As such, this formulation would also appear likely to meet the U.S.P. "Buffer Stage" release of "Delayed-release (Enteric-coated) Articles". It should be noted that the data does not, in fact pass the Level B1 U.S.P. criteria (80% released within 45 minutes in 6.8 pH buffer in each of 6 units) However, it is believed that the formulation would likely meet the Level B2 U.S.P. criteria (average release at 45 minutes in 6.8 pH buffer for 12 units is at least 75%, with none of the 12 units releasing less than 60% in 45 minutes) and the Level B3 U.S.P. criteria (average release at 45 minutes in 6.8 pH buffer for 24 units is at least 75%, with none of the 24 units releasing less than 50% in 45 minutes, and no more than two of the 24 units releasing less than 60% in 45 minutes). It should be noted that the pH 6.8 buffer phase drug release for this formulation is faster than the corresponding pH 6.8 buffer release in the formulations of Examples 12-15.

Example 12

Melt-granulated Sureteric Coated Indomethacin Formulation

Step 1: Sureteric Coating of Indomethacin

[0254] An aqueous dispersion containing 15% (w/w) Sureteric (available from Colorcon) and 0.33% (w/w) simethicone was prepared in an amount sufficient to apply a 15% weight gain of Sureteric solids to 100 grams of indomethacin . The MP-Micro fluid bed drier with the Precision Coater Module attached was used. The Precision Coater Module was preheated at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. The indomethacin (pulverized) was loaded into the Precision Coater Module and heated at 60°C at an airflow sufficient to fluidise the indomethacin (hereinafter, the "product"). Once a product temperature of 40 – 45°C was achieved, the product was sprayed with the dispersion of Sureteric, until a 15% weight gain was achieved. At this point, the pump and atomising air was stopped, and the sprayed product was dried until the product temperature begins to increase. The inlet air temperature was then reduced to 25°C and the drying operation was stopped. Any material having a diameter greater than 600 microns was removed by sieving.

Step 2 Melt Granulation

[0255] Using the Diosna Mixer-Granulator P1-6 equipped with a 1 litre jacketed bowl, 100g of the material of step 1 was equilibrated at 70°C for 10 minutes at a mixer speed of 600rpm. 20g of powdered polyethylene glycol (PEG) 6000 was added to the bowl. The massing time, impeller and chopper speeds were varied to achieve the required granule size distribution (in this case, 100-400 microns in diameter). Once granulated, the material was cooled by reducing the temperature of the bowl jacket to 25°C whilst mixing at a speed of 100rpm and a chopper speed of 50rpm. The mixing continued until the temperature of the powder bed stabilized to around the temperature of the jacketed bowl.

[0256] Dissolution testing was then performed using the USP Type IV apparatus described above in connection with Example 10. A flow rate of 32ml/min was used. The drug release was quantified by UV absorbance measured at 318nm. Dissolution studies were performed in both

acidic dissolution media (0.1N Hydrochloric Acid for 2 hours) and basic dissolution media (45 minutes pH 6.8 Phosphate Buffer (3:1 ratio of 0.1N HCl : 0.2M Na_3PO_4).

[0257] Figure 7 is a plot of the the dissolution data of the Melt-granulated Sureteric Coated Indomethacin Formulation (Indomethacin and 15% Sureteric and 10% PEG6000) in .1 N Hydrochloric acid. The corresponding data plotted in this Figure is shown in the following table:

Table 5

	% Dissolved					
Time (min)	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6
0	0	0	0	0	0	0
30	3.18	3.74	4.47	4.14	4.04	2.58
60	4.75	5.41	6.49	5.8	6	4.13
90	5.81	6.52	7.65	6.84	7.03	5.05
120	6.57	7.31	8.37	7.59	7.64	5.76

[0258] It is evident from the acid phase release shown in Figure 7 and Table 5 that Sureteric-coated indomethacin can be melt granulated with PEG6000 without adversely affecting the integrity of the polymer coat. Moreover, the formulation meets the U.S.P. acceptance criteria for "Acid Stage" release of "Delayed-release (Enteric-coated) Articles" (Level A1: less than 10% released in 2 hours in 0.1 N hydrochloric acid in each of 6 units)

[0259] Figure 8 is a plot of the the dissolution data of the Melt-granulated Sureteric Coated Indomethacin Formulation (Indomethacin and 15% Sureteric and 10% PEG6000) using a pH 6.8 phosphate buffer. The corresponding data plotted in this Figure is shown in the following table:

Table 6

% Dissolved						
Time (min)	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6
0	0	0	0	0	0	0
1	13.15	14.8	18.27	18.68	19.35	14.02
3	27.14	27.59	32.03	31.92	30.51	23.47
5	35.82	36.15	40.53	40.26	37.8	30.49
10	48.9	49.8	53.32	53.07	48.2	42.78
15	56.46	57.52	60.46	60.91	53.41	50.6
20	61.4	62.35	65.16	66.64	56.42	56.12
25	64.94	65.72	68.46	71.05	58.62	60.22
30	67.58	68.18	71.11	74.51	60.48	63.25
35	69.62	70.25	73.2	77.17	61.97	65.67
40	71.33	71.78	75.08	79.38	63.24	67.64
45	72.81	73.12	76.71	81.28	64.45	69.24

[0260] As shown, the total buffer-phase drug release for melt granulated Sureteric-coated indomethacin is slower than the Acryl-eze coated melt granulated indomethacin of Example 11. In particular, only one of the six cells reached 80% drug-release in 45 minutes, with an average 45 minute release of 72.93%. It is believed that the slow release may be attributed either to the increased payload on the granules or a deleterious affect on the polymer coat due to the melt granulation process.

Example 13

Indomethacin Wet Granulation with a 15% Sureteric Enteric Coat

Step 1: Wet Granulation of Indomethacin

[0261] Prior to commencing granulation of the Indomethacin (pulverized), the vessel of the MP Micro was pre-warmed by heating at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. 96g of Indomethacin and 4g of PVP K-30 was added to the vessel and the process temperature set to 70°C. The airflow is then increased until the product is fluidised. Once a constant temperature was achieved within the powder bed, spray granulation of the product was commenced by the introduction of distilled water as the granulation fluid. An atomising pressure of 2 bar was used. Once the material was granulated, the addition of the granulation fluid was stopped and the powder bulk was dried. The end point of the drying process was indicated by a constant temperature within the powder bed. At this point the temperature of the inlet air was

reduced to 25°C and the bulk material removed. Once cooled, the material was screened through a 600 micron sieve.

Step 2: Spray Coating of Wet-Granulated Indomethacin

[0262] An aqueous dispersion containing 15% (w/w) Sureteric (available from Colorcon) and 0.33% (w/w) simethicone was prepared in an amount sufficient to apply a 15% weight gain of Sureteric solids to 100 grams of indomethacin . The MP-Micro fluid bed drier with the Precision Coater Module attached was used. The Precision Coater Module was preheated at 70°C for 15 minutes with a nominal airflow of 6.0m3/Hr. The indomethacin-PVP granulation was loaded into the Precision Coater Module and heated at 60°C at an airflow sufficient to fluidise the indomethacin-PVP granulation (hereinafter, the "product"). Once a product temperature of 40 - 45°C was achieved, the product was sprayed with the dispersion of Sureteric, until a 15% weight gain was achieved. At this point, the pump and atomising air was stopped, and the sprayed product was dried until the product temperature begins to increase. The inlet air temperature was then reduced to 25°C and the drying operation was stopped. Any material having a diameter greater than 600 microns was removed by sieving.

[0263] Dissolution testing was then performed using the USP Type IV apparatus described above in connection with Example 10. A flow rate of 32ml/min was used. The drug release was quantified by UV absorbance measured at 318nm. Dissolution studies were performed in both acidic dissolution media (0.1N Hydrochloric Acid for 2 hours) and basic dissolution media (45 minutes pH 6.8 Phosphate Buffer (3:1 ratio of 0.1N HCl : 0.2M Na_3PO_4).

[0264] Figure 9 is a plot of the dissolution data of the Indomethacin Granulation with a 15% Sureteric Enteric Coat (Indomethacin and 15% Sureteric) in .1 N Hydrochloric acid. The corresponding data plotted in this Figure is shown in the following table:

Table 7

%Dissolved						
Time (min)	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6
0	0	0	0	0	0	0
30	4.67	6.21	7.24	4.28	4.64	5.48
60	6.53	8.1	7.88	5.93	6.28	7.19
90	7.48	8.93	8.71	6.72	7.1	7.96
120	8.12	9.38	9.27	7.31	7.58	8.63

[0265] As such, this formulation meets the U.S.P. acceptance criteria for "Acid Stage" release of "Delayed-release (Enteric-coated) Articles" (less than 10% released in 2 hours in 0.1 N hydrochloric acid in each of 6 units (U.S.P. Level A1)).

[0266] Figure 10 is a plot of the the dissolution data of Indomethacin Granulation with a 15% Sureteric Enteric Coat in a pH 6.8 phosphate buffer. The corresponding data plotted in this Figure is shown in the following table:

Table 8

% Dissolved						
Time (min)	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6
0	0	0	0	0	0	0
1	26.02	29.74	23.48	21.58	42.41	31.79
3	42.35	46.91	36.02	33.41	50.45	44.38
5	51.39	56.98	43.54	44.72	56.17	52.24
7	57.32	63.61	48.53	51.86	60.18	57.39
9	61.46	68.38	52.49	56.66	64.53	61.23
11	64.57	71.84	55.65	60.1	66.63	64.04
13	66.93	74.55	58.21	62.75	68.89	66.3
15	68.76	76.62	60.46	64.87	70.33	68.06
20	72.11	80.22	64.02	68.89	73.78	71.26
25	74.27	82.39	66.3	71.89	75.88	73.36
30	75.82	83.88	68.02	74.11	77.35	74.88
35	77.03	85.01	69.09	75.79	78.63	76.06
40	78.02	85.97	69.87	77.24	79.67	77.04
45	78.87	86.61	70.41	78.48	80.68	77.84

[0267] As illustrated by the data in Figure 10 and Table 8, this formulation would also appear likely to meet the U.S.P. "Buffer Stage" release of "Delayed-release (Enteric-coated) Articles". It should be noted that the data does not, in fact pass the Level B1 U.S.P. criteria (80% released

within 45 minutes in 6.8 pH buffer in each of 6 units) However, it is believed that the formulation would likely meet the Level B2 U.S.P. criteria (average release at 45 minutes in 6.8 pH buffer for 12 units is at least 75%, with none of the 12 units releasing less than 60% in 45 minutes) and the Level B3 U.S.P. criteria (average release at 45 minutes in 6.8 pH buffer for 24 units is at least 75%, with none of the 24 units releasing less than 50% in 45 minutes, and no more than two of the 24 units releasing less than 60% in 45 minutes).

Example 14

Sureteric and LustreClear Coated Indomethacin

Steps 1 and 2: Sureteric Coating of Indomethacin

[0268] Indomethacin (pulverized) was coated with Sureteric in the same manner as described in steps 1 and 2 of Example 13.

Step 3: Overcoating with LustreClear

[0269] An aqueous dispersion containing 9 % (w/w) LustreClear (available from FMC Biopolymer) was prepared in an amount sufficient to apply a 10% weight gain of LustreClear solids to the sureteric coated indomethacin of steps 1 and 2. The MP-Micro fluid bed drier with the Precision Coater Module attached was used. The Precision Coater Module was preheated at 70°C for 15 minutes with a nominal airflow of 6.0m^3/Hr. The Sureteric Coated Indomethacin was loaded into the Precision Coater Module and heated at 60°C at an airflow sufficient to fluidise the indomethacin (hereinafter, the "product"). Once a product temperature of 40 – 45°C was achieved, the product was sprayed with the dispersion of LustreClear, until a 10% weight gain was achieved. At this point, the pump and atomising air was stopped, and the sprayed product was dried until the product temperature began to increase. The inlet air temperature was then reduced to 25°C and the drying operation was stopped. Any material having a diameter greater than 600 microns was removed by sieving.

[0270] Dissolution testing was then performed using the USP Type IV apparatus described above in connection with Example 10. A flow rate of 32ml/min was used. The drug release was

quantified by UV absorbance measured at 318nm. Dissolution studies were performed in both acidic dissolution media (0.1N Hydrochloric Acid for 2 hours) and basic dissolution media (45 minutes pH 6.8 Phosphate Buffer (3:1 ratio of 0.1 N HCl : 0.2M Na_3PO_4).

[0271] Figure 11 is a plot of the dissolution data for the Indomethacin and 15% Sureteric with 10% LustreClear in .1N Hydrochloric Acid. The corresponding data plotted in this Figure is shown in the following table:

Table 9

% Dissolved						
Time (min)	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6
0	0	0	0	0	0	0
30	2.17	3.22	3.75	3.9	3.01	2.91
60	2.49	4.91	5.39	5.47	4.15	4.19
90	3.21	5.65	6.14	6.21	4.86	4.89
120	3.94	6.39	6.82	6.98	5.32	5.36

[0272] It should be noted that the acid-phase drug release of Figure 11 and Table 9 shows more variability than in the sureteric coated melt-granulation of Example 12, Figure 7 and Table 5. This suggests that the coating of the PEG6000 of Example 12 may aid the wetting of the particles and hence result in a more reproducible dissolution profile in vitro.

[0273] Figure 12 is a plot of the dissolution data for Indomethacin and 15% Sureteric with 10% LustreClear in the pH 6.8 phosphate buffer. The corresponding data plotted in this Figure is shown in the following table:

Table 10

% Dissolved						
Time (min)	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6
0	0	0	0	0	0	0
1	23.11	30.34	26.24	32.83	31.27	31
3	33.2	40.65	37.14	44.71	42.09	40.67
5	38.95	46.5	42.72	50.98	47.86	46.15
7	42.85	50.75	46.72	55.45	52.15	50.35
9	45.83	54.12	49.69	58.93	55.53	53.72
11	48.12	56.88	52.01	61.69	58.18	55.95
13	50.05	59.09	54	64.05	60.52	58.15
15	51.61	60.94	55.58	66.14	62.5	60.07
20	54.69	64.7	58.72	70.38	66.43	64.41
25	56.88	67.7	61.01	73.67	69.38	67.24
30	58.48	70.02	62.8	76.39	71.62	69.61
35	59.81	71.93	64.28	78.63	73.38	71.19
40	60.93	73.54	65.55	80.64	74.86	72.71
45	61.88	75.01	66.7	82.37	76.17	73.88

[0274] The buffer-phase dissolution profile for this formulation is slow in that only one of the six cells reached 80% drug-release in 45 minutes, with an average 45 minute release of 72.67%. This formulation shows a similar profile to the PEG 6000 melt-granulated, Sureteric-coated indomethacin of Example 12 and Figure 8.

Example 15

Lab Scale melt granulation of Indomethacin and PEG 6000

[0275] The formulation was prepared in the same manner as Example 11, step 1, except that the indomethacin (pulverized) and PEG 600 were mixed in a beaker on a hot-plate using an overhead stirrer, rather than in the Diosna Mixer-Granulator P1-6.

Example 16

[0276] A particle size distribution for the formulations of Examples 10, 11 (steps 1 & 2), and Example 11 (step 1) is shown in Figure 13. The data was generated by laser diffraction of particles suspended in an airstream using a Malvern Mastersizer 2000. Referring to Figure 13,

it is shown that the formulation of Example 11 (steps 1 and 2) has the overall largest particle sizes (almost 100% of particles are at least 60 microns), followed the formulation of Example 11 (step 1, only), followed by the formulation of Example 10.

[0277] A Twin Stage Impinger Apparatus (glass with a 12.8 mm jet) was used to determine the fine particle fraction of the formulations of Examples 10, 11(steps 1 & 2), 11 (step 1 only), 14, and 15, with the following results:

Material	Average %Fine Particle Fraction at 60l/min (n=5)
1) Raw indomethacin (pulverized)	3.89
2) Indomethacin (pulverized) & 4% PVP K-30 (Example 10)	0.32
3) Indomethacin (pulverized) & 10% PEG 6000 (Example 15)	0.14
4) Indomethacin (pulverized) & 10% PEG 6000 (Exampe 11, step 1)	0.04
5) Indomethacin (pulverized) & 10% PEG 6000 & 15% Acryl-eze (Example 11, steps 1 and 2)	0.05
6) Indomethacin (pulverized) & 15% Sureteric & 10% LustreClear (Example 14)	0.09

[0278] This fine particle fraction data is consistent with the particle size distribution data of Figure 13 in that the % Fine Particle Fraction is lowest for Example 11 (steps 1& 2) and highest for Example 10. Example 14 exhibited a fine particle fraction which was lower than Example 14, but higher than Example 11. The formulation of Example 15 had a fine particle fraction which was lower than Example 10, but higher than Examples 11 and 14. This illustrates that high shear mixing (e.g., with the Dionsna Mixer-Granulator P1-6) produces denser particles having a smaller fine particle fraction than simple mixing in a beaker with an overhead stirrer.

We Claim:

1. A drug formulation for gastrointestinal deposition comprising a non-compressed free flowing plurality of particles comprising a core comprising a drug and a pharmaceutically acceptable excipient, said core overcoated with a functional coating, said drug particles having a mean diameter of greater than 10 μm to about 1 mm, said particles comprising at least about 40% drug.

2. The drug formulation of claim 1 wherein said core comprises drug coated with said excipient and said functional coat overcoats the excipient coat.

3. The drug formulation of claim 1 wherein said core comprises a drug interdispersed in said excipient.

4. The formulation of claim 3 wherein said drug and said excipient are wet granulated.

5. The formulation of claim 3 wherein said drug and said excipient are melt granulated.

6. The formulation of claim 3 wherein said drug and a first portion of said excipient are wet granulated and the resultant wet granulated particles are melt granulated with a second portion of said excipient.

7. The formulation of claim 6 wherein said first portion of excipient and said second portion of excipient comprise the same material.

8. The formulation of claim 6 wherein said first portion of excipient and said second portion of excipient comprise different materials.

9. The formulation of claim 1 wherein said functional coated particles are melt granulated with a pharmaceutically acceptable excipient.

10. The formulation of claim 5 wherein a difference between a film forming temperature of the melt granulating excipient and the film forming temperature of the functional coat is more than 15 degrees C.

11. The formulation of claim 10 wherein the difference between a film forming temperature of a melt granulating excipient and the film forming temperature of a functional coat is more than 20 degrees C.

12. The formulation of claim 11 wherein a difference between a film forming temperature of the melt granulating excipient and a film forming temperature of the functional coat is more than 25 degrees C.

13. The formulation of claim 5 wherein the melt granulating excipient is selected from the group consisting of beeswax, white wax, emulsifying wax, hydrogenated vegetable oil, cetyl alcohol, stearyl alcohol, stearic acid; esters of wax acids; propylene glycol monostearate, glyceryl monostearate; carnauba wax, glyceryl palmitostearate, glyceryl behenate, polyethylene glycol, and a combination thereof.

14. The drug formulation of claims 1-3 wherein said excipient provides a controlled release of the drug upon gastrointestinal deposition.

15. The drug formulation of claim 14 wherein said excipient provides a controlled release of the drug upon gastrointestinal deposition to provide a therapeutic effect for at least 12 hours after oral administration.

16. The drug formulation of claim 14 wherein said excipient provides a controlled release of the drug upon gastrointestinal deposition to provide a therapeutic effect for at least 24 hours after oral administration.

17. The drug formulation of claim 1 wherein said excipient provides a delayed release of the drug upon gastrointestinal deposition.

18. The drug formulation of claim 17 wherein said excipient provides a delayed release of the drug upon gastrointestinal deposition to effect intestinal absorption.

19. The drug formulation of claims 1-3 wherein said excipient provides tastemasking.

20. The drug formulation of claims 1-3 wherein said excipient comprises a salivary stimulant.

21. The drug formulation of claim 2 wherein said excipient provides a moisture barrier.

22. The drug formulation of claim 1 wherein said excipient provides a texture modifier.

23. The drug formulation of claims 1-3 wherein said functional coating provides a controlled release of the drug upon gastrointestinal deposition.

24. The drug formulation of claim 12 wherein said functional coating provides a controlled release of the drug upon gastrointestinal deposition to provide a therapeutic effect for at least 12 hours after oral administration.

25. The drug formulation of claim 12 wherein said functional coating provides a controlled release of the drug upon gastrointestinal deposition to provide a therapeutic effect for at least 24 hours after oral administration.

26. The drug formulation of claim 1 wherein said functional coating provides a delayed release of the drug upon gastrointestinal deposition.

27. The drug formulation of claim 26 wherein said functional coating provides a delayed release of the drug upon gastrointestinal deposition to effect intestinal absorption.

28. The drug formulation of claims 1-3 wherein said functional coating provides tastemasking.

29. The drug formulation of claims 1-3 wherein said functional coating comprises a salivary stimulant.

30. The drug formulation of claim 1 wherein said functional coating provides a moisture barrier.

31. The drug formulation of claim 1 wherein said functional coating provides a texture modifier.

32. The drug formulation of claim 1 wherein said functional coating minimizes asperities on the surface of said particles.

33. The drug formulation of claim 1 wherein said functional coating is resistant to chipping.

34. The drug formulation of claim 1 wherein said functional coating provides pliability to said particles.

35. The drug formulation of claim 1 wherein said drug particles have a mean diameter of greater than about 50 μm.

36. The drug formulation of claim 1 wherein greater than 90% of said particles have a diameter of greater than about 10 μm.

37. The drug formulation of claim 1 wherein greater than 95% of said particles have a diameter of greater than about 10 μm.

38. The drug formulation of claim 1 wherein greater than 99% of said particles have a diameter of greater than about 10 μm.

39. The drug formulation of claim 1 wherein greater than 90% of said particles have a diameter of greater than about 50 μm.

40. The drug formulation of claim 1 wherein greater than 95% of said particles have a diameter of greater than about 50 μm.

41. The drug formulation of claim 1 wherein greater than 99% of said particles have a diameter of greater than about 50 μm.

42. The drug formulation of claims 14 and 23 wherein said controlled release excipient is a hydrophobic material.

43. The drug formulation of claim 42 wherein said hydrophobic material is selected from the group consisting of an acrylic polymer, a cellulosic material, shellac, zein and mixtures thereof.

44. The drug formulation of claim 42 wherein said hydrophobic material is an acrylic polymer.

45. The drug formulation of claim 44 wherein said acrylic polymer is selected from the group consisting of acrylic acid and methacrylic acid copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, methyl methacrylate, copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, methyl methacrylate copolymers, methyl methacrylate copolymers, methacrylic acid copolymer, aminoalkyl methacrylate copolymer, methacrylic acid copolymers, methyl methacrylate copolymers, poly(acrylic acid), poly(methacrylic acid, methacrylic acid alkylamide copolymer, poly(methyl methacrylate), poly(methacrylic acid) (anhydride), methyl methacrylate, polymethacrylate, methyl methacrylate copolymer, poly(methyl methacrylate), poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), glycidyl methacrylate copolymers and mixtures thereof.

46. The drug formulation of claim 42 wherein said controlled release excipient is a cellulosic material.

47. The drug formulation of claim 46 wherein said cellulosic material is selected from the group consisting of cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate, cellulose acetate butyrate and mixtures thereof.

48. The drug formulation of claims 17 and 26 wherein said delayed release material is an enteric polymer.

49. The drug formulation of claim 37 wherein said enteric polymer is selected from the group consisting of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose and mixtures thereof.

50. The drug formulation of claims 19 and 28 wherein said tastemasking material is selected from the group consisting of water-soluble sweetening agents, water-soluble artificial sweeteners, dipeptide based sweeteners and mixtures thereof.

51. The drug formulation of claim 50 wherein said water-soluble sweetening agent is selected from the group consisting of monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, sugar, maltose, partially hydrolyzed starch, or corn syrup solids and sugar alcohols such as sorbitol, xylitol, or mannitol and mixtures thereof.

52. The drug formulation of claim 50 wherein said water-soluble artificial sweetener is selected from the group consisting of soluble saccharin salts, such as sodium or calcium saccharin salts, cyclamate salts, acesulfam-K, the free acid form of saccharin and mixtures thereof.

53. The drug formulation of claim 50 wherein said dipeptide based sweetener is L-aspartyl L-phenylalanine methyl ester.

54. The drug formulation of claims 20 and 29 wherein said salivary stimulant is selected from the group consisting of citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides thereof, acid salts thereof and combinations thereof.

55. The drug formulation of claims 21 and 30 wherein said moisture barrier material is selected from the group consisting of acacia gum, acrylic acid polymers and copolymers (polyacrylamides, polyacryldextrans, polyalkyl cyanoacrylates, polymethyl methacrylates), agar--agar, agarose, albumin, alginic acid and alginates, carboxyvinyl polymers, cellulose derivatives such as cellulose acetate, polyamides (nylon 6-10, poly (adipyl-L-lysines, polyterephthalamides and poly-(terephthaloyl-L-lysines)), poly-.epsilon.-caprolactam, polydimethylsiloxane, polyesters, poly (ethylene-vinyl acetate), polyglycolic acid, polyactic acid and its copolymers, polyglutamic acid, polylysine, polystyrene, shellac, xanthan gum, anionic polymers of methacrylic acid and methacrylic acid esters, hydroxyalkylcelluloses and mixtures thereof.

56. The drug formulation of claim 55 wherein said hydroxyalkylcellulose is hydroxypropylmethylcellulose.

57. The drug formulation of claims 22 and 31 wherein said texture modifier is selected from the group consisting of acacia gum, acrylic acid polymers and copolymers (polyacrylamides, polyacryldextrans, polyalkyl cyanoacrylates, polymethyl methacrylates), agar--agar, agarose, albumin, alginic acid and alginates, carboxyvinyl polymers, cellulose derivatives such as cellulose acetate, polyamides (nylon 6-10, poly (adipyl-L-lysines, polyterephthalamides and poly-(terephthaloyl-L-lysines)),

poly-epsilon.-caprolactam, polydimethylsiloxane, polyesters, poly (ethylene-vinyl acetate), polyglycolic acid, polyactic acid and its copolymers, polyglutamic acid, polylysine, polystyrene, shellac, xanthan gum, anionic polymers of methacrylic acid and methacrylic acid esters, hydroxyalkylcelluloses and mixtures thereof.

58. The drug formulation of claim 32 wherein said particulates have a mean rugosity of from about 1.0 to about 1.5.

59. The drug formulation of claim 33 wherein said chip resistant coating comprises a material selected from the group consisting of acacia gum, alginic acid and alginates, carboxymethylcellulose, ethylcellulose, gelatine, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, xanthan gum, pectin, tragacanth, microcrystalline cellulose, hydroxyethylcellulose, ethylhydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycols, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid, gum arabic, lactose, starch (wheat, maize, potato and rice starch), sucrose, glucose, mannitol, sorbitol, xylitol, stearic acid, hydrogenated cottonseed oil, hydrogenated castor oil, vinylpyrrolidone-vinyl acetate copolymers, fructose, methylhydroxyethylcellulose, agar-agar, carrageenan, karaya gum, chitosan, starch hydrolysates and mixtures thereof.

60. The drug formulation of claim 34 wherein said pliable coating comprises a plasticizer selected from the group consisting of dibutyl sebacate, diethyl phthalate, triethyl citrate, tibutyl citrate, triacetin and mixtures thereof.

61. A drug delivery system comprising a dosing device comprising a housing and an actuator, said device containing at least one unit dose of a drug formulation according to claims 1-60, said device upon actuation delivering a unit dose of said drug formulation such that an effective dose of said drug cannot be delivered into the lower lung of a human patient.

62. A drug delivery system comprising a multiple unit dosing device comprising a housing and an actuator, said device containing multiple unit doses of a drug formulation according to claims 1-60, said device upon actuation delivering a unit dose of said drug formulation such that an effective dose of said drug cannot be delivered into the lower lung of a human patient.

63. A drug delivery system comprising a multiple unit dosing device comprising a housing and an actuator, said device containing at least one unit dose of a drug formulation comprising a non-compressed free flowing plurality of particles comprising a core comprising a drug and a pharmaceutically acceptable excipient, said core overcoated with a functional coating, said drug particles having a mean diameter of greater than 10 μm to about 1 mm, said device upon actuation delivering a unit dose of said drug formulation such that an effective dose of said drug cannot be delivered into the lower lung of a human patient.

64. The formulation of claim 63 wherein said drug and said excipient are wet granulated.

65. The formulation of claim 63 wherein said drug and said excipient are melt granulated.

66. The formulation of claim 63 wherein said drug and a first portion of said excipient are wet granulated and the resultant wet granulated particles are melt granulated with a second portion of said excipient.

67. The formulation of claim 66 wherein said first portion of excipient and said second portion of excipient comprise the same material.

68. The formulation of claim 66 wherein said first portion of excipient and said second portion of excipient comprise different materials.

69. The formulation of claim 63 wherein said functional coated particles are melt granulated with a pharmaceutically acceptable excipient.

70. The formulation of claim 65 wherein a difference between a film forming temperature of the melt granulating excipient and a film forming temperature of a functional coat is more than 15 degrees C.

71. The formulation of claim 70 wherein a difference between a film forming temperature of a melt granulating excipient and a film forming temperature of the functional coat is more than 20 degrees C.

72. The formulation of claim 71 wherein a difference between a film forming temperature point of the melt granulating excipient and a film forming temperature of the functional coat is more than 25 degrees C.

73. The formulation of claim 65 wherein the melt granulating excipient is selected from the group consisting of beeswax, white wax, emulsifying wax, hydrogenated vegetable oil, cetyl alcohol, stearyl alcohol, stearic acid; esters of wax acids; propylene glycol monostearate, glyceryl monostearate; carnauba wax, glyceryl palmitostearate, glyceryl behenate, polyethylene glycol, and a combination thereof.

74. A method of administering a drug to a human patient for gastrointestinal deposition comprising formulating a drug formulation comprising a non-compressed free flowing plurality of particles comprising a core comprising a drug and a pharmaceutically acceptable excipient, said core overcoated with a functional coating, said drug particles having a mean diameter of greater than 10 μm to about 1 mm, containing said drug formulation in a drug delivery device capable of administering multiple unit doses of said multiparticulates into the oral cavity; administering a unit dose of the multiparticulates to the oral cavity wherein greater than about 80% of the unit dose is deposited in the gastrointestinal tract.

75. A method of preparing a drug delivery system for delivering multiple doses of a drug for gastrointestinal deposition comprising preparing a drug formulation comprising a non-compressed free flowing plurality of particles comprising a core comprising a drug and a pharmaceutically acceptable excipient, said core overcoated with a functional coating, said drug particles having a mean diameter of greater than 10 μm to about 1 mm; and placing multiple unit doses of said drug formulation in a device which meters a single unit dose for delivery.

76. The method of claims 74 and 75 wherein said core comprises drug coated with said excipient and said functional coat overcoats the excipient coat.

77. The method of claims 74 and 75 wherein said core comprises a drug interdispersed in said excipient.

78. The formulation of claim 77 wherein said drug and said excipient are wet granulated.

79. The formulation of claim 77 wherein said drug and said excipient are melt granulated.

80. The formulation of claim 77 wherein said drug and a first portion of said excipient are wet granulated and the resultant wet granulated particles are melt granulated with a second portion of said excipient.

81. The formulation of claim 80 wherein said first portion of excipient and said second portion of excipient comprise the same material.

82. The formulation of claim 80 wherein said first portion of excipient and said second portion of excipient comprise different materials.

83. The formulation of claims 74 and 75 wherein said functional coated particles are melt granulated with a pharmaceutically acceptable excipient.

84. The formulation of claim 79 wherein a difference between a film forming temperature of the melt granulating excipient and a film forming temperature of the functional coat is more than 15 degrees C.

85. The formulation of claim 84 wherein a difference between a film forming temperature of the melt granulating excipient and a film forming temperature of the functional coat is more than 20 degrees C.

86. The formulation of claim 85 wherein a difference between a film forming temperature of the melt granulating excipient and a film forming temperature of the functional coat is more than 25 degrees C.

87. The formulation of claim 79 wherein the melt granulating excipient is selected from the group consisting of beeswax, white wax, emulsifying wax, hydrogenated vegetable oil, cetyl alcohol, stearyl alcohol, stearic acid; esters of wax acids; propylene glycol monostearate, glyceryl monostearate; carnauba wax, glyceryl palmitostearate, glyceryl behenate, polyethylene glycol, and a combination thereof.

88. The method of claims 74-77 wherein said excipient provides a controlled release of the drug upon gastrointestinal deposition.

89. The method of claim 88 wherein said excipient provides a controlled release of the drug upon gastrointestinal deposition to provide a therapeutic effect for at least 12 hours after oral administration.

90. The method of claim 88 wherein said excipient provides a controlled release of the drug upon gastrointestinal deposition to provide a therapeutic effect for at least 24 hours after oral administration.

91. The method of claims 74 and 75 wherein said excipient provides a delayed release of the drug upon gastrointestinal deposition.

92. The method of claim 91 wherein said excipient provides a delayed release of the drug upon gastrointestinal deposition to effect intestinal absorption.

93. The method of claims 74-77 wherein said excipient provides tastemasking.

94. The method of claims 74-77 wherein said excipient comprises a salivary stimulant.

95. The method of claim 76 wherein said excipient provides a moisture barrier.

96. The method of claims 74 and 75 wherein said excipient provides a texture modifier.

97. The method of claims 74-77 wherein said functional coating provides a controlled release of the drug upon gastrointestinal deposition.

98. The method of claim 97 wherein said functional coating provides a controlled release of the drug upon gastrointestinal deposition to provide a therapeutic effect for at least 12 hours after oral administration.

99. The method of claim 97 wherein said functional coating provides a controlled release of the drug upon gastrointestinal deposition to provide a therapeutic effect for at least 24 hours after oral administration.

100. The method of claims 74 and 75 wherein said functional coating provides a delayed release of the drug upon gastrointestinal deposition.

101. The method of claim 100 wherein said functional coating provides a delayed release of the drug upon gastrointestinal deposition to effect intestinal absorption.

102. The method of claims 74-77 wherein said functional coating provides tastemasking.

103. The method of claims 74-77 wherein said functional coating comprises a salivary stimulant.

104. The method of claims 74 and 75 wherein said functional coating provides a moisture barrier.

105. The method of claims 74 and 75 wherein said functional coating provides a texture modifier.

106. The method of claims 74 and 75 wherein said functional coating minimizes asperities on the surface of said particles.

107. The method of claims 74 and 75 wherein said functional coating is resistant to chipping.

108. The method of claims 74 and 75 wherein said functional coating provides pliability to said particles.

109. The system of claims 74 and 75 wherein said drug particles have a mean diameter of greater than about 50 μm.

110. The method of claims 74 and 75 wherein greater than 90% of said particles have a diameter of greater than about 10 μm.

111. The method of claims 74 and 75 wherein greater than 95% of said particles have a diameter of greater than about 10 μm.

112. The method of claims 74 and 75 wherein greater than 99% of said particles have a diameter of greater than about 10 μm.

113. The method of claims 74 and 75 wherein greater than 90% of said particles have a diameter of greater than about 50 μm.

114. The method of claims 74 and 75 wherein greater than 95% of said particles have a diameter of greater than about 50 μm.

115. The method of claims 74 and 75 wherein greater than 99% of said particles have a diameter of greater than about 50 μm.

116. The method of claims 88 and 97 wherein said controlled release excipient is a hydrophobic material.

117. The method of claim 116 wherein said hydrophobic material is selected from the group consisting of an acrylic polymer, a cellulosic material, shellac, zein and mixtures thereof.

118. The method of claim 116 wherein said hydrophobic material is an acrylic polymer.

119. The method of claim 118 wherein said acrylic polymer is selected from the group consisting of acrylic acid and methacrylic acid copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, methyl methacrylate, copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, methyl methacrylate copolymers, methyl methacrylate copolymers, methacrylic acid copolymer, aminoalkyl methacrylate copolymer, methacrylic acid copolymers, methyl methacrylate copolymers, poly(acrylic acid), poly(methacrylic acid, methacrylic acid alkylamide copolymer, poly(methyl methacrylate), poly(methacrylic acid) (anhydride), methyl methacrylate, polymethacrylate, methyl methacrylate copolymer, poly(methyl methacrylate), poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), glycidyl methacrylate copolymers and mixtures thereof.

120. The method of claim 116 wherein said controlled release excipient is a cellulosic material.

121. The method of claim 120 wherein said cellulosic material is selected from the group consisting of cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate, cellulose acetate butyrate and mixtures thereof.

122. The method of claims 91 and 100 wherein said delayed release material is an enteric polymer.

123. The method of claim 122 wherein said enteric polymer is selected from the group consisting of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose and mixtures thereof.

124. The method of claims 93 and 102 wherein said tastemasking material is selected from the group consisting of water-soluble sweetening agents, water-soluble artificial sweeteners, dipeptide based sweeteners and mixtures thereof.

125. The drug formulation of claim 124 wherein said water-soluble sweetening agent is selected from the group consisting of monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, sugar, maltose, partially hydrolyzed starch, or corn syrup solids and sugar alcohols such as sorbitol, xylitol, or mannitol and mixtures thereof.

126. The method of claim 124 wherein said water-soluble artificial sweetener is selected from the group consisting of soluble saccharin salts, such as sodium or calcium saccharin salts, cyclamate salts, acesulfam-K, the free acid form of saccharin and mixtures thereof.

127. The method of claim 124 wherein said dipeptide based sweetener is L-aspartyl L-phenylalanine methyl ester.

128. The method of claims 94 and 103 wherein said salivary stimulant is selected from the group consisting of citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides thereof, acid salts thereof and combinations thereof.

129. The method of claims 95 and 104 wherein said moisture barrier material is selected from the group consisting of acacia gum, acrylic acid polymers and copolymers (polyacrylamides, polyacryldextrans, polyalkyl cyanoacrylates, polymethyl methacrylates), agar--agar, agarose, albumin, alginic acid and alginates, carboxyvinyl polymers, cellulose derivatives such as cellulose acetate, polyamides (nylon 6-10, poly (adipyl-L-lysines, polyterephthalamides and poly-(terephthaloyl-L-lysines)), poly-.epsilon.-caprolactam, polydimethylsiloxane, polyesters, poly (ethylene-vinyl acetate), polyglycolic acid, polyactic acid and its copolymers, polyglutamic acid, polylysine, polystyrene, shellac, xanthan gum, anionic polymers of methacrylic acid and methacrylic acid esters, hydroxyalkylcelluloses and mixtures thereof.

130. The method of claim 129 wherein said hydroxyalkylcellulose is hydroxypropylmethylcellulose.

131. The method of claims 96 and 105 wherein said texture modifier is selected from the group consisting of acacia gum, acrylic acid polymers and copolymers (polyacrylamides, polyacryldextrans, polyalkyl cyanoacrylates, polymethyl methacrylates), agar--agar, agarose, albumin, alginic acid and alginates, carboxyvinyl polymers, cellulose derivatives such as cellulose acetate, polyamides (nylon 6-10, poly (adipyl-L-lysines, polyterephthalamides and poly-(terephthaloyl-L-lysines)), poly-.epsilon.-caprolactam, polydimethylsiloxane, polyesters, poly (ethylene-vinyl acetate), polyglycolic acid, polyactic acid and its copolymers, polyglutamic acid, polylysine, polystyrene, shellac, xanthan gum, anionic polymers of methacrylic acid and methacrylic acid esters, hydroxyalkylcelluloses and mixtures thereof.

132. The method of claim 116 wherein said particulates have a mean rugosity of from about 1.0 to about 1.5.

133. The drug formulation of claim 77 wherein said chip resistant coating comprises a material selected from the group consisting of acacia gum, alginic acid and alginates, carboxymethylcellulose, ethylcellulose, gelatine, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, xanthan gum, pectin, tragacanth, microcrystalline cellulose, hydroxyethylcellulose, ethylhydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycols, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid, gum arabic, lactose, starch (wheat, maize, potato and rice starch), sucrose, glucose, mannitol, sorbitol, xylitol, stearic acid, hydrogenated cottonseed oil, hydrogenated castor oil, vinylpyrrolidone-vinyl acetate copolymers, fructose, methylhydroxyethylcellulose, agar-agar, carrageenan, karaya gum, chitosan, starch hydrolysates and mixtures thereof.

134. The method of claim 108 wherein said pliable coating comprises a plasticizer selected from the group consisting of dibutyl sebacate, diethyl phthalate, triethyl citrate, tibutyl citrate, triacetin and mixtures thereof.

135. A method of preparing a multiparticulate drug formulation for gastrointestinal deposition with minimal potential for surface water coalesence comprising preparing a non-compressed free flowing plurality of particles comprising a core comprising a drug and a pharmaceutically acceptable excipient, and overcoating said core with a coating minimizes water coalesence on the surface of said particles.

136. A method of preparing a multiparticulate drug formulation for gastrointestinal deposition with minimal static charge comprising preparing a non-compressed free flowing plurality of particles comprising a core comprising a drug and a pharmaceutically acceptable excipient, and overcoating said core with a coating which minimizes static charge between said particles.

137. A method of preparing a multiparticulate drug formulation for gastrointestinal deposition comprising preparing a non-compressed free flowing plurality of particles comprising a core comprising a drug and a pharmaceutically acceptable excipient air jet sieving said particles to separate said cores from fine particles; and overcoating said core with a functional coating.

138. A method of preparing a multiparticulate drug formulation with improved weight uniformity for gastrointestinal deposition comprising preparing a non-compressed free flowing plurality of particles comprising a core comprising a drug and a pharmaceutically acceptable excipient; and overcoating said core with a functional coating.

139. A method of preparing a multiparticulate drug formulation for gastrointestinal deposition with minimal change in cohesiveness in response to humidity change comprising preparing a non-compressed free flowing plurality of particles comprising a core comprising a drug and a pharmaceutically acceptable excipient; and overcoating said core with a functional coating such that the cohesiveness of said particles does not substantially change over a humidity gradient from about 10% relative humidity to about 90% relative humidity.

140. The method of claim 137 wherein said fine particles are less than about 50 micrometers.

141. The method of claim 137 wherein said fine particles are less than about 25 micrometers.

142. The method of claim 137 wherein said fine particles are less than about 10 micrometers.

143. The method of claim 137 and 140-142 further comprising filtering said particles prior to air jet sieving to remove particles greater than about 500 micrometers.

144. The method of claim 143 further comprising filtering said particles prior to air jet sieving to remove particles greater than about 750 micrometers.

145. The method of claim 144 further comprising filtering said particles prior to air jet sieving to remove particles greater than about 1 mm.

146. The method of claims 135-139 comprising preparing said particles with an amount of coloring agents which minimizes weakening of the adhesion of the overcoat to the core.

147. The method of claim 146 wherein said coloring agent is selected from the group consisting of a lake, an opacifier or a combination thereof.

148. The method of claim 146 wherein said coloring agent does not comprise a lake.

149. The method of claim 146 wherein said coloring agent does not comprise an opacifier.

150. The method of claim 146 wherein said coloring agent does not comprise a lake or an opacifier.

151. The method of claim 135-139 wherein said overcoat comprises a plasticizer.

152. The method of claim 139 wherein the cohesiveness of said particles does not substantially change over a humidity gradient from about 20% relative humidity to about 80% relative humidity.

153. The method of claim 152 wherein the cohesiveness of said particles does not substantially change over a humidity gradient from about 40% relative humidity to about 60% relative humidity.

154. The method of claim 137 wherein said overcoat comprises a conductive polymer.

155. The method of claims 135-139 wherein said drug particles having a mean diameter of greater than 10 μm to about 1 mm.

156. The method of claim 155 wherein said drug particles having a mean diameter of greater than 50 μm to about 500 μm.

157. The method of claims 135-139 wherein said particles comprise at least about 40%, at least about 50%, at least about 60%, at least about 70% or at least about 80 % drug.

158. The method of claims 135-139 wherein said core comprises drug coated with said excipient and said functional coat overcoats the excipient coat.

159. The method of claims 135-139 wherein said core comprises a drug interdispersed in said excipient.

160. The method of claim 159 wherein said drug and said excipient are wet granulated.

161. The method of claim 159 wherein said drug and said excipient are melt granulated.

162. The method of claim 159 wherein said drug and a first portion of said excipient are wet granulated and the resultant wet granulated particles are melt granulated with a second portion of said excipient.

163. The method of claim 162 wherein said first portion of excipient and said second portion of excipient comprise the same material.

164. The method of claim 162 wherein said first portion of excipient and said second portion of excipient comprise different materials.

165. The method of claims 135-139 wherein said functional coated particles are melt granulated with a pharmaceutically acceptable excipient.

166. The method of claim 161 wherein a difference between a film forming temperature of the melt granulating excipient and a film forming temperature of the functional coat is more than 15 degrees C.

167. The method of claim 166 wherein a difference between a film forming temperature of the melt granulating excipient and a film forming temperature of the functional coat is more than 20 degrees C.

168. The method of claim 166 wherein a difference between a film forming temperature of a melt granulating excipient and a film forming temperature of the functional coat is more than 25 degrees C.

169. The method of claim 161 wherein the melt granulating excipient is selected from the group consisting of beeswax, white wax, emulsifying wax, hydrogenated vegetable oil, cetyl alcohol, stearyl alcohol, stearic acid; esters of wax acids; propylene glycol monostearate, glyceryl monostearate; carnauba wax, glyceryl palmitostearate, glyceryl behenate, polyethylene glycol, and a combination thereof.

170. A multiparticulate formulation obtained according to a process of claims 135-169.

171. A controlled release formulation comprising a drug and a sufficient amount of a lacquer agent to provide a controlled release of the drug.

172. The formulation of claim 171 wherein said lacquer agent is selected from the group consisting of corn oil, cottonseed oil, menhaden oil, pine oil, peanut oil, safflower oil, sesame oil, soybean oil, linseed oil and mixtures thereof.

173. The formulation of claim 171 wherein said lacquer agent is selected from the group consisting of fatty acids of C8-C20 oils which can be saturated, unsaturated, glycerides thereof, and combination thereof.

174. The formulation of claim 171 wherein said lacquer agent is selected from the group consisting of branched or polycarboxylated oils such as linoleic acid, linolenic acid, oleic acid and combinations thereof.

175. The formulation of claim 171 wherein said lacquer agent is selected from the group consisting of caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid, lignoceric acid and combinations thereof.

176. The formulation of claims 171-176 wherein said lacquer agent is at least partially interdispersed with said drug.

177. The formulation of claims 171-176 wherein said lacquer agent is coated onto said drug.

178. The formulation of claims 171-177 wherein said formulation is in multiparticulate form.

179. The formulation of claims 171-177 wherein said formulation is a tablet.

180. The formulation of claims 171-179 further comprising a channeling agent such as polyvinylpyrrolidone, polyethyleneglycols, dextrose, sucrose, mannitol, xylitol, lactose and combinations thereof.

181. The formulation of claims 171-180 further comprising a dispersing agent such as colloidal silicone dioxide, talc, kaolin, silicone dioxide, colloidal calcium carbonate, bentonite, Fuller's earth, magnesium aluminum silicate and mixtures thereof.

182. A method of preparing a multiparticulate drug formulation for gastrointestinal deposition comprising preparing a non-compressed free flowing plurality of particles comprising a drug and air jet sieving said particles to separate fine particles.

183. The method of claim 182 wherein said fine particles are less than about 50 micrometers.

184. The method of claim 182 wherein said fine particles are less than about 25 micrometers.

185. The method of claim 182 wherein said fine particles are less than about 10 micrometers.

186. The method of claims 182-185 further comprising filtering said particles prior to air jet sieving to remove particles greater than about 500 micrometers.

187. The method of claims 182-185 further comprising filtering said particles prior to air jet sieving to remove particles greater than about 750 micrometers.

188. The method of claims 182-185 further comprising filtering said particles prior to air jet sieving to remove particles greater than about 1 mm.

189. The method of claims 182-188 further comprising placing a plurality of said multiparticulates in a dosing device capable of metering a unit dose of said formulation for oral delivery.

190. A composition obtained from a method of claims 182-188.

191. A formulation for gastrointestinal deposition comprising a non-compressed free flowing plurality of particles comprising a core comprising chlorpheniramine or a salt thereof and a pharmaceutically acceptable excipient, said core overcoated with a functional coating, said particles having a mean diameter of greater than 10 μm to about 1 mm.

FIG. 1

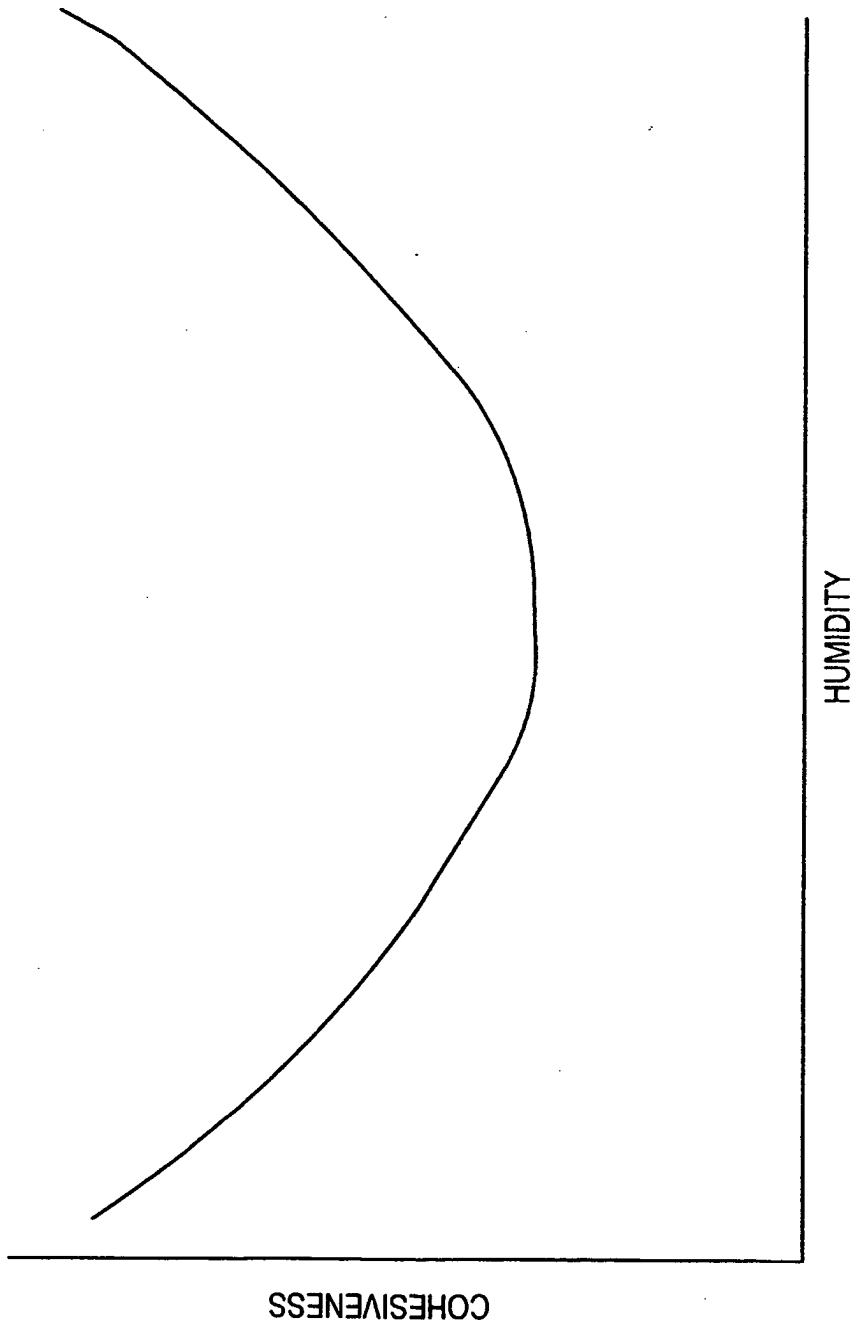


FIG. 2

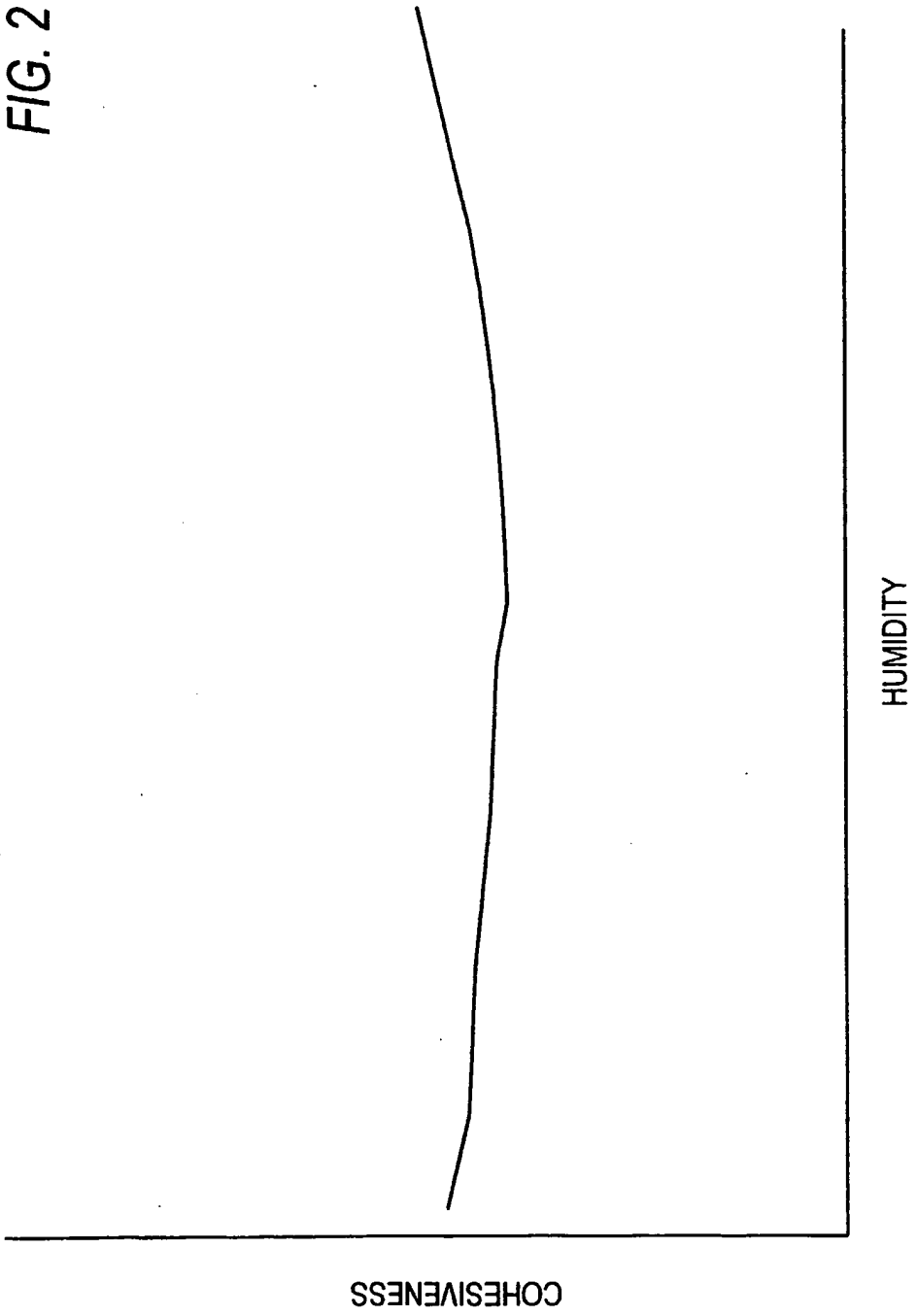


FIG. 3

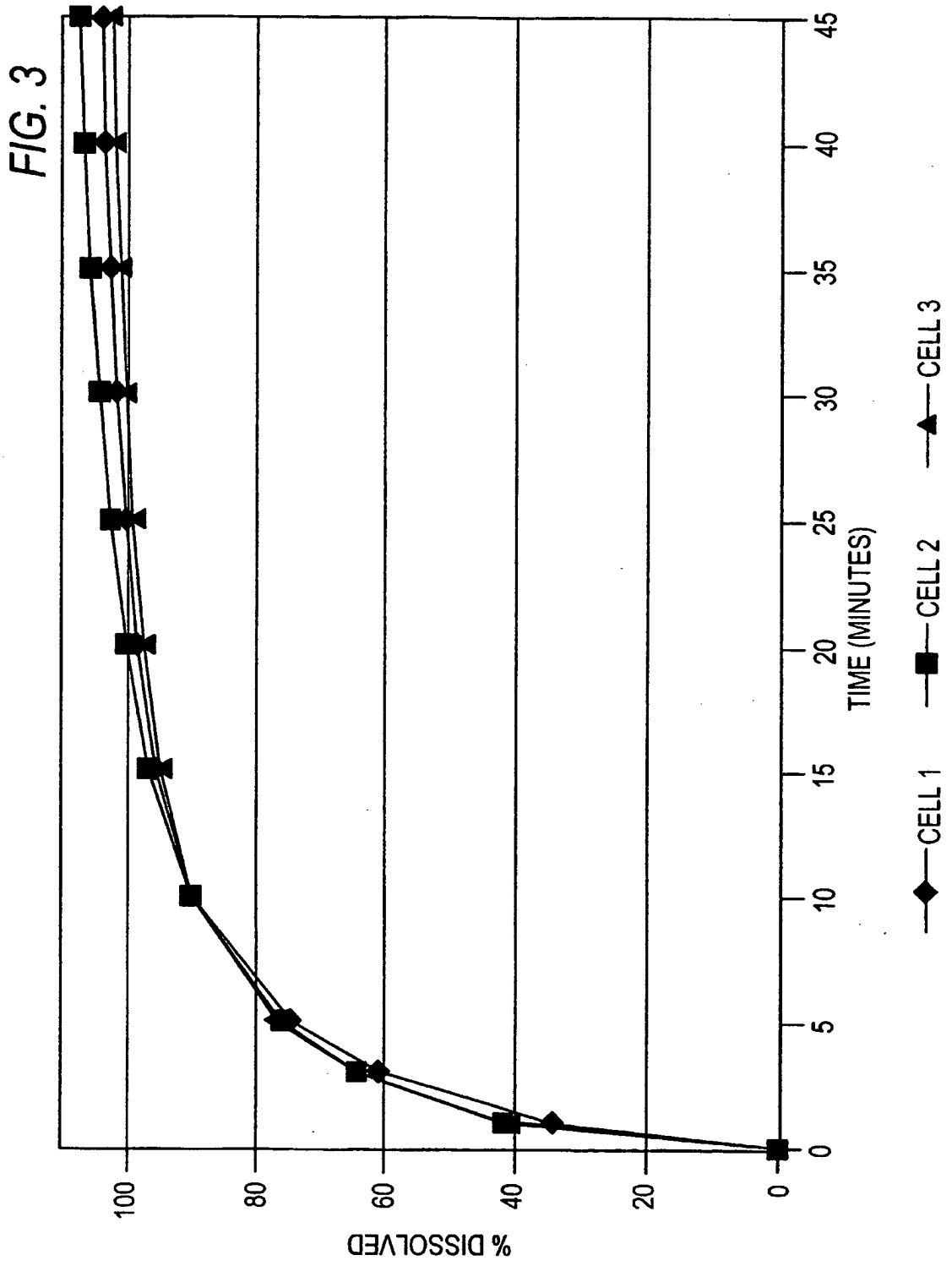


FIG. 4

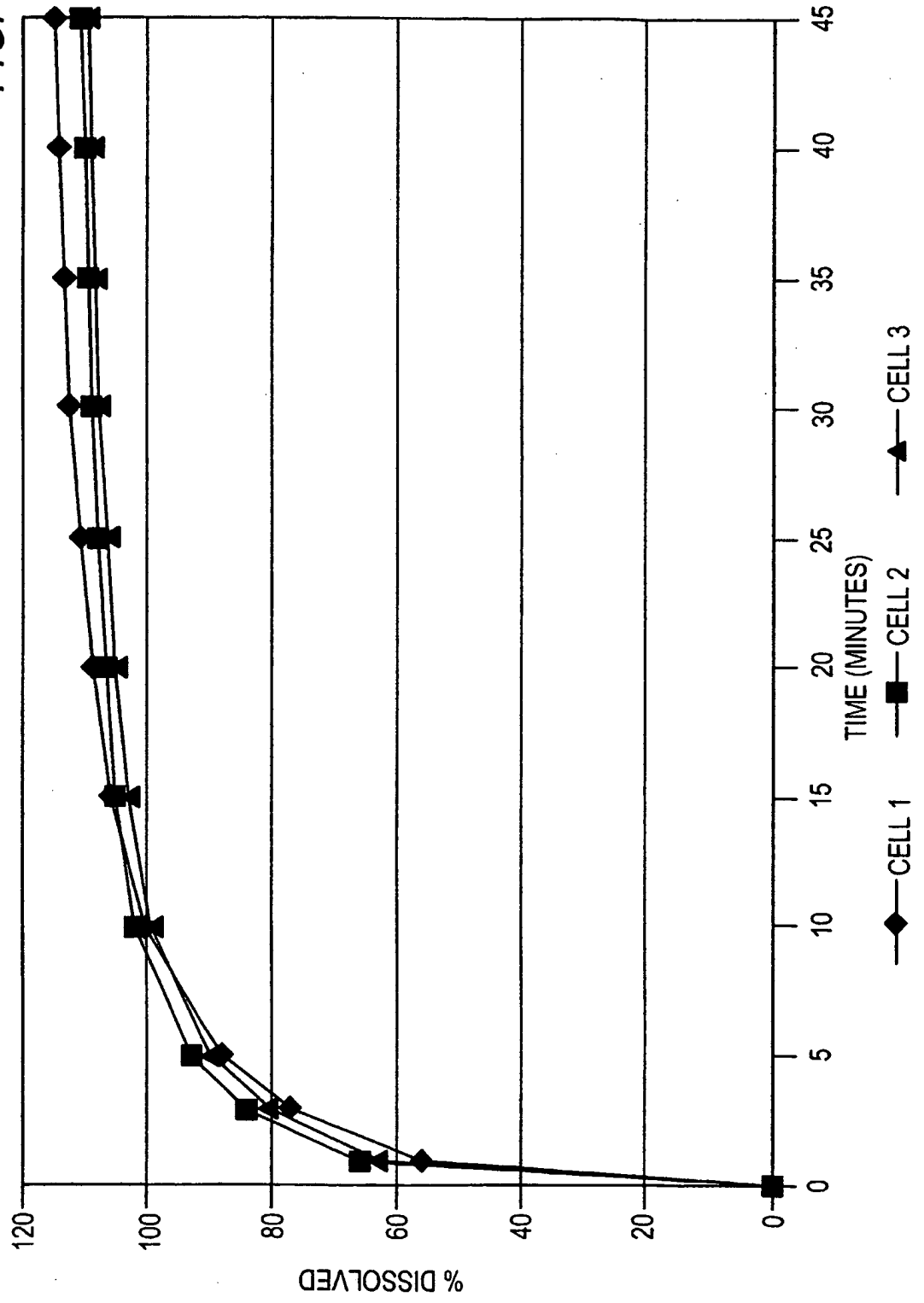


FIG. 5

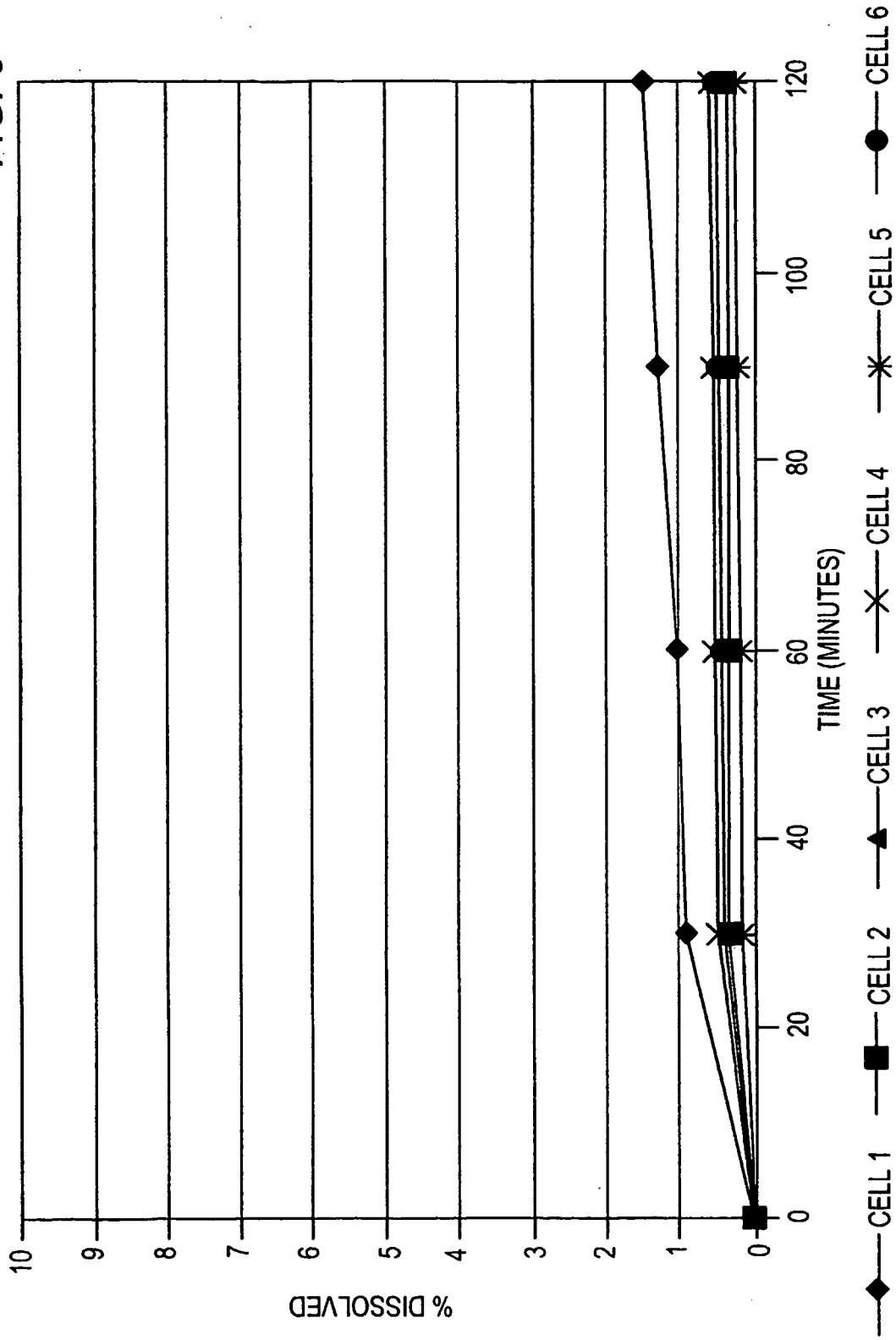


FIG. 6

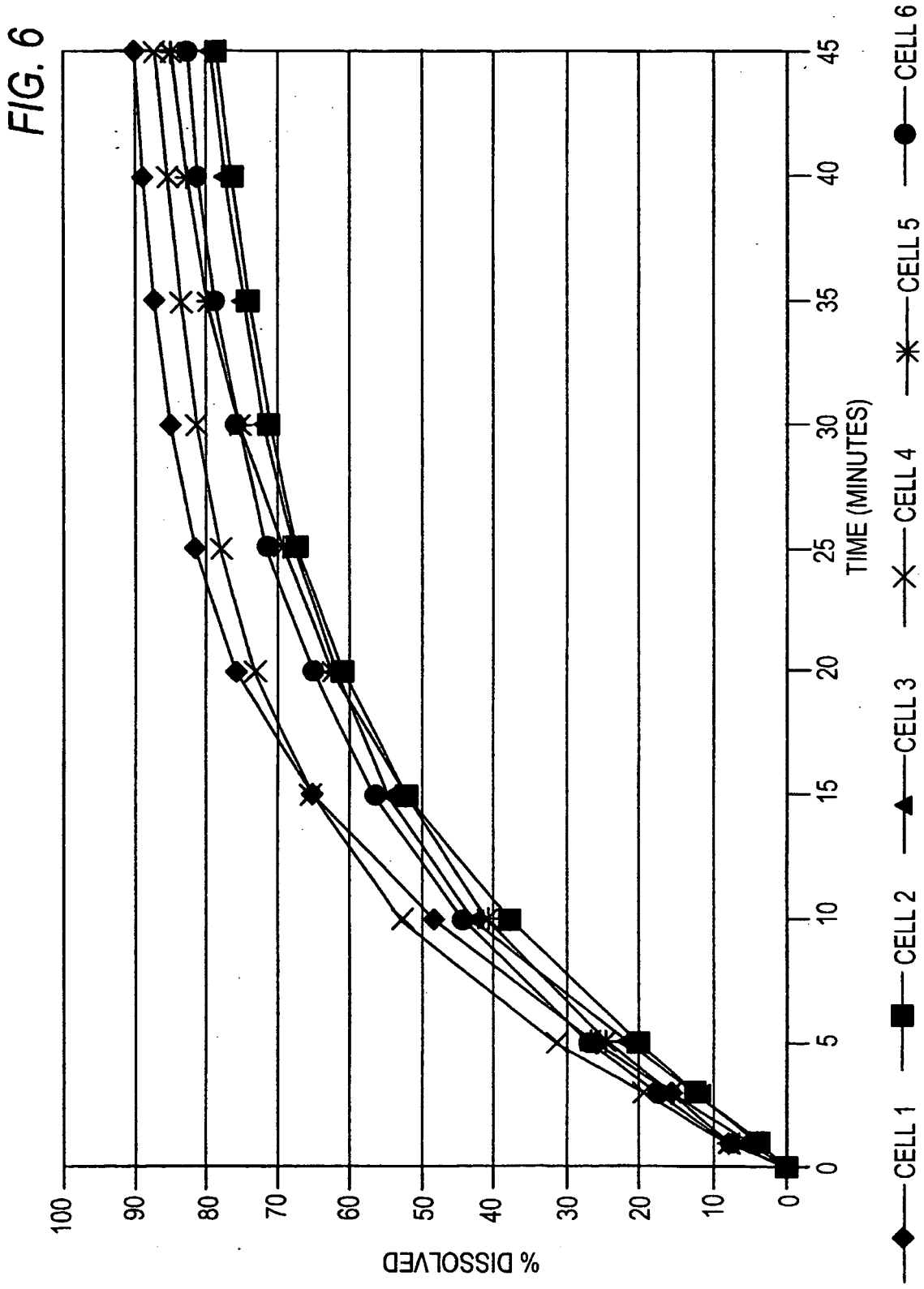


FIG. 7

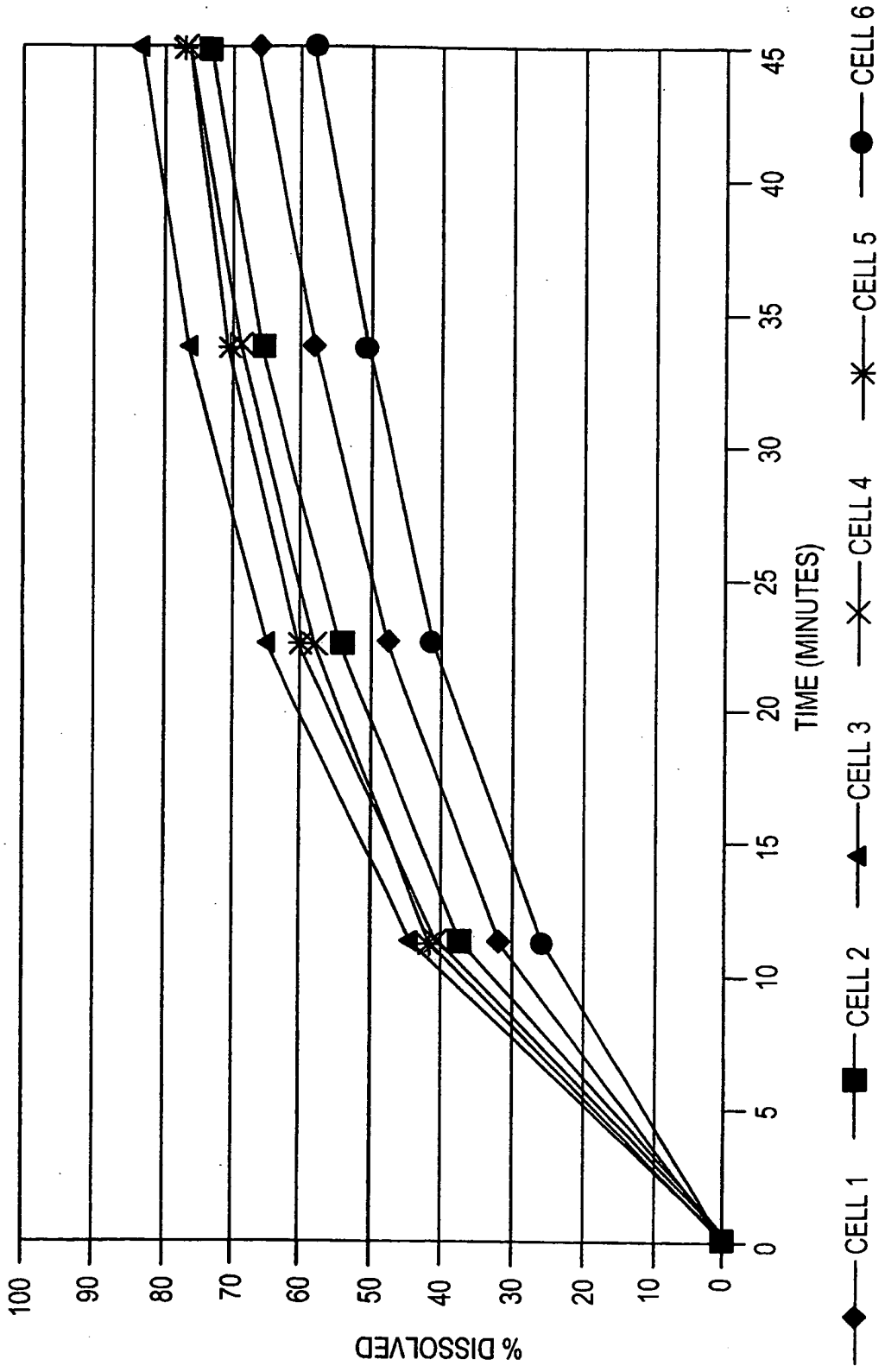


FIG. 8

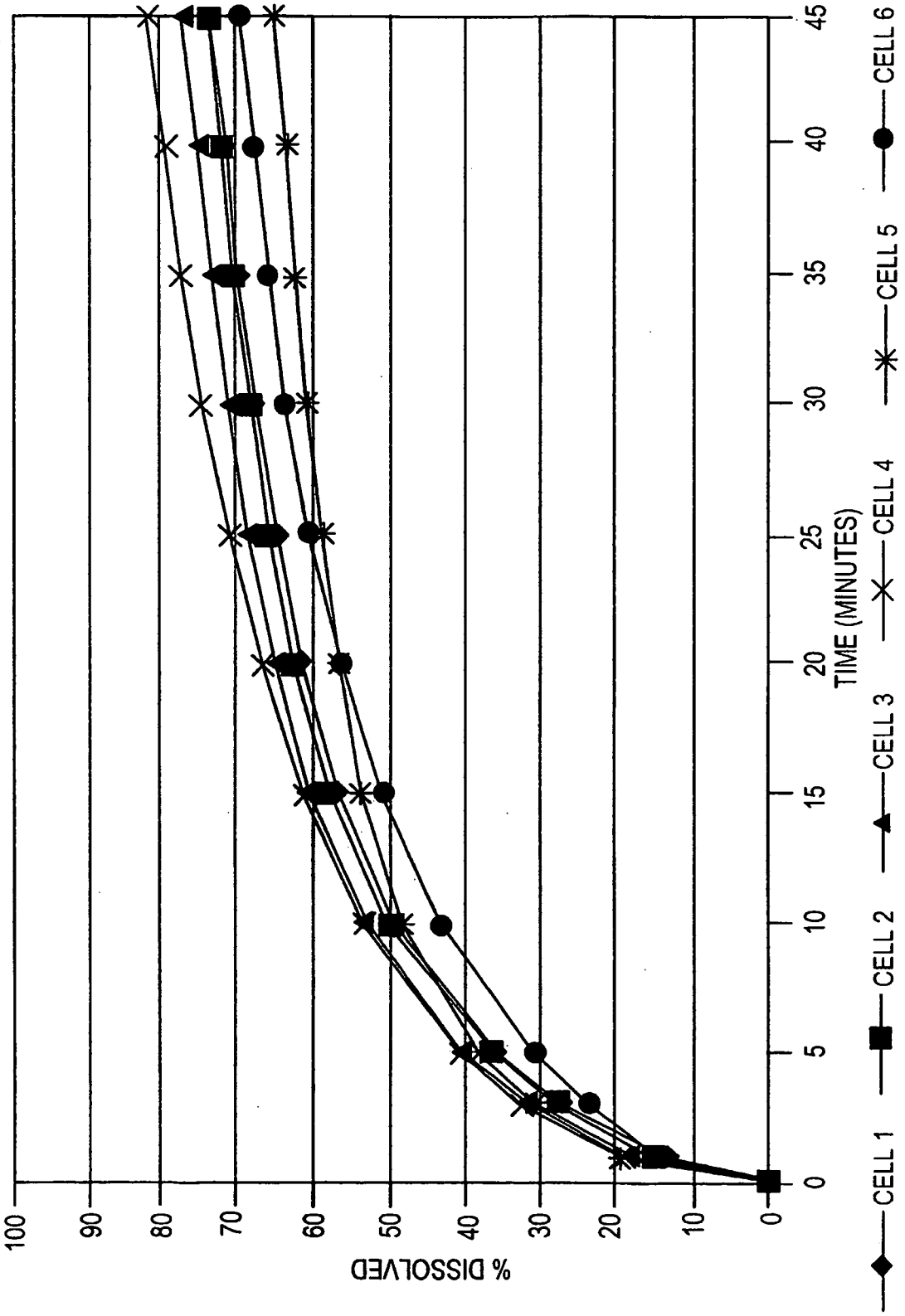


FIG. 9

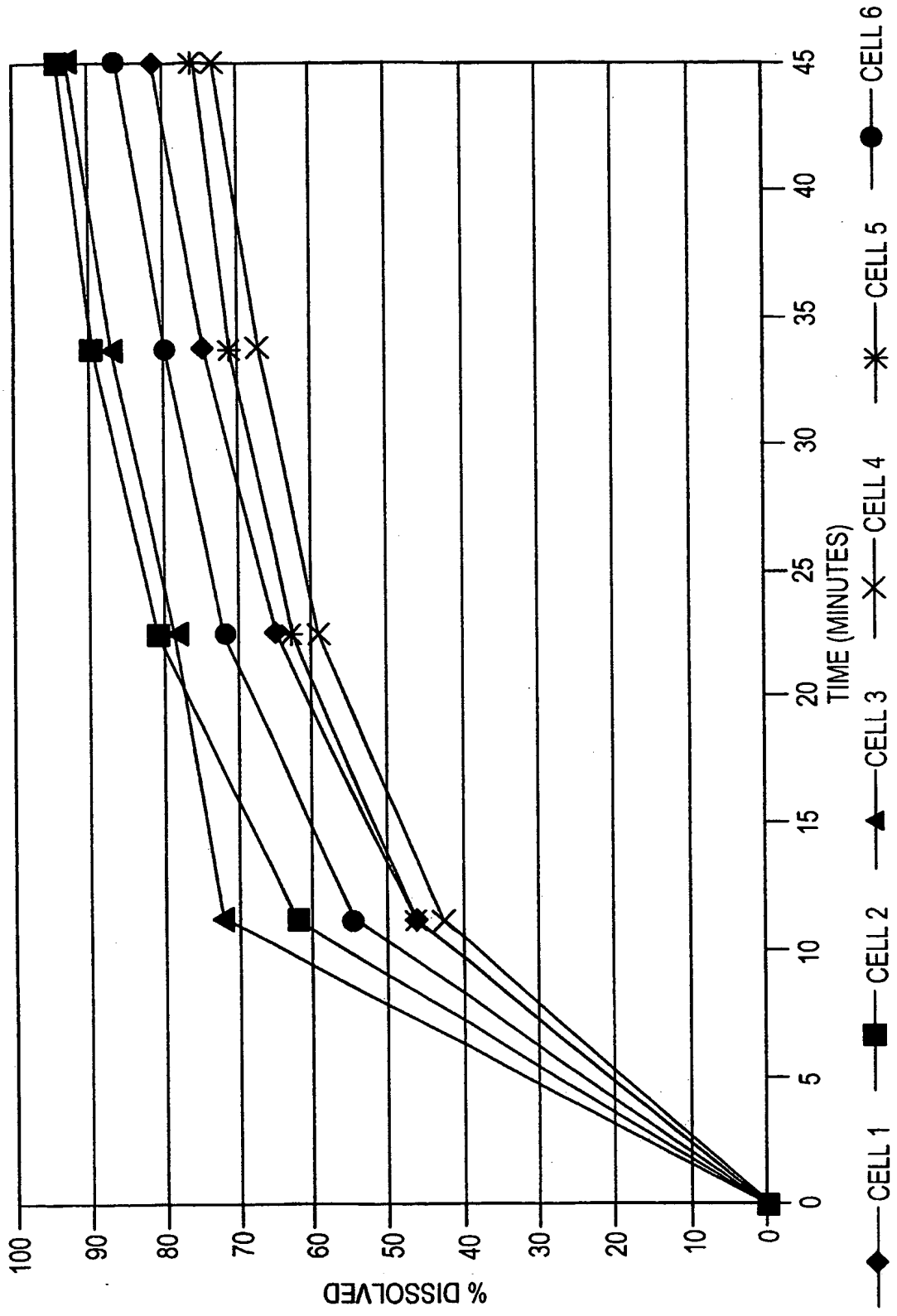


FIG. 10

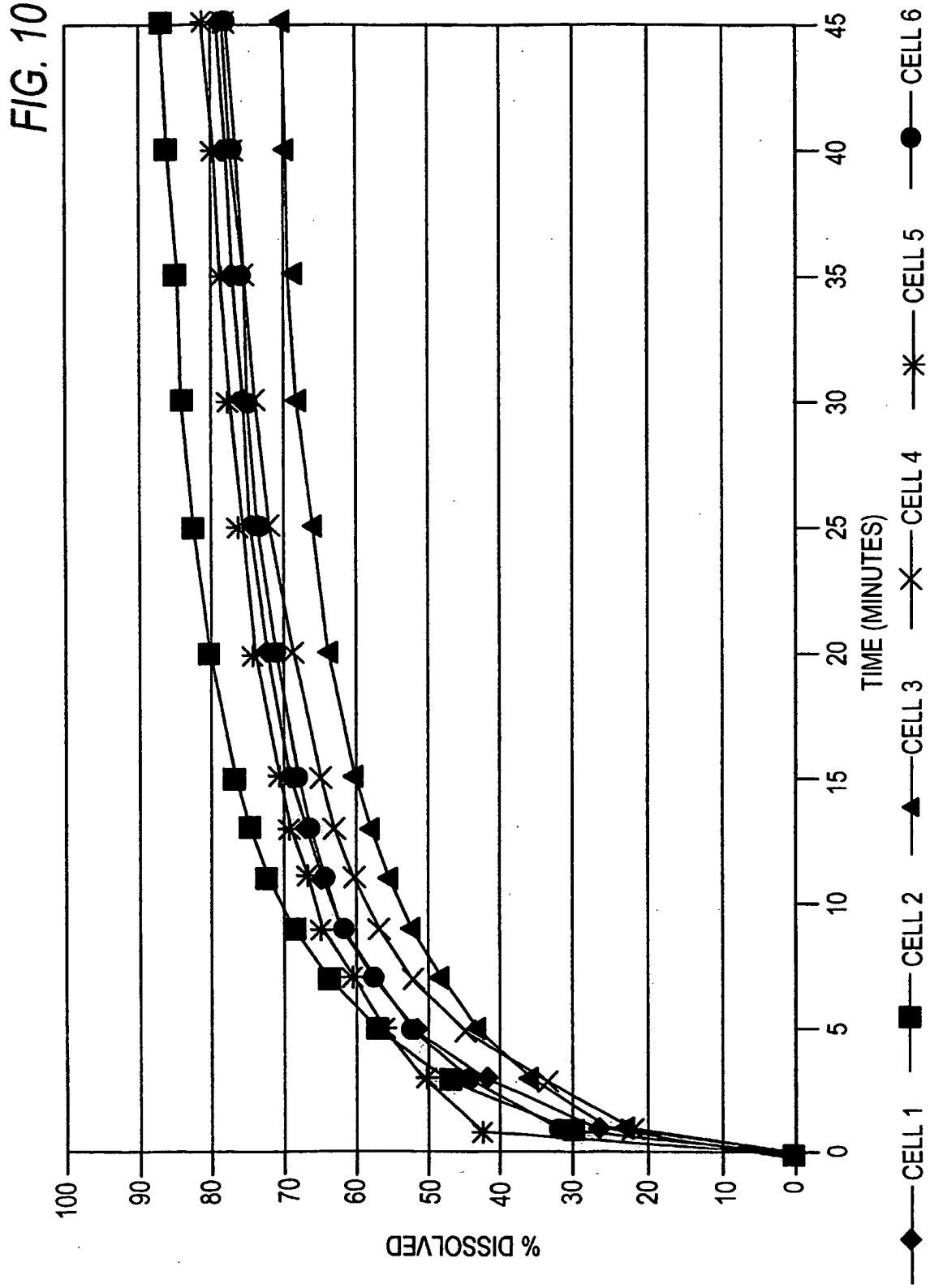


FIG. 11

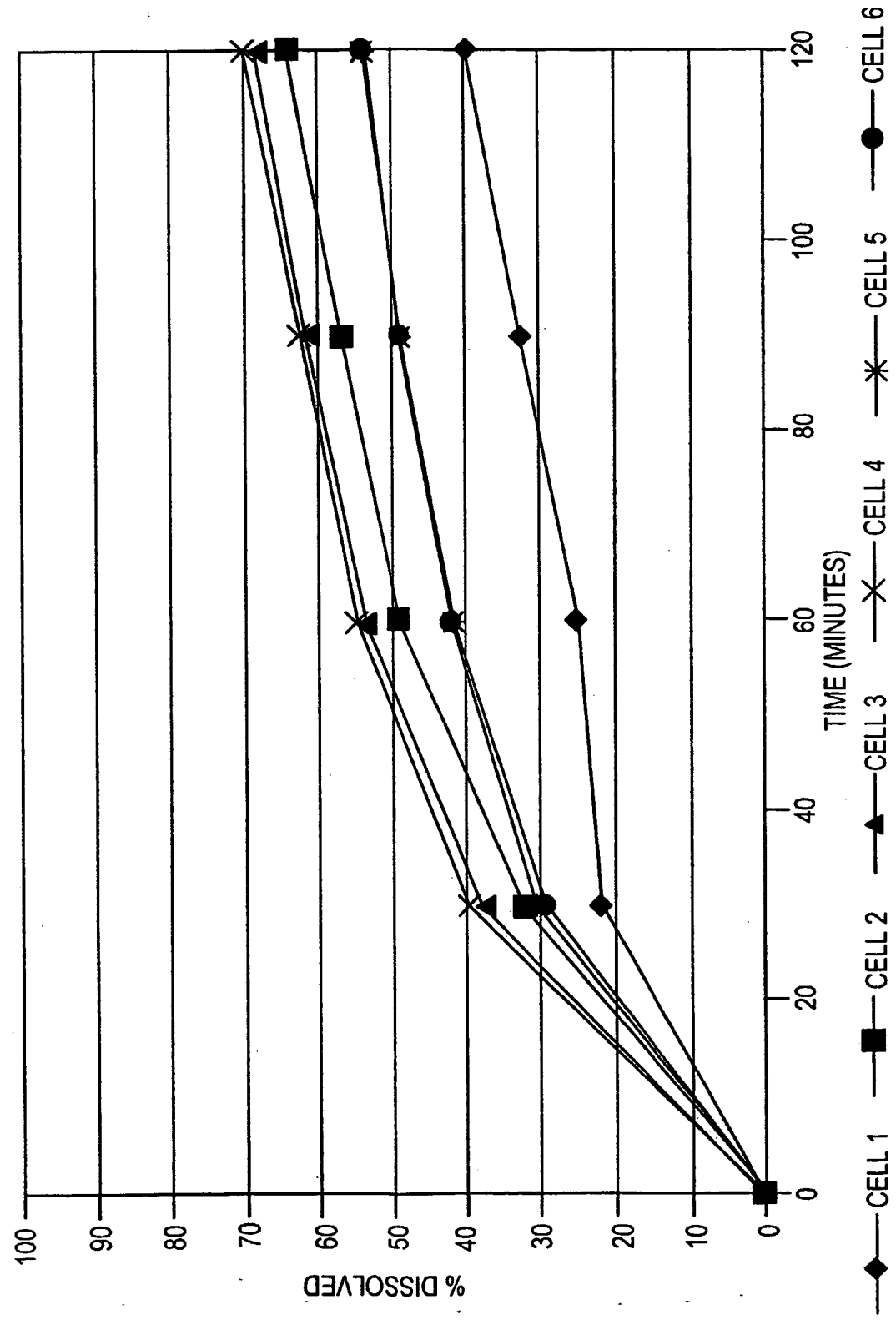
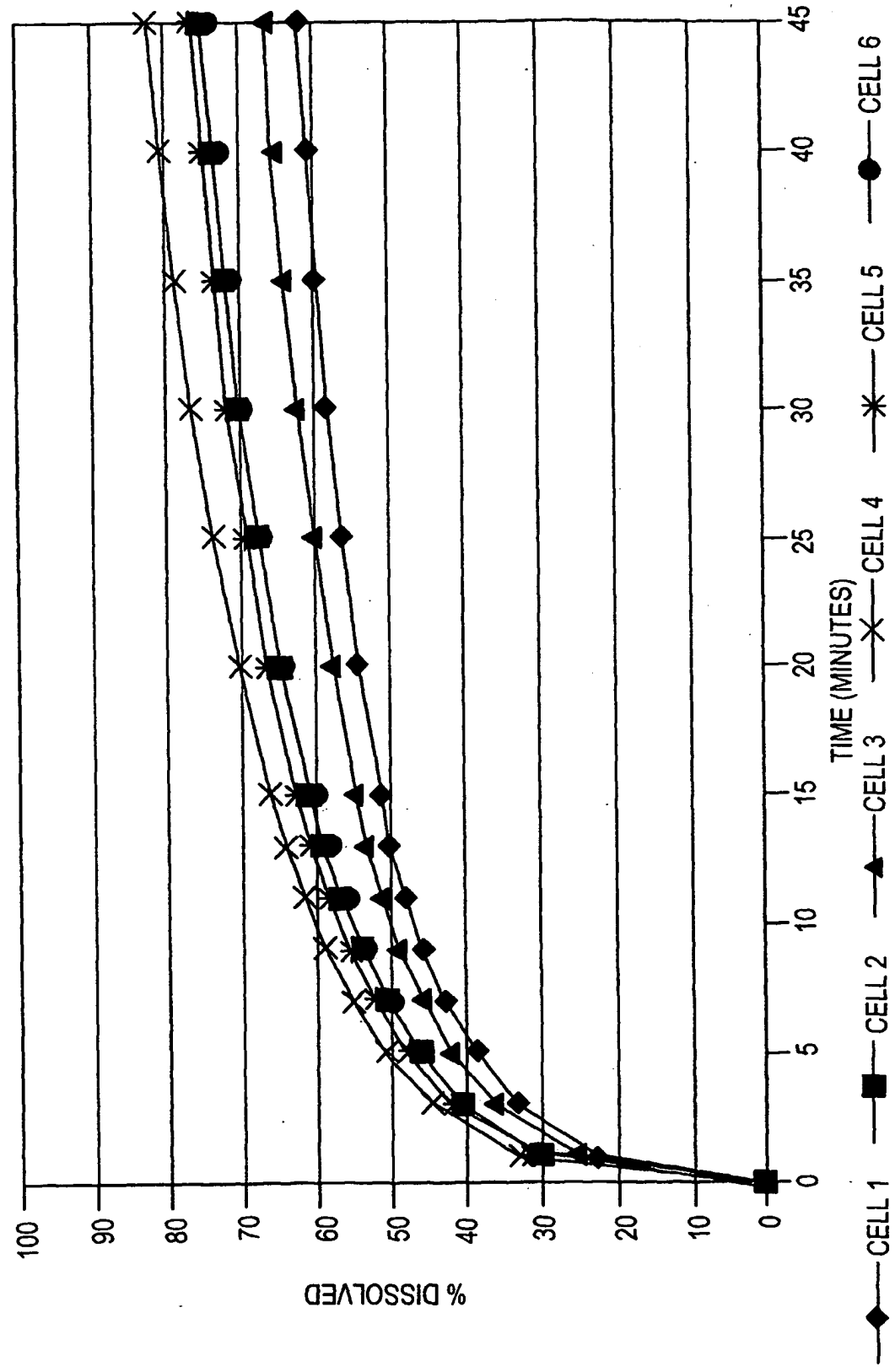


FIG. 12



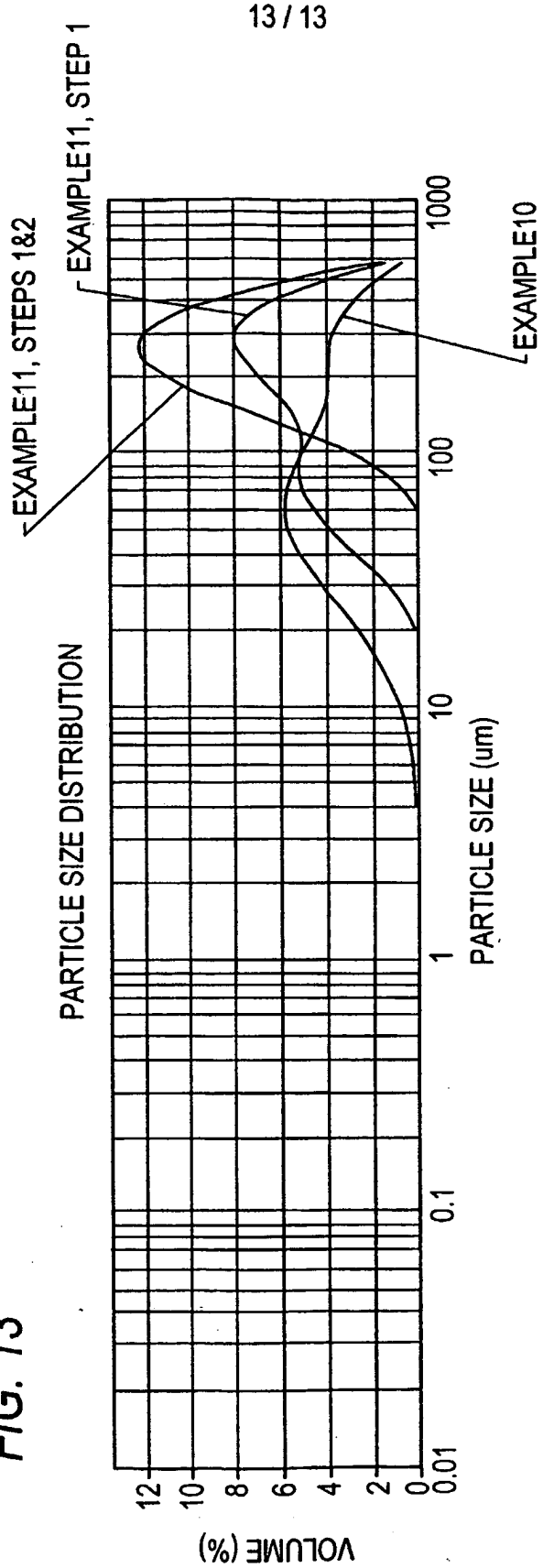


FIG. 13

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(54) Title: PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF URINARY DISORDERS

(57) Abstract: The present invention concerns the field of urology. The invention provides a novel pharmaceutical composition, comprising a pharmaceutically effective combination of (i) a first compound selected from the group consisting of muscarinic receptor antagonists, 5α-reductase inhibitors, and α-adrenergic receptor antagonists, and precursors and pharmaceutically acceptable salts thereof, and (ii) a second compound selected from the group consisting of 5-HT¿la? receptor agonists and antagonists, and precursors and pharmaceutically acceptable salts thereof, and optionally a pharmaceutically acceptable carrier or diluent therefor. There is also provided a method of therapeutical treatment of urinary disorder in a mammal, including man, comprising administering to said mammal, including man, in need of such treatment, a therapeutically effective amount of a composition according to the invention.

WO 2003/026564 A3

Pharmaceutical compositions for the treatment of urinary disorders.

Technical field

The present invention is within the field of urology. More specifically, it is generally based on the use of a combination of certain agonists and/or antagonists for therapeutical treatment of urinary disorder.

Background of the invention

Urinary disorders and symptoms thereof include some or all of the following: urgency, frequency, incontinence, urine leakage, enuresis, dysuria, hesitancy, and difficulty of emptying bladder. In particular, urinary disorders include urinary incontinence, caused by e.g. unstable or overactive urinary bladder.

The term Lower Urinary Tract Symptoms (LUTS) describes a well-recognized medical condition. LUTS include some or all of the following: obstructive urinary symptoms, such as slow urination, dribbling at the end of a urination, inability to urinate and/or the need to strain to urinate at an acceptable rate, or irritative symptoms, such as frequency and/or urgency. These irritative symptoms may result from detrusor overactivity secondary to bladder outlet obstruction resulting from prostatic enlargement or proximal urethral smooth muscle hyperreactivity.

A substantial part (5-10%) of the adult population suffers from urinary incontinence, and the prevalence, particularly of so-called urge incontinence, increases with age. The symptoms of an unstable or overactive bladder comprise urge incontinence, urgency and urinary frequency. Urge incontinence in combination with stress incontinence (mixed incontinence) is frequently encountered by clinicians.

It is assumed that unstable or overactive bladder is caused by uncontrolled contractions of the bundles of smooth muscle fibers forming the muscular coat of the urinary bladder (the detrusor muscle) during the filling phase of the bladder. These contractions are mainly controlled by cholinergic muscarinic receptors, and the pharmacological treatment of unstable or overactive bladder has traditionally been based on muscarinic receptor antagonists.

The reason why the bladder muscle contracts inappropriately is unclear in many cases. For some people it may be due to a problem with the nerve signals that run from the brain to the bladder. Sometimes minor nerve damage is caused by surgery or childbearing. This muscle squeezes or contracts more often than normal and at inappropriate times. Instead of staying at rest as urine fills the bladder, the detrusor contracts while the bladder is filling with urine. This causes a person to feel a sudden and sometimes overwhelming urge to urinate even when the bladder is not full.

Another major urinary disorder is interstitial cystitis. Cystitis is an inflammation of the urinary bladder and associated structures. There is currently no universal effective treatment program. Symptoms from cystitis include urgency for urination, increased frequency of urination and suprapubic pain, usually relieved by voiding, arthritis, spastic colon, low grade fever and irritability. Mammals with cystitis can be significantly disabled and may require surgery. Cystitis can result from e.g. infection, trauma, allergy and malignancy.

US Patent 5,382,600 discloses 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl)-4-methylphenol, also known as N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, with the generic name of tolterodine, as well as other substituted 3,3-diphenylpropylamines, as being useful to treat urinary incontinence. H Postlind *et*

al, Drug Metabolism and Disposition, 26(4): 289-293 (1998) discloses that tolterodine is a muscarinic receptor antagonist. The active metabolites of tolterodine, as well as other substituted 3,3-diphenylpropylamines, are disclosed in US Patent 5,559,269.

US Patent 4,377,584 discloses the use of finasteride, a 5α-reductase inhibitor, for the treatment of benign prostatic hypertrophy.

US Patent 4,026,894 discloses the use of terazosin, an α-adrenergic receptor antagonist, as an anti-hypertensive agent. α-adrenergic receptor antagonists relax smooth muscle.

US Patent 5,990,114 discloses the use of certain 5-HT_{1a} receptor antagonists for the treatment of urinary incontinence.

Despite the above advances in the art, it is desirable to develop novel pharmaceutical compositions that further improve the quality of life for a large number of individuals.

Summary of the invention

For these and other purposes, it is an object of the present invention to provide a novel pharmaceutical composition for treating urinary disorder in a mammal, including man, which composition inhibits, or suppresses, unstable bladder contractions and diminishes problems associated with incomplete bladder emptying.

It is also an object of the present invention to provide a novel method of treating urinary disorder in a mammal, including man, which method effectively inhibits, or suppresses, unstable bladder contractions and diminishes problems associated with incomplete bladder emptying.

For these and other objects that will be evident from the following disclosure, the present invention provides a novel pharmaceutical composition, comprising a

pharmaceutically effective combination of
(i) a first compound selected from the group consisting of muscarinic receptor antagonists, 5α-reductase inhibitors, and α-adrenergic receptor antagonists, and precursors and pharmaceutically acceptable salts thereof, and
(ii) a second compound selected from the group consisting of 5-HT_{1a} receptor agonists and antagonists, and precursors and pharmaceutically acceptable salts thereof, and optionally a pharmaceutically acceptable carrier or diluent therefor.

The invention is based on the insight that a combination of at least one compound selected from the group consisting of muscarinic receptor antagonists, 5α-reductase inhibitors, and α-adrenergic receptor antagonists, with a 5-HT_{1a}-agonist or -antagonist produces a favorable simultaneous effect on bladder contractility and bladder storage, as will be described more below. The 5-HT_{1a}-agonist could e.g. be an inverse agonist and the 5-HT_{1a} -antagonist could be a neutral 5-HT_{1a} receptor antagonist

In a preferred embodiment of the composition according to the invention, said first compound is a muscarinic receptor antagonist, or a precursor or a pharmaceutically acceptable salt thereof.

In a more preferred embodiment of the composition according to the invention, said muscarinic receptor antagonist is a substituted 3,3-diphenylpropylamine. Among substituted 3,3-diphenylpropylamines with muscarinic receptor antagonist activity are those referred to in the background of the invention.

In an even more preferred embodiment of the composition according to the invention, said substituted 3,3-diphenylpropylamine is selected from the group consisting of tolterodine and hydroxytolterodine. Preferably, said substituted 3,3-diphenylpropylamine is tolterodine. In the most preferred embodiment of the

composition according to the invention, said first compound is tolterodine L-tartrate.

In another preferred embodiment of the composition according to the invention, said muscarinic receptor antagonist is selected from oxybutynin and active derivatives thereof. Among active derivatives thereof is its active metabolite N-desethyloxybutynin. Preferably, said muscarinic receptor antagonist is oxybutynin.

In yet another preferred embodiment of the composition according to the invention, said muscarinic receptor antagonist is selected from darifenacin and active derivatives thereof. Among active derivatives thereof is its active 3'-hydroxyl metabolite. Preferably, said muscarinic receptor antagonist is darifenacin.

In one preferred embodiment of the composition according to the invention, said first compound is present in an amount of from about 0.1 mg to about 100 mg.

In a preferred embodiment of the composition according to the invention, said second compound is a neutral 5-HT_{1a} receptor antagonist.

In one preferred embodiment of the composition according to the invention, said second compound is present in an amount of from about 0.1 mg to about 1 g.

In another preferred embodiment of the composition according to the invention, said first compound and said second compound are maintained in the same delivery vehicle.

In yet another preferred embodiment of the composition according to the invention, said first compound and said second compound are maintained in different delivery vehicles.

In a preferred embodiment of the composition according to the invention, said composition is for treating urinary disorder in a mammal, especially man but also animals are included, e.g. pets like dogs and cats. In a more preferred embodiment of the composition

according to the invention, said disorder is selected from the group consisting of lower urinary tract symptoms, unstable or overactive urinary bladder, bladder outflow obstruction, urinary incontinence, particularly stress incontinence, and interstitial cystitis.

In another preferred embodiment of the composition according to the invention, said composition is for treating depression in said mammal, which depression is concomitant with said urinary disorder.

Furthermore, the present invention provides use of the composition according to the invention for the manufacture of a medicament for therapeutical treatment of urinary disorder in a mammal, including man. In a preferred embodiment of the use according to the invention, the medicament is for treatment of depression in said mammal, which depression is concomitant with said urinary disorder.

Furthermore, the present invention provides a method of therapeutical treatment of urinary disorder in a mammal, including man, comprising
administering to said mammal, including man, in need of such treatment, a therapeutically effective amount of a composition according to the invention.

In a preferred embodiment of the method according to the invention, said disorder is selected from the group consisting of lower urinary tract symptoms, unstable or overactive urinary bladder, bladder outflow obstruction, urinary incontinence, particularly stress incontinence, and interstitial cystitis.

In another preferred embodiment of the method according to the invention, said method is also for treating depression in said mammal, which depression is concomitant with said urinary disorder.

In a preferred embodiment of the method according to the invention, said composition is administered rectally, intravaginally, topically, orally, sublingually, intranasally, transdermally or parenterally.

In another preferred embodiment of the method according to the invention, said first compound and said second compound of said composition are simultaneously administered.

In yet another preferred embodiment of the method according to the invention said first compound and said second compound of said composition are concomitantly administered.

Finally, the present invention provides a pharmaceutical kit for therapeutical treatment of urinary disorder in a mammal, including man, comprising
(i) a first container comprising a first compound as described above
(ii) a second container comprising a second compound as described above, and
(iii) instructions for use of the kit.

Description of the invention

In describing the preferred embodiment, certain terminology will be utilized for the sake of clarity. Such terminology is intended to encompass the recited embodiments, as well as all technical equivalents that operate in a similar manner for a similar purpose to achieve a similar result. To the extent that any pharmaceutically active compound is disclosed or claimed, it is expressly intended to include all active metabolites produced in vivo, and, is expressly intended to include all enantiomers, isomers or tautomers where the compound is capable of being present in its enantiomeric, isomeric or tautomeric form.

The present invention provides a novel composition, which is a combination of
at least one muscarinic receptor antagonist or 5α-reductase inhibitor or α-adrenergic receptor antagonist or norepinephrine and/or serotonin reuptake inhibitor

and

a 5-HT_{1a} agonist or antagonist.

The inventive composition is useful for the treatment of urinary disorder.

A particularly preferred composition for the treatment of urinary disorder is a combination of an anti-muscarinic agent and a neutral 5-HT_{1a}-antagonist.

According to the invention, it has now surprisingly and inventively been found that treatment with a combination of an anti-muscarinic agent and a neutral 5-HT_{1a}-antagonist produces a simultaneous effect on bladder contractility and bladder storage.

Anti-muscarinic treatment acts on the effector organ by inhibiting the response to efferent impulses from the central nervous system. Thus, anti-muscarinic treatment inhibits unstable bladder contractions during the filling phase but also inhibits the contractions elicited during the elimination phase, especially at higher doses, thereby resulting in a decrease in micturition pressure, eventually leading to the negative consequence of incomplete bladder emptying. This effect limits the possibilities of otherwise acceptable dosing of these agents. Furthermore, anti-muscarinic treatment leads to side-effects outside of the urogenital systems, mainly due to blockade of muscarinic receptors in other tissues such as the salivary glands, the gut, and the CNS, leading to side effects such as dry mouth, constipation, and confusion, respectively. To some extent, these side effects have been reduced by the introduction of newer anti-muscarinic agents such as tolterodine with selectivity for bladder smooth muscle. However, even bladder-selective anti-muscarinic agents will always be limited as a treatment of overactive bladder by their effect on the micturition contraction described above.

The effects of anti-muscarinic agents have been studied in a range of animal models and they have

consistently been shown to reduce the amplitude of voiding or micturition contraction without direct effects on bladder capacity. For these agents, the effects on bladder capacity have always been shown to be secondary to a significant decrease in micturition pressure.

No clinically available agents have any direct effect on the storage function of the bladder. However, it has now been realized that a combination of 5-HT_{1a}-agonists or -antagonists, particularly neutral 5-HT_{1a}-antagonists, and antimuscarinic agents or 5α-reductase inhibitors or α-adrenergic receptor antagonists or norepinephrine and/or serotonin reuptake inhibitors, particularly antimuscarinic agents, increases bladder capacity without negative consequences on bladder contractility.

Importantly, in models for the evaluation of the effects of an anti-muscarinic agent on bladder contractility, simultaneous administration of a neutral 5-HT-antagonist with an anti-muscarinic does not attenuate the effects of the anti-muscarinic agent on bladder contractility.

Furthermore, in models used for evaluation of the effects of neutral 5-HT_{1a} antagonists on bladder capacity and inhibition of the micturition reflex, simultaneous administration of an anti-muscarinic agent with a neutral 5-HT_{1a}-antagonist does not attenuate the effects of the 5-HT_{1a}-antagonist on bladder capacity or its effect on the micturition reflex.

The muscarinic receptor antagonists, or antimuscarinic agents, useful in the pharmaceutical compositions of this invention include, but are not limited to, non-selective agents, bladder-selective agents and muscarinic M3 receptor-selective agents. Examples of muscarinic receptor antagonists include, but are not limited to, tolterodine and active metabolites thereof, such as hydroxytolterodine, YM905, propiverine,

oxybutynin, trospium, propantheline, darifenacin, temiverine, and ipratropium, as well as pharmaceutically acceptable salts thereof. YM905 is butanedioic acid, compd. with (1S)-(3R)-1-azabicyclo[2.2.2]oct-3-yl 3,4-dihydro-1-phenyl-2(1H)-isoquinolinecarboxylate (1:1) (9CI). Propiverine is 1-methyl-4-piperidyl .alpha.,.alpha.-diphenyl-.alpha.-(n-propoxy)acetate and is disclosed in East German Patent 106,643 and in CAS 82-155841s (1975). Oxybutynin is 4-(diethylamino)-2-butynylalphaphenylcyclohexaneglycolate and is disclosed in UK Patent 940,540. Trospium is 3alpha-hydroxyspiro[1alphaH,5alphaH-nortropane-8,1'pyrrolidinium]chloride benzilate and is disclosed in US Patent 3,480,623. Darifenacin is (S)-2-{1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenyl-acetamide, and is disclosed in US Patent 5,096,890. Temiverine is benzeneacetic acid, .alpha.-cyclohexyl-.alpha.-hydroxy-, 4-(diethylamino)-1,1-dimethyl-2-butynyl ester and is disclosed in US Patent 5,036,098. Ipratropium is 8-isopropylnoratropine methobromide and is disclosed in US Patent 3,505,337.

Preferred muscarinic receptor antagonists may be selected from substituted 3,3-diphenylpropylamines (such as those disclosed in US Patent 5,382,600) with antimuscarinic activity, as well as pharmaceutically acceptable salts thereof. Preferred muscarinic receptor antagonists include, but are not limited to tolterodine and hydroxytolterodine, oxybutynin and active derivatives thereof, such as N-desethyloxybutynin, and darifenacin and active derivatives thereof, such as its 3'-hydroxyl metabolite, as well as pharmaceutically acceptable salts thereof.

The 5α-reductase inhibitors useful in the pharmaceutical compositions of this invention include, but are not limited to, finasteride (US Patent 4,377,584), dutasteride (US Patent 5,565,467), epristeride (US Patent 5,017,568), and turosteride (US

Patent 5,155,107), as well as pharmaceutically acceptable salts thereof.

The α-adrenergic receptor antagonists useful in the pharmaceutical compositions of this invention include, but are not limited to, terazosin (US Patent 4,026,894), doxazosin (US Patent 4,188,390), prazosin (US Patent 3,511,836), bunazosin (US Patent 3,920,636), indoramin (US Patent 3,527,761), alfuzosin (US Patent 4,315,007), abanoquil (US Patent 4,686,228), naftopidil (US Patent 3,997,666), phentolamine, tamsulosin (US Patent 4,703,063), trazodone, dapiprazole, phenoxybenzamine, idazoxan (US Patent 4,818,764), efaroxan (US Patent 4,411,908), yohimbine, dibenzamine, trimazosin, tolazoline, corynthanine, rauwolscine, tamsulosin, and piperoxan, as well as pharmaceutically acceptable salts thereof.

The norepinephrine and/or serotonin reuptake inhibitors useful in the pharmaceutical compositions of this invention include, but are not limited to, duloxetine (US Patent 4,956,388), reboxetine, [S,S]-reboxetine succinate salt and the racemates of reboxetine and sertraline (Zoloft).

The selection of the dosage of the first compound is that which can provide relief to the patient. As is well known, the dosage and administrative regimen (i.e., one, two, three or more administrations per day) of this compound depends on several factors such as the potency of the selected specific compound, the mode of administration, the age and weight of the patient, the severity of the condition to be treated, and the like. This is considered to be within the skill of the artisan, and one can review the existing literature on the components to determine optimal dosing.

When the first compound is an antimuscarinic agent, it is preferred that the average adult daily dosage of

the first compound is from about 0.05 mg to about 5 mg per kilogram of body weight, administered in one or more doses, e.g. containing from about 0.05 mg to about 250 mg each.

When the first compound is a 5α-reductase inhibitor, it is preferred that the first compound is present in an amount ranging from about 2 mg to about 20 mg, preferably about 5 mg per dose.

When the first compound is an α-adrenergic receptor antagonist, it is preferred that the first compound is present in an amount ranging from about 1 mg to about 25 mg, and preferably about 10 mg per dose.

The 5-HT_{1a} receptor agonists and antagonists useful in the pharmaceutical compositions of this invention include, but are not limited to, compounds that act on the central nervous system by binding to 5-HT receptors of the 5-HT_{1a} subtype. Non-limiting examples of 5-HT_{1a} receptor antagonists are WAY-100,635, i.e. cyclohexanecarboxamide, N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinyl-, trihydrochloride, robalzotan, i.e. (3R)-3-(dicyclobutylamino)-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide, and LY426965, i.e. [(2S)-(+)-1-cyclohexyl-4-[4-(2-methoxyphenyl)-1-piperazinyl]2-methyl-2-phenyl-1-butanone monohydrochloride]. In general, the compounds selectively bind to receptors of the 5-HT_{1a} subtype to a much greater extent than they bind to other receptors, such as α_1 and D_2 receptors. Moreover, they exhibit activity as 5-HT_{1a}-agonists or -antagonists in pharmacological testing. The 5-HT_{1a} receptor agonists and antagonists of the invention can be used for the treatment of CNS disorders, such as anxiety in mammals, particularly humans. They may also be used as antidepressants, hypotensives, as agents for regulating the sleep/wake cycle, feeding behavior and/or sexual function, for treating cognition disorders, and for treating neuromuscular dysfunction of the lower

urinary tract, particularly those involving micturition (urination), such as dysuria, incontinence, and enuresis.

A neutral antagonist is a compound that binds to a receptor, is devoid of intrinsic activity at the receptor, but blocks the receptor-mediated functional activity elicited by an agonist. In this respect, an agonist is defined as a compound that binds to a receptor and activates a receptor-mediated functional response such as, but not limited to, 5-HT_{1a}-mediated inhibition of adenylyl cyclase activity or activation of potassium channels.

The dosage and administrative regimen (i.e., one, two, three or more administrations per day) of the second compound depends on the factors referred to in connection with the dosage selection of the first compound. The average adult daily dosage of the second compound is from about 1 µg to about 10 mg per kilogram of body weight, administered in one or more doses, e.g. containing from about 50 µg to about 1 g each. Pediatric dosages may be less.

Examples of pharmaceutically acceptable salts for use in the composition according to the invention include, but are not limited to, acetate, benzoate, hydroxybutyrate, bisulfate, bisulfite, bromide, butyne-1,4-dioate, carpoate, chloride, chlorobenzoate, citrate, dihydrogenphosphate, dinitrobenzoate, fumarate, glycollate, heptanoate, hexyne-1,6-dioate, hydroxybenzoate, iodide, lactate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, oxalate, phenylbutyrate, phenylproionate, phosphate, phthalate, phylacetate, propanesulfonate, propiolate, propionate, pyrophosphate, pyrosulfate, sebacate, suberate, succinate, sulfate, sulfite, sulfonate, tartrate, xylenesulfonate, and the like.

Compositions of the present invention can conveniently be administered in a pharmaceutical composition containing the active compounds in combination with a suitable excipient. Such pharmaceutical compositions can be prepared by methods and contain excipients which are well known in the art. A generally recognized compendium of such methods and ingredients is Remington's Pharmaceutical Sciences by E.W. Martin (Mark Publ. Co., 15th Ed., 1975). To the extent necessary for completion, this reference is hereby incorporated by reference. The compositions of the present invention can be administered parenterally (for example, by intravenous, intraperitoneal, subcutaneous or intramuscular injection), topically, orally, sublingually, transdermally, intranasally, intravaginally, or rectally, with oral administration being particularly preferred.

For oral therapeutic administration, the inventive composition may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums, foods and the like. Such compositions and preparations preferably contain at least 0.1% of active compounds. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 0.1 to about 100% of the weight of a given unit dosage form. The amount of active compounds in such therapeutically useful compositions is such that effective dosage levels will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or

a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. The above listing is merely representative, and one skilled in the art could envision other binders, excipients, sweetening agents and the like. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active components may be incorporated into sustained-release preparations and devices including, but not limited to, those relying on osmotic pressures to obtain a desired release profile. Once daily formulations for each of the active components are specifically included.

The inventive composition, containing the two, or more, active compounds, may be administered in the same physical form or concomitantly according to the above-described dosages and in the above-described delivery vehicles. The dosages for each active compound can be measured separately and can be given as a single combined dose or given separately. They may be given at the same or at different times as long as both actives are in the patient at one time over a 24-hour period. Concomitant or concurrent administration means that the patient takes one drug within about 5 minutes of taking the other drug.

The present invention also provides a pharmaceutical kit for therapeutical treatment of urinary disorder in a mammal, including man. In analogy with the composition,

the kit comprises a first container comprising a first compound as described above, a second container comprising a second compound as described above, and instructions for use of the kit.

"Pharmaceutically acceptable" refers to those properties and/or substances that are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

The inventive composition is to be used in the treatment of urinary disorders. In particular, the composition is useful for treating LUTS or incontinence of any type, e.g. stress incontinence, genuine stress incontinence, and mixed incontinence. Stress urinary incontinence is a symptom describing involuntary loss of urine on carrying out any activity that raises intra-abdominal pressure such as coughing or sneezing. Stress incontinence is also a clinical sign, that is the observation by a care giver of a jet of urine escaping from the urethral meatus (opening) when the patient coughs or strains. Genuine Stress Incontinence (urge incontinence) is the pathological diagnosis of an incompetent urethral sphincter as diagnosed by Urodynamic testing. Mixed incontinence is stress incontinence in combination with urge incontinence. The latter is a part of the symptom complex of the Overactive Bladder. Retention may be due to outflow obstruction (e.g., high urethral pressure), poor detrusor (bladder muscle) contractility or lack of coordination between detrusor contraction and urethral relaxation. The inventive drug combination can be used in connection with stress incontinence, urge incontinence or mixed incontinence.

The composition according to the invention is also to be used in the treatment of interstitial cystitis.

In a situation where anti-muscarinic treatment of a urinary disorder is limited by an increase in residual urine, treatment can be augmented by the addition of a neutral 5-HT_{1a} antagonist. This situation is especially likely to occur in patients with overactive bladder secondary to bladder outflow obstruction, e.g. due to prostate enlargement.

In other cases, anti-muscarinic treatment might be limited by intolerable side effects, such as dry mouth. In such a case, the anti-muscarinic dose might be reduced but efficacy maintained by the addition of a neutral 5-HT_{1a} antagonist. This combination allows the use of anti-muscarinic agents that are not selective for the bladder in a situation where these agents are preferred over other, more bladder selective, agents.

In another situation, treatment with a neutral 5-HT_{1a} antagonist might be limited due to absence of an effect on bladder contractility. In such a case, addition of an anti-muscarinic agent brings additional efficacy. Such a situation might be patients with bladder hyperreflexia, a condition known to be associated with increased reflex bladder contractions.

In yet another situation, the effectiveness of a neutral 5-HT_{1a} antagonist might be limited by side effects. In such a case, adjustment of the dose of the 5-HT antagonist, and thereby its effectiveness can be compensated for by the addition of an anti-muscarinic agent.

The novel composition is considered to provide rapid relief to those suffering from the above diseases or disorders with a minimal amount of deleterious side effects.

The invention is described in greater detail by the following non-limiting examples.

Examples

Example 1

A pharmaceutical composition is prepared by combining tolterodine with a neutral 5-HT_{1a} receptor antagonist in a pharmaceutically acceptable carrier. The composition contains between about 0.05 mg to about 4 mg of tolterodine per kilogram of patient body weight (for example, 3 mg to 240 mg tolterodine for a person weighing 60 kg) and between about 0.01 mg to about 1 mg of neutral 5-HT_{1a} receptor antagonist per kilogram of patient body weight. The composition is administered to a patient for the treatment of incontinence, and particularly stress incontinence, urge incontinence or mixed incontinence.

Example 2

A first pharmaceutical composition is prepared by combining a neutral 5-HT_{1a} receptor antagonist in a pharmaceutically acceptable carrier such that it can deliver between about 0.5 mg to about 50 mg on a daily basis. A second pharmaceutical composition is prepared by combining tolterodine in a pharmaceutically acceptable carrier such that it can deliver between about 0.05 mg to about 4 mg of tolterodine per kilogram of patient body weight on a daily basis.

The first composition is administered to a patient suffering from one or more forms of incontinence once, twice, three times, four times or six times daily such that the daily dosage is between about 0.5 mg to about 50 mg. The second composition is administered to the same patient at the same time as the administration of the first composition or any time within 24 hours of the administration of the first composition once, twice, three times, four times or six times daily such that the daily dosage is between about 0.05 mg to about 4 mg of tolterodine per kilogram of patient body weight. Alternatively, the second composition could first be

administered, followed by the administration of the first composition as disclosed at the same time, or within 24 hours thereof.

Example 3

A pharmaceutical composition is prepared by combining a 5α-reductase inhibitor with a neutral 5-HT_{1a} receptor antagonist in a pharmaceutically acceptable carrier. The composition contains between about 2 mg to about 20 mg of 5α-reductase inhibitor and between about 0.5 mg to about 50 mg of neutral 5-HT_{1a} receptor antagonist. The composition is administered to a patient for the treatment of urinary disorder.

Example 4

A pharmaceutical composition is prepared by combining an α-adrenergic receptor antagonist with a neutral 5-HT_{1a} receptor antagonist in a pharmaceutically acceptable carrier. The composition contains between about 1 mg to about 25 mg of α-adrenergic receptor antagonist and between about 0.5 mg to about 50 mg of neutral 5-HT_{1a} receptor antagonist. The composition is administered to a patient for the treatment of urinary disorder.

Having described the invention in detail and by reference to the preferred embodiments thereof, it will be apparent that modifications and variations are possible without departing from the scope of the appended claims.

CLAIMS

1. A pharmaceutical composition comprising a pharmaceutically effective combination of

(i) a first compound selected from the group consisting of muscarinic receptor antagonists, 5α-reductase inhibitors, and α-adrenergic receptor antagonists, and precursors and pharmaceutically acceptable salts thereof, and

(ii) a second compound selected from the group consisting of 5-HT_{1a} receptor agonists and antagonists, and precursors and pharmaceutically acceptable salts thereof, and optionally a pharmaceutically acceptable carrier or diluent therefor.

2. A pharmaceutical composition according to claim 1, wherein said first compound is a muscarinic receptor antagonist, or a precursor or a pharmaceutically acceptable salt thereof.

3. A composition according to claim 2, wherein said muscarinic receptor antagonist is a substituted 3,3-diphenylpropylamine.

4. A composition according to claim 3, wherein said substituted 3,3-diphenylpropylamine is selected from the group consisting of tolterodine and hydroxytolterodine.

5. A composition according to claim 4, wherein said substituted 3,3-diphenylpropylamine is tolterodine.

6. A composition according to claim 5, wherein said first compound is tolterodine L-tartrate.

7. A composition according to claim 2, wherein said muscarinic receptor antagonist is selected from oxybutynin and active derivatives thereof, such as N-desethyloxybutynin.

8. A composition according to claim 7, wherein said muscarinic receptor antagonist is oxybutynin.

9. A composition according to claim 2, wherein said muscarinic receptor antagonist is selected from

darifenacin and active derivatives thereof, such as its 3'-hydroxyl metabolite.

10. A composition according to claim 9, wherein said muscarinic receptor antagonist is darifenacin.

11. A composition according to any one of claims 1-10, wherein said first compound is present in an amount of from about 0.1 mg to about 100 mg.

12. A composition according to any one of claims 1-11, wherein said second compound is a neutral 5-HT_{1a} receptor antagonist.

13. A composition according to any one of claims 1-12, wherein said second compound is present in an amount of from about 0.1 mg to about 1 g.

14. A composition according to any one of claims 1-13, wherein said first compound and said second compound are maintained in the same delivery vehicle.

15. A composition according to any one of claims 1-13, wherein said first compound and said second compound are maintained in different delivery vehicles.

16. A composition according to any one of claims 1-15, which is for treating urinary disorder in a mammal, including man.

17. A composition according to claim 16, wherein said disorder is lower urinary tract symptoms.

18. A composition according to claim 16, wherein said disorder is unstable or overactive urinary bladder.

19. A composition according to claim 16, wherein said disorder is bladder outflow obstruction.

20. A composition according to claim 16, wherein said disorder is urinary incontinence.

21. A composition according to claim 20, wherein said disorder is stress incontinence.

22. A composition according to claim 16, wherein said disorder is interstitial cystitis.

23. A composition according to any one of claims 16-22, which is for treating depression in said mammal,

which depression is concomitant with said urinary disorder.

24. Use of a pharmaceutical composition according to any one of claims 1-15 for the manufacture of a medicament for therapeutical treatment of urinary disorder in a mammal, including man.

25. Use of a pharmaceutical composition according to claim 24, wherein said disorder is lower urinary tract symptoms.

26. Use of a pharmaceutical composition according to claim 24, wherein said disorder is unstable or overactive urinary bladder.

27. Use of a pharmaceutical composition according to claim 24, wherein said disorder is bladder outflow obstruction.

28. Use of a pharmaceutical composition according to claim 24, wherein said disorder is urinary incontinence.

29. Use of a pharmaceutical composition according to claim 28, wherein said disorder is stress incontinence.

30. Use of a pharmaceutical composition according to claim 24, wherein said disorder is interstitial cystitis.

31. Use of a pharmaceutical composition according to any one of claims 24-30, wherein the medicament is for treatment of depression in said mammal, which depression is concomitant with said urinary disorder.

32. A method of therapeutical treatment of urinary disorder in a mammal, including man, comprising administering to said mammal, including man, in need of such treatment, a therapeutically effective amount of a composition according to any one of claims 1-15.

33. A method of therapeutical treatment according to claim 32, wherein said disorder is lower urinary tract symptoms.

34. A method of therapeutical treatment according to claim 32, wherein said disorder is unstable or overactive urinary bladder.

35. A method of therapeutical treatment according to claim 32, wherein said disorder is bladder outflow obstruction.

36. A method of therapeutical treatment according to claim 32, wherein said disorder is urinary incontinence.

37. A method of therapeutical treatment according to claim 36, wherein said disorder is stress incontinence.

38. A method of therapeutical treatment according to claim 32, wherein said disorder is interstitial cystitis.

39. A method of therapeutical treatment according to any one of claims 32-38, which is also for treatment of depression in said mammal, which depression is concomitant with said urinary disorder.

40. A method of therapeutical treatment according to any one of claims 32-39, wherein said composition is administered rectally, intravaginally, topically, orally, sublingually, intranasally, transdermally or parenterally.

41. A method of therapeutical treatment according to any one of claims 32-40, wherein said first compound and said second compound of said composition are simultaneously administered.

42. A method of therapeutical treatment according to any one of claims 32-40, wherein said first compound and said second compound of said composition are concomitantly administered.

43. A pharmaceutical kit for therapeutical treatment of urinary disorder in a mammal, including man, comprising

(i) a first container comprising a first compound according to any one of claims 1-10,

(ii) a second container comprising a second compound according to claim 1 or 12, and optionally

(iii) instructions for use of the kit.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01748

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/137, A61K 31/165, A61K 31/216, A61K 31/343, A61K 31/4025, A61P 13/02, A61P 13/10

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)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA, EPO, INTERNAL, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 0121167 A1 (MERCK & CO., INC.), 29 March 2001 (29.03.01), (5alpha-reductase inhibitors, alpha-adrenergic receptor antagonistrs and muscarinic receptor antagonists are known for the treatment of Lower Urinary Tract Symptoms (LUTS). See page 1, lines 6-16 and 21-23; page 2, line 7 - page 5, line 2.) --	1-43
Y	UROLOGY, Vol. 56, Suppl. 6A, 2000, Roger R. Dmochowski et al: "Advancements in pharmacologic management of the overactive bladder", page 41 - page 49 --	1-43

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 December 2002	18 -12- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Per Renström/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01748

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Life Sciences, Vol. 64, No. 6/7, 1999, Robert M. Walles et al: "Muscarinic antagonists in development for disorders of smooth muscle function", page 395 - page 401	1-43
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Y	EP 0930298 A1 (BANYU PHARMACEUTICAL CO., LTD.), 21 July 1999 (21.07.99), (Muscarinic (M3) antagonists for the treatment of urinary disorders like urinary incontinence. See abstract; page 3, lines 25-33; page 4, lines 4-10; examples; claims.)	1-43
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Y	WO 9921563 A1 (MERCK & CO., INC.), 6 May 1999 (06.05.99), (Use of a 5alpha-reductase inhibitor (e.g. finasteride) for the treatment of urinary retention. See page 1, lines 20-25; page 3, line 11 - page 4, line 4; examples; claims.)	1-43
	--	
Y	WO 0129022 A1 (RECORDATI INDUSTRIA CHIMICA E FARMACEUTICA SPA), 26 April 2001 (26.04.01), (Alpha-1 adrenoceptor antagonists for treating lower urinary tract.symptoms such as contractions of urethra and incontinence. See page 1-9.)	1-43
	--	
Y	WO 9605817 A1 (MEDINNOVA SF), 29 February 1996 (29.02.96), (Partial 5-HT1A agonists(e.g. azapirones such as buspirone, ipsapirone, gepirone and tandospirone) in the treatment of urinary incontinence, urinary retention and urethral	1-43
Y	resistance. Example with buspirone. See pages 4-7; pages 13-15, examples 6-8; table 1 on page 16; claims.)	
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Form PCT/ISA/210 (continuation of second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01748

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 9731637 A1 (RECORDATI INDUSTRIA CHIMICA E FARMACEUTICA S.P.A. ET AL), 4 Sept 1997 (04.09.97), (Use of 5-HT1A receptor antagonists for the treatment of urinary incontinence, dysuria and enuresis.) --	1-43

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/01748

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 32-42
because they relate to subject matter not required to be searched by this Authority, namely:
see extra sheet

2. ☒ Claims Nos.: 1-43
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see extra sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/10/02

International application No.
PCT/SE 02/01748

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0121167 A1	29/03/01	AU 7703700 A	24/04/01
EP 0930298 A1	21/07/99	AU 716050 B	17/02/00
		AU 3635197 A	25/02/98
		BG 103114 A	30/11/99
		BR 9711108 A	17/08/99
		EE 9900038 A	16/08/99
		IL 127685 D	00/00/00
		JP 3063164 B	12/07/00
		NO 990472 A	01/02/99
		NZ 333842 A	25/05/01
		SK 12299 A	16/05/00
		CN 1226888 A	25/08/99
		CZ 9900331 A	14/07/99
		HR 970426 A	31/08/98
		HU 9902381 A	29/11/99
		JP 3282617 B	20/05/02
		JP 3282618 B	20/05/02
		JP 2000169449 A	20/06/00
		JP 2000178231 A	27/06/00
		PL 331431 A	19/07/99
		TR 9900204 T	00/00/00
		TR 200001482 T	00/00/00
		US 5948792 A	07/09/99
		US 6040449 A	21/03/00
		WO 9805641 A	12/02/98
		ZA 9706813 A	11/02/98
WO 9921563 A1	06/05/99	AU 731576 B	05/04/01
		AU 1279099 A	17/05/99
		CA 2308070 A	06/05/99
		EP 1032400 A	06/09/00
		JP 2001521000 T	06/11/01
		US 5942519 A	24/08/99
WO 0129022 A1	26/04/01	AU 1384701 A	30/04/01
		EP 1222183 A	17/07/02
		IT MI992174 A	18/04/01
		US 6403594 B	11/06/02
WO 9605817 A1	29/02/96	AU 3263795 A	14/03/96
		GB 9417135 D	00/00/00
WO 9731637 A1	04/09/97	AU 2093297 A	16/09/97
		EP 0906100 A	07/04/99
		IT 240675 Y	02/04/01
		IT 1282705 B	31/03/98
		IT MI960378 A,U	28/08/97
		JP 2001511763 T	14/08/01
		US 5990114 A	23/11/99

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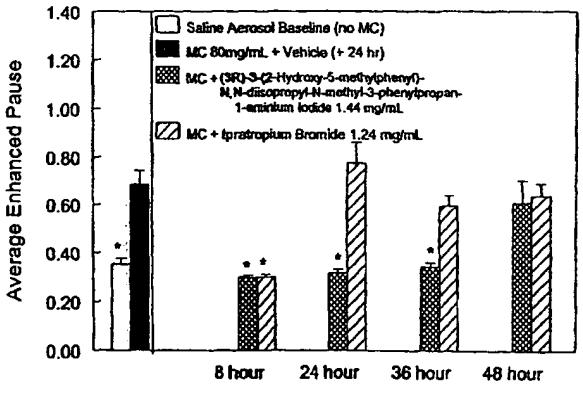
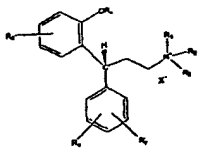
(54) Title: QUARTERNARY AMMONIUM COMPOUNDS AND THEIR USE AS ANTIMUSCARINIC AGENTS





(I)

(57) Abstract: Novel quaternary ammonium compounds of the formula (I) and any stereoisomers thereof, wherein, R_1, R_2, and R_3 independently represent C_1-C_6 alkyl, optionally substituted with phenyl or hydroxyl, or both, and wherein any two of R_1, R_2 and R_3 may form a ring together with the quaternary ammonium nitrogen; R_4 represents -H, $-CH_3$, or -CO-R_{4-1}, wherein R_{4-1} represents -(C_1-C_4 alkyl), -(C_1-C_4 alkoxy), or $NR_{4-2}R_{4-3}$, wherein R_{4-2} and R_{4-3} independently represent -H or -(C_1-C_4 alkyl); R_5, R_6 and R_7 independently represent -H, $-OCH_3$, -OH, $-CONH_2$, $-SO_2NH_2$, -F, -Cl, -Br, -I, $-CF_3$, or -(C_1-C_4 alkyl), optionally substituted with one or two -OH, -(C_1-C_4 alkoxy), -COOH, or -CO-O-(C_1-C_3 alkyl); and X represents an anion of a pharmaceutically acceptable acid, the compounds for use as medicaments, use of the compounds for the manufacture of specific medicaments, and pharmaceutical compositions comprising the compounds. The present invention also concerns a method of treatment involving administration of the compounds.

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QUATERNARY AMMONIUM COMPOUNDS AND THEIR USE AS ANTIMUSCARINIC AGENTS

This application claims the benefit of US Provisional Patent Application No. 60/348 930, filed 26 October 2001, US Provisional Patent Application No. 60/361 979, filed 6 March 2002, and US Provisional Patent Application No. 60/391 521, filed 25 June 2002, and the entire disclosures of which are herein incorporated by reference.

Technical Field

The present invention concerns a novel class of quaternary ammonium compounds, pharmaceutical compositions containing the same, the compounds for use as medicaments, and use of the compounds for the manufacture of specific medicaments. The present invention also concerns a method of treatment involving administration of the compounds.

The novel compounds are useful as antimuscarinic agents. In particular, the novel compounds are useful for the treatment of asthma, a group of breathing disorders termed Chronic Obstructive Pulmonary Disease (COPD), allergic rhinitis, and rhinorrhea due to the common cold.

Background of the Invention

US Patent 5,382,600 discloses (substituted) 3,3-diphenylpropylamines useful for treating urinary incontinence. In particular, it discloses 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl)-4-methylphenol, also known as N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, with the generic name of tolterodine, as being useful to treat urinary incontinence. Tolterodine is the compound of Example 22 of US 5,382,600.

It is preferred that tolterodine is prepared by the processes of International Publication WO98/29402 (US 5,922,914).

H Postlind *et al*, Drug Metabolism and Disposition, 26(4): 289-293 (1998) discloses that tolterodine is a muscarinic receptor antagonist. It is presently being sold in a number of different countries for treatment of urinary incontinence under the name Detrol®, marketed by Pharmacia. When tolterodine is used to treat urinary incontinence it is administered perorally as a tablet. The major, active metabolite of tolterodine is the 5-hydroxymethyl derivative of tolterodine.

US Patent 5,559,269 and H Postlind *et al*, Drug Metabolism and Disposition, 26(4): 289-293 (1998) disclose hydroxytolterodine. US Patent 5,559,269 discloses this compound as being useful to treat urinary incontinence. Pharmacol. Toxicol., 81: 169-172 (1997) discloses that hydroxytolterodine has antimuscarinic activity.

The international patent application WO98/43942 discloses therapeutically active diarylpropylamines, which have favorable anticholinergic properties, and which can be used for the treatment of disorders related to urinary incontinence.

WO 02/34245 discloses the use of tolterodine for treating asthma, COPD, and allergic rhinitis.

The currently marketed administration form of tolterodine is film-coated tablets containing 1 mg or 2 mg of tolterodine L-tartrate, or extended release capsules containing 2 mg or 4 mg of tolterodine L-tartrate for release in the gastrointestinal tract. Consumers constantly require alternative delivery forms with favorable efficacy and/or which simplify the treatment, thus improving their quality of life.

Atropine methonitrate and ipratropium are quaternary ammonium derivatives of atropine. Ipratropium bromide is

used by inhalation to produce bronchodilation. Ipratropium is 8-isopropylnoratropine methobromide and is disclosed in US Patent 3,505,337.

Yono M *et al*, European Journal of Pharmacology (1999) 368:223-230, is concerned with the pharmacological effects of tolterodine, an antimuscarinic drug, in isolated human urinary bladder smooth muscle.

Ruffmann R *et al*, The Journal of International Medical Research (1998) 16:317-330, reviews use of flavoxate hydrochloride or alternative compounds, such as terodiline hydrochloride and emepronium bromide, in the treatment of urge incontinence.

Stewart BH *et al*, The Journal of Urology (1976) 115:558-559 discloses therapy of mild to moderate stress urinary incontinence with a combination of phenylpropanolamine hydrochloride, chlorpheniramine maleate, and isopropamide iodide in a sustained release capsule.

WO 95/10269 and WO 95/10270 disclose the use of R- and S-terodiline, respectively, as drugs for treating conditions related to the compounds' activities as anticholinergic agents.

Despite the above advances in the art, it is desirable to develop novel pharmaceutical compounds that further improve the quality of life for a large number of individuals.

Summary of the Invention

For these and other purposes, it is an object of the present invention to provide highly efficient pharmaceutical compounds for treatment of asthma.

It is also an object of the present invention to provide highly efficient pharmaceutical compounds for treatment of Chronic Obstructive Pulmonary Disease (COPD).

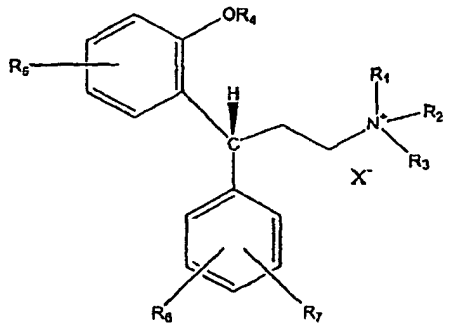
It is a further object of the present invention to provide highly efficient pharmaceutical compounds for treatment of allergic rhinitis.

It is an object of the present invention to provide highly efficient pharmaceutical compounds for treatment of rhinorrhea due to the common cold.

It is also an object of the present invention to provide pharmaceutically effective 3,3-diphenylpropylamine derivatives having an increased residence time in lung upon pulmonary administration.

It is an object of the present invention to provide a novel class of 3,3-diphenylpropylamine derivatives having favorable properties.

For these and other objects that will be evident from the following disclosure, the present invention provides a quaternary ammonium compound of the formula



and any stereoisomers thereof, wherein

R_1, R_2 and R_3 independently represent C_1-C_6 alkyl, optionally substituted with phenyl or hydroxyl, or both, and wherein any two of R_1, R_2 and R_3 may form a ring together with the quaternary ammonium nitrogen;

R_4 represents

-H,

$-CH_3$, or

$-CO-R_{4-1}$ wherein R_{4-1} represents

$-(C_1-C_4$ alkyl),

$-(C_1-C_4$ alkoxy), or

$-NR_{4-2}R_{4-3}$, wherein R_{4-2} and R_{4-3} independently represent -H or -(C_1-C_4 alkyl), and

R_5, R_6 and R_7 independently represent

-H,

$-OCH_3$,

-OH,

$-CONH_2$,

$-SO_2NH_2$,

-F, -Cl, -Br, -I,

$-CF_3$, or

-(C_1-C_4 alkyl), optionally substituted with one or two

-OH,

-(C_1-C_4 alkoxy),

-COOH, or

-CO-O-(C_1-C_3 alkyl), and

X^- represents an anion of a pharmaceutically acceptable acid.

In an embodiment of the compound according to the invention, the carbon stereocenter is (R). In another embodiment of the compound according to the invention, the carbon stereocenter is (S). In yet another embodiment, the compound according to the invention is a mixture of stereoisomers.

In a preferred embodiment of the compound according to the invention, at least one of R_1, R_2 and R_3 represents C_1-C_3 alkyl. In a more preferred embodiment, at least one, preferably at least two, of R_1, R_2 and R_3 represents isopropyl. In another more preferred embodiment, at least one of R_1, R_2 and R_3 represents methyl. In yet another more preferred embodiment, at least one of R_1, R_2 and R_3 represents ethyl.

In one preferred embodiment of the compound according to the invention, R_1 and R_2 jointly form a ring together with the quaternary ammonium nitrogen. In a more

preferred embodiment, said ring comprises from 4 to 6 carbon atoms.

In a preferred embodiment of the compound according to the invention, R_4 represents -H, $-CH_3$, or $-CO-R_{4-1}$, wherein R_{4-1} represents C_1-C_4 alkyl. In a more preferred embodiment, R_4 represents -H.

In a preferred embodiment of the compound according to the invention, R_5 represents -H, -Br, -Cl, $-CH_3$, or $-CH_2OH$, more preferably $-CH_3$.

In a preferred embodiment of the compound according to the invention, at least one, more preferably both, of R_6 and R_7 represents -H.

In a preferred embodiment of the compound according to the invention, X^- is selected from the group consisting of the anions of the following acids: tartaric, hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, nitric, citric, methanesulfonic, $CH_3-(CH_2)_n-COOH$ where n is 0 thru 4, $HOOC-(CH_2)n-COOH$ where n is 1 thru 4, HOOC-CH=CH-COOH, and benzoic. In a more preferred embodiment, X^- is selected from the group consisting of iodide, bromide, and chloride. In an even more preferred embodiment, X^- represents iodide. In another even more preferred embodiment, X^- represents chloride. In yet another even more preferred embodiment, X^- represents bromide.

More specifically, preferred embodiments of the compound according to the invention include the title compounds of the examples. Particularly preferred embodiments are selected from the group consisting of

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide, and

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium chloride.

Moreover, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a quaternary ammonium compound according to the invention, and a suitable pharmaceutical carrier therefor.

The present invention also provides a quaternary ammonium compound according to the invention for use as a medicament.

The present invention provides use of a quaternary ammonium compound according to the invention for the manufacture of a medicament for treating asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, rhinorrhea due to the common cold, or urinary disorder.

Finally, the present invention provides a method of treating asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, rhinorrhea due to the common cold, or urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of a quaternary ammonium compound according to the invention.

Brief Description of the Drawings

Figures 1-3 are diagrams showing average enhanced pause (lung resistance) as a function of time upon inhalation of quaternary ammonium salts according to the invention in Balb/c mice.

Figure 4 is a diagram showing the effects of inhalation of tolterodine and a compound according to the invention, respectively, on the average enhanced pause (lung resistance) as a function of time in Balb/c mice.

Figure 5 is a diagram showing the effects of inhalation of a compound according to the invention and ipratropium bromide, respectively, on the average enhanced pause (lung resistance) as a function of time in Balb/c mice.

Figure 6 is a diagram showing the plasma concentration (pg/ml) of a compound according to the invention with time (hours) following aerosol administration of various amounts in Balb/c mice.

Figure 7 is a diagram showing the plasma concentration (ng/ml) of tolterodine with time (hours) following aerosol administration of various amounts in mice.

Description of the Invention

In describing the preferred embodiment, certain terminology will be utilized for the sake of clarity. Such terminology is intended to encompass the recited embodiments, as well as all technical equivalents that operate in a similar manner for a similar purpose to achieve a similar result. To the extent that any pharmaceutically active compound is disclosed or claimed, it is expressly intended to include all active metabolites produced in vivo, and, is expressly intended to include all enantiomers, isomers or tautomers where the compound is capable of being present in its enantiomeric, isomeric or tautomeric form.

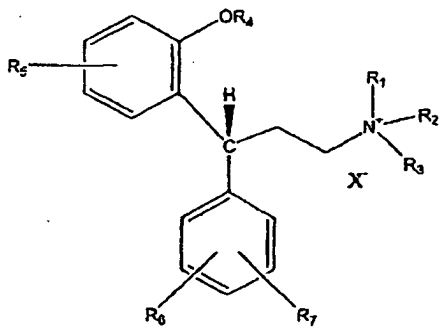
The compounds of the invention can be prepared by one skilled in the art just by knowing the chemical structure of the compound to be prepared. The invention is the compounds themselves, not the process chemistry to make them. The chemistry is known to those skilled in the art.

Accordingly, the compounds of the present invention are quaternary ammonium compounds and are prepared by means, well known to those skilled in the art, for preparing quaternary ammonium compounds from tertiary amines, using the tertiary amines of US Patent 5,382,600 and other known compounds as starting materials. The general term "quaternary ammonium compound" relates to

any compound that can be regarded as derived from ammonium hydroxide or an ammonium salt by replacement of all four hydrogen atoms of the NH_4^+-ion by organic groups.

The specific compounds are for nomenclature reasons (see e.g. Chemical Abstracts) named as "aminium" compounds, but it is possible to use the term "ammonium" in the names. For example, (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide can also be named as an ammonium compound: (3R)-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]diisopropylmethylammonium bromide.

More specifically, the invention concerns quaternary ammonium compounds of the formula:



and any stereoisomers thereof, wherein R_1-R_7 and X^- are as follows.

R_1, R_2 and R_3 independently represent C_1-C_6 alkyl, optionally substituted with phenyl or hydroxyl, or both, and any two of R_1, R_2 and R_3 may form a ring together with the quaternary ammonium nitrogen.

R_4 represents -H, $-CH_3$, or $-CO-R_{4-1}$, wherein R_{4-1} represents -(C_1-C_4 alkyl), -(C_1-C_4 alkoxy), or $-NR_{4-2}R_{4-3}$, wherein R_{4-2} and R_{4-3} independently represent -H or -(C_1-C_4 alkyl).

R_5, R_6 and R_7 independently represent -H, $-OCH_3$, -OH, $-CONH_2$ (carbamoyl), $-SO_2NH_2$ (sulphamoyl), -F, -Cl, -Br, -I, $-CF_3$, or -(C_1-C_4 alkyl), optionally substituted with

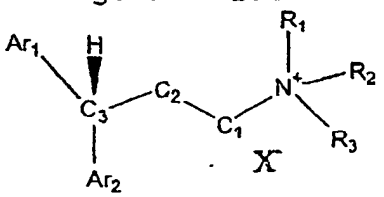
one or two -OH, -(C_1-C_4 alkoxy), -COOH, or -CO-O-(C_1-C_3 alkyl), and X^- represents an anion of a pharmaceutically acceptable acid.

By way of example, a tertiary amine according to US Patent 5,382,600, or its salt, is dissolved in a suitable solvent. The tertiary amine is allowed to react with an organic substrate, e.g. an organic halide.

The substrate contains a C_1-C_6 alkyl, preferably a C_1-C_3 alkyl, optionally substituted with phenyl, and a leaving group. The identity of the leaving group is not critical, but it is preferred that the leaving group is a halide, such as iodide or bromide. Thus, exemplary substrates include methyl iodide, methyl bromide, ethyl iodide, propyl iodide, benzyl bromide or benzyl iodide.

The resulting reaction product is a quaternary ammonium compound, which is readily crystallized in suitable solvents, known to those skilled in the art. The crystals thus produced are quaternary ammonium salts. Their identity is confirmed by standard methods, such as melting point determination, nuclear magnetic resonance (NMR) analysis and mass spectrometry.

The quaternary ammonium compounds of the invention have at least one stereocenter, i.e. the carbon in position 3 (C_3 in the formula below), to which two (substituted) aryl groups are attached. Optionally, there may be a second stereocenter (when R_1, R_2 and R_3 all are different), the positively charged quaternary ammonium nitrogen atom. See the general formula:



wherein Ar_1 and Ar_2 denote (substituted) aryl groups, R_1, R_2, R_3 and X^- are as above, and C_1, C_2 and C_3 denote individual carbon atoms in the propylammonium backbone. Accordingly, stereoisomers (enantiomers and/or diastereomers) are produced. All stereoisomers have useful activity. Therefore, the invention includes use of each stereoisomer separately, as well as mixtures thereof. Specifically, the stereoisomers in which the C_3 carbon stereocenter is in the (R) form have useful activity. Moreover, the stereoisomers in which the C_3 carbon stereocenter is in the (S) form have useful activity. A mixture of stereoisomers, comprising the stereoisomers in which the C_3 carbon stereocenter is in the (R) form and the stereoisomers in which the C_3 carbon stereocenter is in the (S) form, also has useful activity.

The quaternary ammonium compounds of the invention are preferably administered as salts with a pharmaceutically acceptable acid. Where R_4 is -H, the compounds can be isolated as internal salts, which have a phenoxide anion to balance the positive charge on the quaternized nitrogen. The preferred pharmaceutically acceptable salts include salts of the following acids: tartaric, hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, nitric, citric, methanesulfonic, $CH_3-(CH_2)_n-COOH$ where n is 0 thru 4, $HOOC-(CH_2)_n-COOH$ where n is 1 thru 4, HOOC-CH=CH-COOH, and benzoic. For other acceptable salts, see Int. J. Pharm., 33, 201-217 (1986). Particularly preferred salts are chloride, iodide and bromide salts, especially bromide salts and iodide salts.

Accordingly, X^- represents an anion of a pharmaceutically acceptable acid. Preferably, X^- is selected from the following anions: tartrate, chloride, bromide, iodide, sulfate, phosphate(s), nitrate, citrate, methanesulfonate, carboxylates with from two to six

carbon atoms, dicarboxylates with from two to six carbon atoms, maleate, fumarate, and benzoate. It is preferred that X^- represents chloride, iodide or bromide, more preferred iodide or bromide.

The substituents R_1, R_2, R_3 may be the same or different. They are selected from the group comprising C_1-C_6 alkyls, preferably C_1-C_5 alkyls, straight or branched, optionally substituted with phenyl or hydroxyl, or both. Thus, R_1, R_2, R_3 independently represent methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, hexyl, or isohexyl, optionally substituted with phenyl or hydroxyl, or both.

It is preferred that at least one of the substituents R_1, R_2, R_3 represents a C_1-C_3 alkyl, straight or branched, i.e. methyl, ethyl, propyl, or isopropyl. It is particularly preferred that one of the substituents R_1, R_2, R_3 represents methyl or ethyl, preferably methyl. It is also preferred that at least one, more preferred two, of the substituents R_1, R_2, R_3 represent(s) isopropyl. It is especially preferred that R_1 and R_2 each represent isopropyl, and R_3 represents methyl or ethyl, preferably methyl. The substituents R_1, R_2, and R_3 together contain at least 3 carbon atoms. It is preferred that the substituents R_1, R_2, and R_3 together contain at least 4 carbon atoms, more preferred at least 5 carbon atoms, even more preferred at least 6 carbon atoms.

According to another aspect of the invention, any two of R_1, R_2, and R_3 may jointly form a ring structure together with the positively charged nitrogen. It is preferred that the resulting ring structure comprises from four to six carbon atoms.

The substituent R_4 is attached via an oxygen atom to its aryl ring. The $-OR_4$ group is attached to the carbon atom in position 2 in the ring, with respect to the

propylammonium group. The substituent R_4 may represent hydrogen, methyl or acyl (-CO-R_{4-1}), wherein acyl includes any one of the following: alkylcarbonyl, straight or branched, having from two to five carbon atoms, alkoxycarbonyl, straight or branched, having from two to five carbon atoms, and amide, optionally mono- or independently disubstituted with alkyl, straight or branched, having from one to four carbon atom(s). Accordingly, the substituent R_{4-1} represents any one of the following: C_1-C_4 alkyl, straight or branched, C_1-C_4 alkoxy, straight or branched, and -$NR_{4-2}R_{4-3}$, wherein R_{4-2} and R_{4-3} may be the same or different and represent -H or -(C_1-C_4 alkyl), straight or branched. Thus, the substituent R_4 may represent any one of the following: hydrogen, methyl or acyl, wherein the acyl group may be acetyl (ethanoyl), propanoyl, butanoyl, isobutanoyl, pentanoyl, isopentanoyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-butylcarbamoyl, or an N,N-dialkylcarbamoyl, wherein the alkyl groups, straight or branched, are the same or different and have from 1 to 4 carbon atoms each. Examples of N,N-dialkylcarbamoyls in this position include N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N,N-dipropylcarbamoyl, as well as N,N-diisobutylcarbamoyl, and N-propyl-N-butylcarbamoyl. It is preferred that R_4 represents hydrogen, since such compounds can be isolated as internal salts, which have a phenoxide anion to balance the positive charge on the quaternized nitrogen. It is also preferred that R_4 represents alkylcarbonyl, straight or branched, having from two to five carbon atoms, e.g. acetyl (ethanoyl), propanoyl, butanoyl, isobutanoyl, pentanoyl, or isopentanoyl. Moreover, it is preferred that R_4 represents methyl.

The substituent R_5 may be connected to any, otherwise not substituted, carbon atom in its aryl ring. In other words, R_5 is not connected to any of the carbon atoms to which the $-OR_4$ group or the (substituted) phenylpropanammonium group is connected, but R_5 may be connected to any one of the remaining four carbon atoms in its aryl ring.

R_5 may represent any one of the following: hydrogen, methoxy, hydroxyl, carbamoyl, sulphamoyl, halogen (fluorine, chlorine, bromine, iodine), trifluoromethyl or an alkyl group, straight or branched, having from one to four carbon atoms. Optionally, this alkyl group may be mono- or independently disubstituted with hydroxyl, with an alkoxy group, straight or branched, having from one to four carbon atoms, with carboxyl, or with alkoxycarbonyl ($-CO-O-(C_1-C_3$ alkyl)), straight or branched, having from one to four carbon atoms. It is preferred that R_5 represents any one of the following: hydrogen, bromine, chlorine, methyl or hydroxymethyl. It is particularly preferred that R_5 represents methyl. If R_5 does not represent hydrogen, it is preferred that R_5 is situated opposite the $-OR_4$ group, i.e. at the carbon atom in position 5 in the ring, with respect to the propylammonium group.

The substituents R_6 and R_7 are connected to the same aryl ring, which is different from the aryl ring to which the substituents R_4 and R_5 are connected. R_6 and R_7 may be the same or different. R_6 and R_7 may independently represent any one of the following: hydrogen, methoxy, hydroxyl, carbamoyl, sulphamoyl, halogen (fluorine, chlorine, bromine, iodine), trifluoromethyl or an alkyl group, straight or branched, having from one to four carbon atoms. Optionally, this alkyl group may be mono- or independently disubstituted with hydroxyl, with an alkoxy group, straight or branched, having from one to four carbon atoms, with carboxyl, or with alkoxycarbonyl

(-CO-O-(C_1-C_3 alkyl)), straight or branched, having from one to four carbon atoms.

It is preferred that at least one, preferably both, of R_6 and R_7 represents hydrogen. When one, but not both, of R_6 and R_7 represents hydrogen, it is preferred that the other (R_7 or R_6, respectively) is attached to the carbon atom in position 2 in the ring, with respect to the propylammonium group. When neither R_6 nor R_7 represent hydrogen, it is preferred that one is attached to the carbon atom in position 2 and the other to any one of the carbon atoms in positions 3, 4, or 5, respectively, in the ring, with respect to the propylammonium group.

The novel class of compounds according to the present invention are antimuscarinic agents. "Antimuscarinic agents" refer to muscarinic receptor antagonists. Examples of known antimuscarinic agents include tolterodine, hydroxytolterodine, 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, propiverine, oxybutynin, trospium, darifenacin, temiverine, ipratropium, and tiotropium.

Propiverine is 1-methyl-4-piperidyl .alpha.,.alpha.-diphenyl-.alpha.-(n-propoxy)acetate and is disclosed in East German Patent 106,643 and in CAS 82-155841s (1975). Oxybutynin is 4-(diethylamino)-2-butynylalphaphenylcyclohexaneglycolate and is disclosed in UK Patent 940,540. Trospium is 3alpha-hydroxyspiro[1alphaH,5alphaH-nortropane-8,1'pyrrolidinium]chloride benzilate and is disclosed in US Patent 3,480,623. Darifenacin is 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-alpha,alpha-diphenyl-, and is disclosed in US Patent 5,096,890. Temiverine is benzeneacetic acid, .alpha. cyclohexyl-.alpha.-hydroxy-, 4-(diethylamino)-1,1-dimethyl-2-butynyl ester and is disclosed in US Patent 5,036,098. Ipratropium is 8-

isopropylnoratropine methobromide and is disclosed in US Patent 3,505,337. Tiotropium is (1-alpha,2-beta,4-beta,5-alpha,7-beta)-7-[(hydroxydi-(2-thienyl)acetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.02,4]nonane and is disclosed in EP 418,716.

The compounds of the invention have anti-cholinergic properties. Thus, they are useful for the treatment of acetylcholine-mediated disorders. In particular, they are useful for treating asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, and rhinorrhea due to the common cold.

"Asthma" refers to a chronic lung disease causing bronchoconstriction (narrowing of the airways) due to inflammation (swelling) and tightening of the muscles around the airways. The inflammation also causes an increase in mucus production, which causes coughing that may continue for extended periods. Asthma is characterized by recurrent episodes of breathlessness, wheezing, coughing, and chest tightness, termed exacerbations. The severity of exacerbations can range from mild to life threatening. The exacerbations can be a result of exposure to e.g. respiratory infections, dust, mold, pollen, cold air, exercise, stress, tobacco smoke, and air pollutants.

"COPD" refers to Chronic Obstructive Pulmonary Disease, primarily associated with past and present cigarette smoking. It involves airflow obstruction, mainly associated with emphysema and chronic bronchitis. Emphysema causes irreversible lung damage by weakening and breaking the air sacs within the lungs. Chronic Bronchitis is an inflammatory disease, which increases mucus in the airways and bacterial infections in the bronchial tubes, resulting in obstructed airflow.

"Allergic rhinitis" refers to acute rhinitis or nasal rhinitis, including hay fever. It is caused by

allergens such as pollen or dust. It may produce sneezing, congestion, runny nose, and itchiness in the nose, throat, eyes, and ears.

"Rhinorrhea due to the common cold" refers to watery discharge from the nose in association with a virus infection, such as the common cold. The rhinorrhea may be caused by rhinitis due to a virus infection (such as the common cold).

"Urinary disorders" and symptoms thereof include some or all of the following: urgency, frequency, incontinence, urine leakage, enuresis, dysuria, hesitancy, and difficulty of emptying bladder. In particular, urinary disorders include urinary incontinence, caused by e.g. unstable or overactive urinary bladder.

Overactive urinary bladder encompasses variants of urinary disorders, including overactive detrusor (detrusor instability, detrusor hyperreflexia) and sensory urgency, as well as symptoms of detrusor overactivity, e.g. urge incontinence, urgency, urinary frequency, and LUTS (Lower Urinary Tract Symptoms), including obstructive urinary symptoms, such as slow urination, dribbling at the end of urination, inability to urinate and/or the need to strain to urinate at an acceptable rate, or irritating symptoms such as frequency, dry overactive bladder, and/or urgency).

Other conditions are also included, which give rise to urinary frequency, urgency and/or urge incontinence. Overactive bladder disorders also include nocturia and mixed incontinence. While overactive bladder is often associated with detrusor muscle instability, disorders of bladder function may also be due to neuropathy of the central nervous system (detrusor hyperreflexia), including spinal cord and brain lesions, such as multiple sclerosis and stroke. Overactive bladder symptoms may also result from, for example, male bladder outlet

obstruction (usually due to prostatic hypertrophy), interstitial cystitis, local edema and irritation due to focal bladder cancer, radiation cystitis due to radiotherapy to the pelvis, and cystitis.

The compounds of the present invention are used to treat mammals, including man and horse. It is preferred that the mammal is a human.

The compounds according to the invention, in the form of free base or salts with pharmaceutically acceptable acids, or solutions thereof, can be brought into suitable dosage forms, such as compositions for administration through the oral, rectal, transdermal, parenteral, nasal, or pulmonary route in accordance with accepted pharmaceutical procedures. In particular, the compositions may be administered via inhalation or insufflation. Such pharmaceutical compositions according to the invention comprise the compounds according to the invention in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives such as stabilizers, wetting agents, emulsifiers, flavoring agents, buffers, binders, disintegrants, lubricants, glidants, antiadherents, propellants, and the like.

The novel compounds according to the present invention can be administered in any suitable way. The compounds according to the invention can be made up in

solid or liquid form, such as tablets, capsules, powders, syrups, elixirs and the like, aerosols, sterile solutions, suspensions or emulsions, and the like. They are advantageously administered via inhalation or insufflation. When the administration form is inhalation or insufflation, the compounds are preferably in the form of either an aerosol or a powder.

The term "effective amount" refers to a therapeutically effective amount for treating asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, rhinorrhea due to the common cold, or urinary disorder. The terms "therapy" and "therapeutically" encompass all kinds of treatments, including prophylaxis. In particular, "therapeutically effective" means that it is effective for anti-cholinergic treatment.

The dosage of the specific compound according to the invention will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated.

Doses administrated by inhaler, such as a dry powder inhaler (DPI) or a metered-dose inhaler (MDI), are preferably given as one or two puffs, preferably comprising the total daily dose. For a human subject, it is preferred that the dosage is in the range of from 1 microgram (1 μg) to one milligram (1 mg).

Doses administrated by nebulizer solution are generally higher than doses administrated by inhaler. For a human subject, it is preferred that the total dosage given by nebulizer solution is in the range of from 1 microgram (1 μg) to ten milligrams (10 mg).

Thus, a clinically effective amount of the compounds according to the invention is from about 1 μg to about 10 mg. It is preferred that the effective amount is from about 1 μg to about 1 mg, preferably from about 0.01 mg to about 1 mg.

The compounds of the invention can be administered from one to four times daily. It is preferable to administer the compounds once or twice daily, more preferable once daily.

The dosage form for inhalation can be an aerosol. The minimum amount of an aerosol delivery is about 0.2 ml and the maximum aerosol delivery is about 5 ml. The concentration of the compounds according to the invention may vary as long as the total amount of spray delivered is within the about 0.2 to about 5 ml amount and it delivers an effective amount. It is well known to those skilled in the art that if the concentration is higher, one gives a smaller dose to deliver the same effective amount.

The non-active ingredient or carrier can be just (sterile) water with the pH adjusted to where the active pharmaceutical agent is very soluble. It is preferred that the pH be at or near 7. Alternatively and preferably, the non-active carrier agent should be physiological saline with the pH adjusted appropriately. Aerosols for inhalation of various pharmaceutical agents are well known to those skilled in the art, including many aerosols for treating asthma.

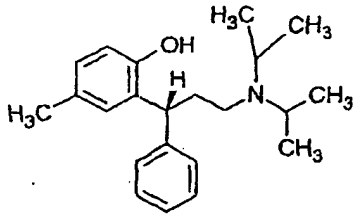
Alternatively, the dosage form for inhalation can be a powder. Powders for inhalation of various pharmaceutical agents are well known to those skilled in the art, including many powders for treating asthma. When the dosage form is a powder, the compounds according to the invention can be administered in pure form or diluted with an inert carrier. When an inert carrier is used, the compounds according to the invention are compounded such that the total amount of powder delivered delivers an "effective amount" of the compounds according to the invention. The actual concentration of the active

compound may vary. If the concentration is lower, then more powder must be delivered; if the concentration is higher, less total material must be delivered to provide an effective amount of the active compound according to the invention.

For treatment of rhinitis, in particular rhinitis due to the common cold, the compounds according to the invention can advantageously be administered in combination with steroids, cromoglycates, and decongestants (alpha agonists). Such combination therapies are useful in the treatment of rhinorrhea due to the common cold.

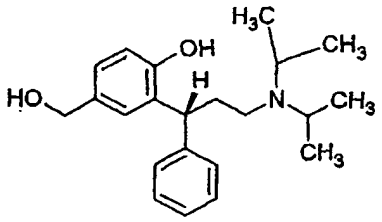
The invention will be further illustrated by the following non-limiting examples and pharmacological tests.

Tolterodine refers to 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol, also known as N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, a compound of the formula:



(R)-stereoisomer

Hydroxytolterodine refers to 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol, a compound of the formula:



(R)-stereoisomer

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

Examples

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

All temperatures are in degrees Celsius.

Ether refers to diethyl ether.

Physiological saline refers to an 0.9% aqueous sodium chloride solution.

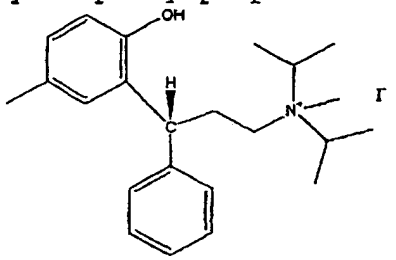
When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

EXAMPLE 1 Tolterodine Free Base

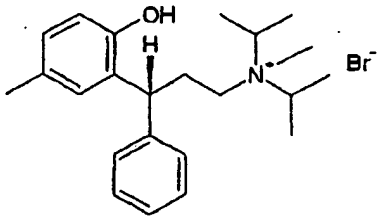
Tolterodine tartrate (2.1 g) is mixed with water (45 ml) and toluene (2.5 ml). Sodium carbonate (800 mg) is added to the slurry. Sodium hydroxide (2.0 N, 1.5 ml) is added. The mixture is extracted three times with toluene (3 ml), saving the organic phase. Anhydrous potassium carbonate is added to the organic phase dissolve the tolterodine tartate, giving the title compound in solution.

EXAMPLE 2 (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



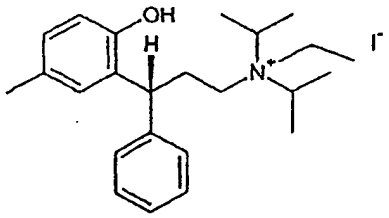
To tolterodine free base (from Example 1, 0.5 M, 2.5 ml) in toluene is added methyl iodide (1 ml). Acetonitrile (5 ml) is added to the mixture and stirred over night at 20-25°C. The solvent is removed by blowing dry nitrogen. Acetone (1 ml) and hexane (2 ml) are added and the mixture is filtered at 20-25°C to give the title compound. Anal Calcd for $C_{23}H_{34}INO$: C, 59.10; H, 7.33; N, 3.00. Found: C, 59.00; H, 7.44; N, 3.00. The identity of the compound has been further verified and characterised by NMR analysis, mass spectrometry, and melting point determination.

EXAMPLE 3 (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



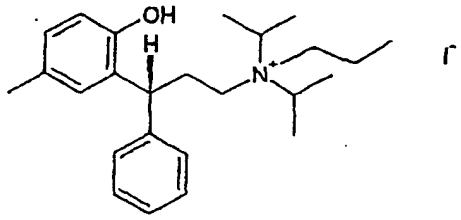
A sealed mixture of methyl bromide (100 g) and 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol (14 g) in acetone (100 ml) is stirred at 20-25°C for 4 days. The mixture is cooled to -10°C and the precipitate is filtered off and washed with ether and dried to give the title compound, mp 189-191°C (dec). Anal Calcd for $C_{23}H_{34}BrNO$: C, 65.71; H, 8.15; Br, 19.00; N, 3.33. Found: C, 65.61; H, 8.34; Br, 19.12; N, 3.32. $[\alpha]_D$ (c=1, MeOH) +25°C. ^1H NMR [$(CD_3)_2SO$] δ 1.25, 2.18, 2.48, 2.81, 3.05, 3.89, 4.22, 6.70, 6.83, 7.08, 7.19, 7.33, and 9.3.

EXAMPLE 4 (3R)-N-Ethyl-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropan-1-aminium iodide



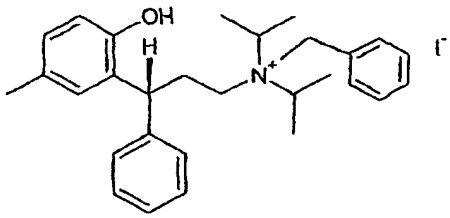
Following the general procedure of Example 2 and making non critical variations, but starting with ethyl iodide, the title compound is obtained.

EXAMPLE 5 (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenyl-N-propylpropan-1-aminium iodide



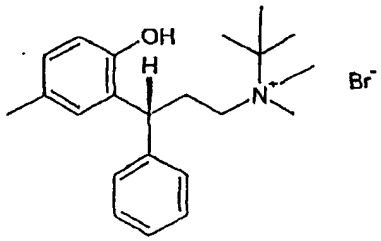
Following the general procedure of Example 2 and making non critical variations, but starting with propyl iodide, the title compound is obtained.

EXAMPLE 6 (3R)-N-Benzyl-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropan-1-aminium iodide



Following the general procedure of Example 2 and making non critical variations, but starting with benzyl iodide, the title compound is obtained.

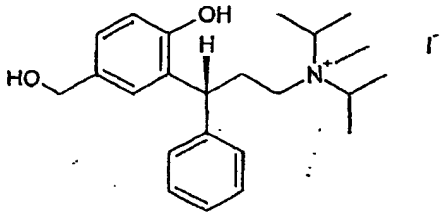
EXAMPLE 7 (3R)-N-(tert-Butyl)-3-(2-hydroxy-5-methylphenyl)-N,N-dimethyl-3-phenylpropan-1-aminium bromide



Following the general procedure of Example 2 and making non critical variations, but starting with methyl bromide

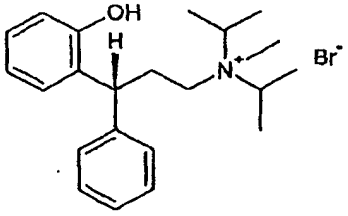
and 2-{(1R)-3-[tert-butyl(methyl)amino]-1-phenylpropyl}-4-methylphenol, the title compound is obtained.

EXAMPLE 8 (3R)-3-[2-Hydroxy-5-(hydroxymethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



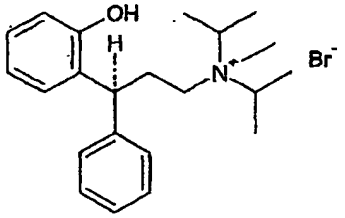
Following the general procedure of Example 2 and making non critical variations, but starting with 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol, the title compound is obtained. Anal Calcd for $C_{23}H_{34}INO_2$: C, 57.14: H, 7.09; N, 2.90. Found: C, 56.33; H, 7.33; N, 2.76. HRMS Calcd 356.2589. Found: 356.2588. ^1H NMR [$(CD_3)_2SO$] δ 1.25, 2.48, 2.81, 3.05, 3.88, 4.26, 4.35, 4.94, 6.75, 6.98, 7.20, 7.33, and 9.5.

EXAMPLE 9 (3R)-3-(2-Hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



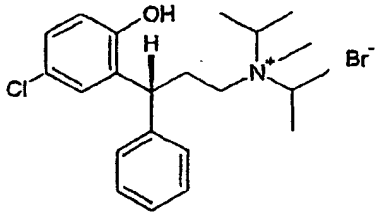
Following the general procedure of Example 3 and making non critical variations but starting with 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]phenol, the title compound is obtained.

EXAMPLE 10 (3S)-3-(2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



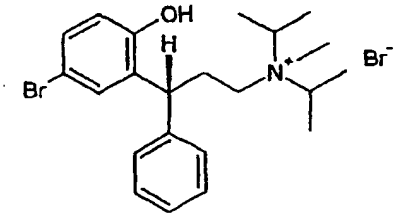
Following the general procedure of Example 3 and making non critical variations, but starting with 2-[(1S)-3-(diisopropylamino)-1-phenylpropyl]phenol, the title compound is obtained.

EXAMPLE 11 (3R)-3-(5-Chloro-2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



Following the general procedure of Example 3 and making non critical variations, but starting with 4-chloro-2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]phenol, the title compound is obtained.

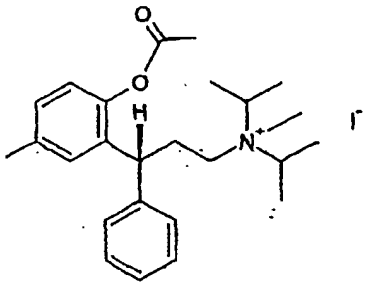
EXAMPLE 12 (3R)-3-(5-Bromo-2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



Following the general procedure of Example 3 and making non critical variations, but starting with 4-

bromo-2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]phenol, the title compound is obtained.

EXAMPLE 13 (3R)-3-[2-(Acetyloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



(A) 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl acetate

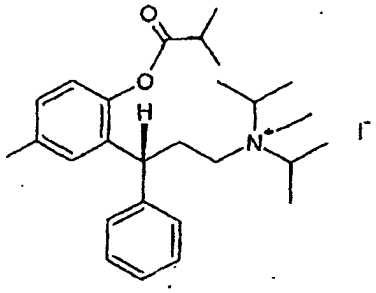
A solution of 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol (0.9 g) in acetylchloride (20 ml) is stirred at room temperature for 18 h. The acetyl chloride is evaporated, ether is added, and the precipitate of 2-(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl acetate hydrochloride is filtered off; mp 126-130°C. Anal Calcd for $C_{24}H_{33}NO_2 \cdot HCl$: C, 71.35; H, 8.48; Cl, 8.78; N, 3.47. Found: C, 71.02; H, 8.30; Cl, 8.64; N, 3.43. $[\alpha]_D$ (c=1, MeOH) +11°.

The hydrochloride salt is partitioned between ether and saturated sodium bicarbonate solution. The ether phase is separated and evaporated to obtain the free base of compound (A).

(B) (3R)-3-[2-(acetyloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide

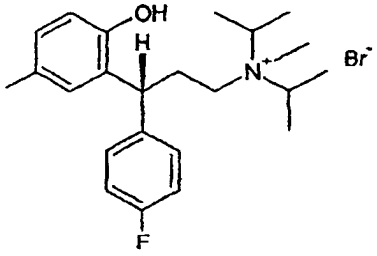
Following the general procedure of Example 2 and making non critical variations, but starting with (A): 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl acetate, the title compound (B) is obtained.

EXAMPLE 14 (3R)-3-[2-(Isobutyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



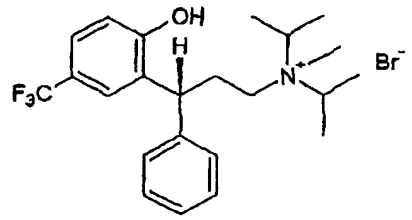
Following the general procedure of Example 2 and making non critical variations, but starting with 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl 2-methylpropanoate, the title compound is obtained.

EXAMPLE 15 (3R)-3-(4-Fluorophenyl)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium bromide



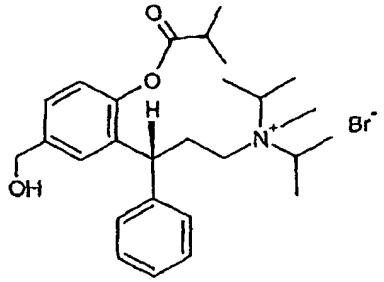
Following the general procedure of Example 3 and making non critical variations, but starting with 2-[(1R)-3-(diisopropylamino)-1-(4-fluorophenyl)propyl]-4-methylphenol, the title compound is obtained.

EXAMPLE 16 (3R)-3-[2-Hydroxy-5-(trifluoromethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



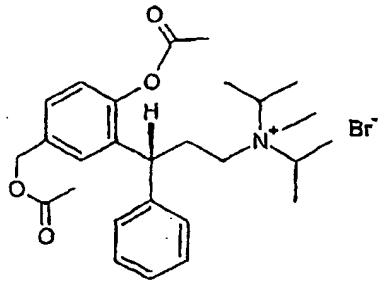
Following the general procedure of Example 3 and making non critical variations, but starting with 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-(trifluoromethyl)phenol, the title compound is obtained.

EXAMPLE 17 (3R)-3-[2-(Isobutyryloxy)-5-hydroxymethylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



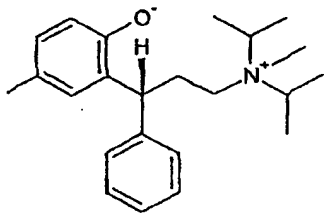
(3R)-3-[2-hydroxy-5-(hydroxymethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide is acylated with isobutyryl bromide to give the title compound.

EXAMPLE 18 (3R)-3-{2-(Acetyloxy)-5-[(acetyloxy)methyl]phenyl}-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



(3R)-3-[2-hydroxy-5-(hydroxymethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide is acylated with acetyl bromide, to give the title compound.

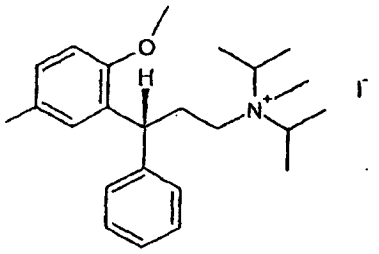
EXAMPLE 19 2-{(1R)-3-[Diisopropyl(methyl)ammonio]-1-phenylpropyl}-4-methylbenzenolate



(3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide from Example 2 is passed through an ion exchange column so as to remove the bromide ion and generate the title compound.

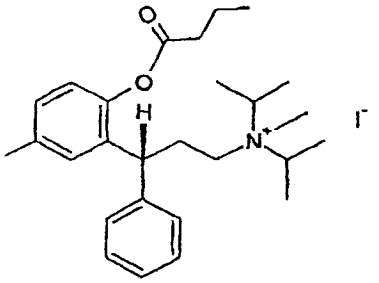
Reacting the above compound with an equivalent amount of an acid, such as methanesulfonic acid, hydrochloric acid, acetic acid, or succinic acid, generates other salts of the title compound.

EXAMPLE 20 (3R)-N,N-Diisopropyl-3-(2-methoxy-5-methylphenyl)-N-methyl-3-phenylpropan-1-aminium iodide



Following the general procedure of Example 2 and making non critical variations, but starting with (3R)-N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropan-1-amine, the title compound is obtained; mp 211 °C (dec). Anal Calcd for $C_{24}H_{36}INO$: C, 59.87; H, 7.54; N, 2.91. Found: C, 59.78; H, 7.56; N, 2.99. $[\alpha]_D$ (c = 1, MeOH) +13°.

EXAMPLE 21 (3R)-3-[2-(Butyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



(A) 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl butyrate

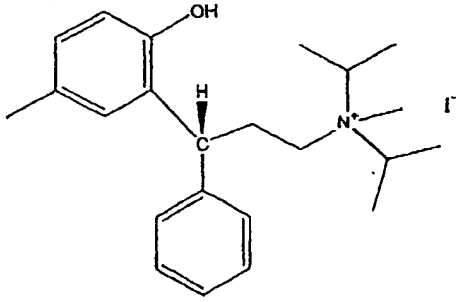
A solution of 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol (1.0 g) in butyryl chloride (5 ml) is heated under reflux for 90 min. Ether is added, and the precipitate of 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl butyrate hydrochloride is filtered off; mp 116-119 °C. Anal Calcd for $C_{26}H_{37}NO_2 \cdot HCl$: C, 72.28; H, 8.86; Cl, 8.21; N, 3.24. Found: C, 72.25; H, 8.71; Cl, 8.17; N, 3.25. $[\alpha]_D$ (c = 1, MeOH) +20°.

The hydrochloride salt is partitioned between ether and saturated sodium bicarbonate solution. The ether phase is separated and evaporated to obtain the free base of the title compound (A).

(B) (3R)-3-[2-(butyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide

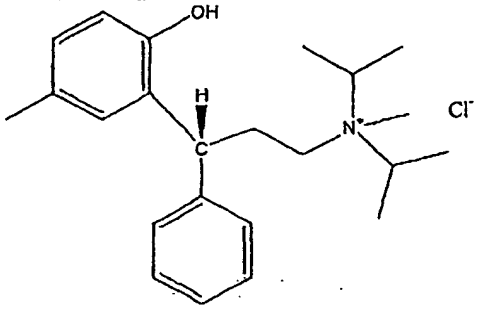
Following the general procedure of Example 2 and making non critical variations, but starting with (A): 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl butyrate, the title compound is obtained; mp 175 °C (dec). Anal Calcd for $C_{27}H_{40}INO_2$: C, 60.33; H, 7.50; N, 2.61. Found: C, 60.37; H, 7.52; N, 2.58.

EXAMPLE 22 (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



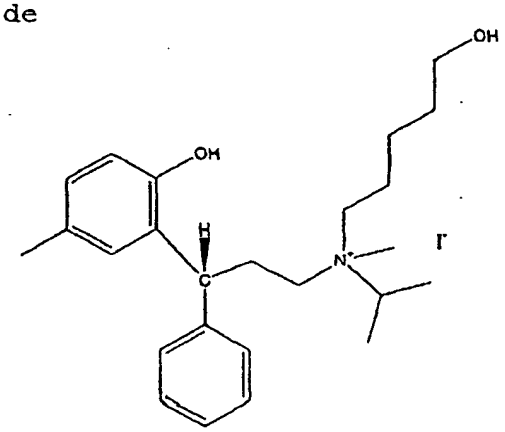
(3R)-3-[2-(butyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide (from Example 22) was hydrolysed with methanol, resulting in the title compound.

EXAMPLE 23 (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium chloride



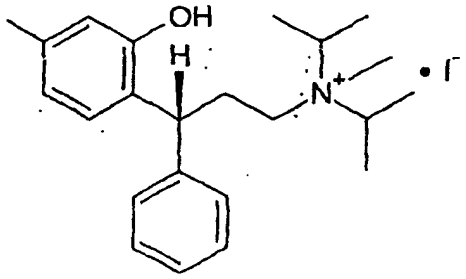
A solution of (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide (4.2 g, 0.01 mol) in water (50 ml) is neutralized by addition of 1 equivalent of 2 N sodium hydroxide solution (5.0 ml). The solvent is evaporated, and the residual oil is chromatographed to separate 2-{(1R)-3-[diisopropyl(methyl)ammonio]-1-phenylpropyl}-4-methylbenzenolate from the sodium bromide. The product is reconstituted in acetone, and a solution of hydrogen chloride in ethyl acetate is added to give a precipitate of the title compound.

EXAMPLE 24 5-Hydroxy-N-[(3R)-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-N-isopropyl-N-methylpentan-1-aminium iodide



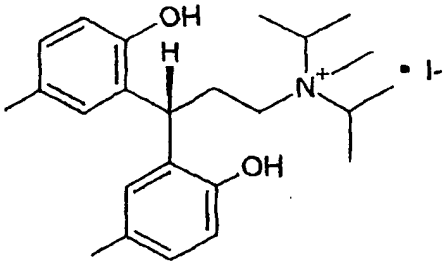
Following the general procedure of Example 2 and making non critical variations, but starting with 2-{(1R)-3-[(5-hydroxypentyl)(isopropyl)amino]-1-phenylpropyl}-4-methylphenol, the title compound is obtained.

EXAMPLE 25 (3R)-3-(2-Hydroxy-4-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



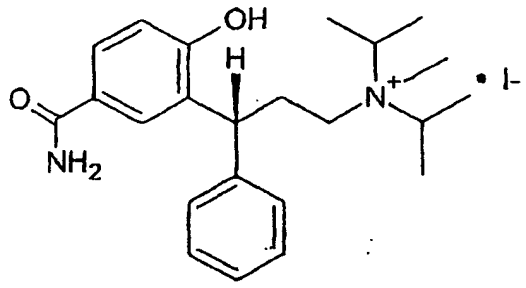
Following the general procedure of Example 2 and making non critical variations, but starting with 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-5-methylphenol, the title compound is obtained.

EXAMPLE 26 3,3-bis(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium iodide



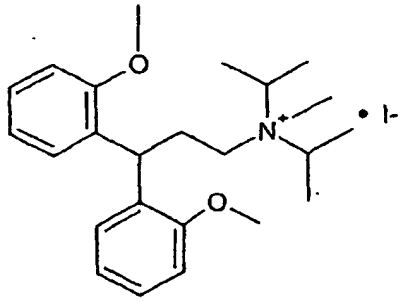
Following the general procedure of Example 2 and making non critical variations, but starting with 2-[3-(diisopropylamino)-1-(2-hydroxy-5-methylphenyl)propyl]-4-methylphenol, the title compound is obtained.

EXAMPLE 27 (3R)-3-[5-(Aminocarbonyl)-2-hydroxyphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



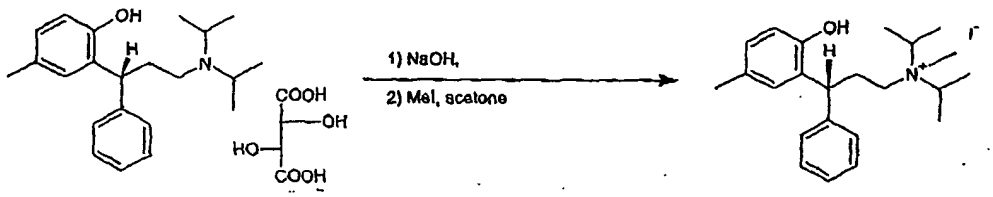
Following the general procedure of Example 2 and making non critical variations, but starting with 3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-hydroxybenzamide, the title compound is obtained.

EXAMPLE 28 3,3-bis(2-Methoxyphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium iodide



Following the general procedure of Example 2 and making non critical variations, but starting with N,N-diisopropyl-3,3-bis(2-methoxyphenyl)propan-1-amine, the title compound is obtained.

EXAMPLE 29 Large scale production of (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



A 5 l erlenmyer flask was charged with 250 g (526 mmol) tolterodine tartrate, water (2000 ml), and methylene chloride (2000 ml). A solution of 84 g of 50% NaOH diluted with 200 ml of water was added, and the mixture was stirred for 1 hour. The pH was kept in the range of 8-9. Both of the two resulting phases are clear and colorless.

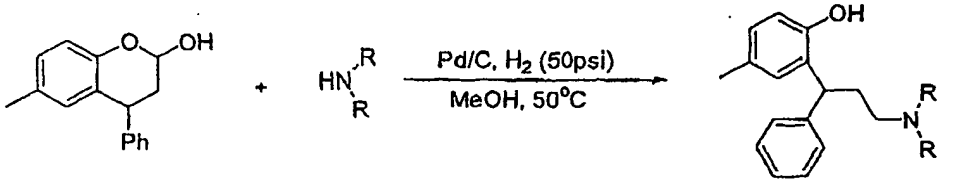
The phases were separated, and the aqueous phase was washed with methylene chloride (1000 ml). The combined organic phases were concentrated on the rotovap (60°C bath). The weight of the residue was determined. The residue was dissolved in acetone (1000 ml), and 263 ml (2.84 mol) methyl iodide was added, all in one portion. The mixture was stirred at room temperature overnight.

The resulting slurry was filtered, washed with acetone (250 ml) and dried in the vacuum oven at 50°C overnight.

This provided 230 g of the desired product, (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide.

EXAMPLE 30 Cyclic amine intermediates

The following general reductive amination procedure was employed:



wherein Ph represents a phenyl group, and R represents an alkyl group according to the following Table I.

Briefly, palladium on activated carbon (1.76 g, 5% by weight, Aldrich 20,568-0) was charged to a hydrogenation vessel under nitrogen, followed by a MeOH (20 mL) solution of a racemic lactol (6-methyl-4-phenyl-2-chromanol, see formula above) (4 g, 16.64 mmol) and a secondary amine (42 mmol, 2.5 equiv). The vessel was filled with hydrogen (50 psi), and the reaction mixture was stirred vigorously at 50°C overnight. The heterogeneous reaction mixture was filtered through celite. The resulting methanolic solution was concentrated under vacuum.

Pure cyclic amines according to the following table I were obtained after trituration with hexanes.

Table I Intermediate compounds

R	Resulting compound	Yield (%)
$(CH_2)_4$	4-methyl-2-(1-phenyl-3-pyrrolidin-1-ylpropyl)phenol	71
$(CH_2)_5$	4-methyl-2-(1-phenyl-3-piperidin-1-ylpropyl)phenol	33
$(CH_2)_6$	2-(3-azepan-1-yl-1-phenylpropyl)-4-methylphenol	29

Characterization of 4-methyl-2-(1-phenyl-3-pyrrolidin-1-ylpropyl)phenol:

^{1}H NMR ($CDCl_3$): δ 1.90 (m, 4H), 2.09 (s, 4H), 2.25-2.45 (m, 2H), 2.57 (m, 2H), 2.63-2.78 (m, 3H), 4.55 (dd, 1H, J=12 Hz, J=3 Hz), 6.47 (s, 1H), 6.85 (s, 2H), 7.19-7.26 (m, 2H), 7.30 (m, 3H), 11.23 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 19.8, 26.0, 33.5, 39.9, 53.5, 54.3, 125.8, 127.3, 128.1, 128.4, 128.7, 131.2145.0, 153.0.

ESI mass spectrum: 296 [M+1$^+$], 297 [M+2$^+$].

Characterization of 4-methyl-2-(1-phenyl-3-piperidin-1-ylpropyl)phenol:

^{1}H NMR ($CDCl_3$): δ 1.52-1.53 (m, 2H), 1.62-1.81 (m, 4H), 1.98 (t, 1H, J=10 Hz), 2.09 (s, 3H), 2.26-2.60 (m, 6H), 4.46 (dd, 1H, J=13 Hz, J=3 Hz), 6.47 (s, 1H), 6.85 (d, 2H, J=0.9 Hz), 7.19-7.24 (m, 2H), 7.30-7.35 (m, 3H), 11.24 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 20.9, 24.4, 25.4, 31.3, 38.4, 53.8, 54.7, 61.0, 102.2, 117.9, 126.3, 128.1, 128.4, 128.6, 129.3, 129.4, 131.4, 145.2, 154.3.

ESI mass spectrum: 310 [M+1$^+$], 311 [M+2$^+$]

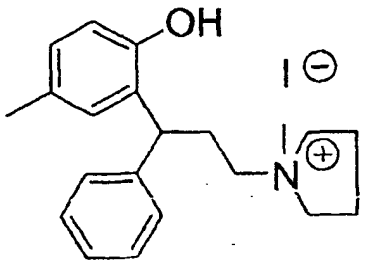
Characterization of 2-(3-azepan-1-yl-1-phenylpropyl)-4-methylphenol:

^{1}H NMR ($CDCl_3$): δ 1.60-1.65 (m, 4H), 1.65-1.85 (m, 4H), 1.95-2.10 (m, 4H), 2.30-2.67 (m, 6H), 2.70-2.80 (m, 2H).

^{13}C NMR ($CDCl_3$): δ 19.6, 26.6, 26.7, 32.0, 40.7, 55.1, 55.7, 115.9, 125.8, 127.3, 128.0, 128.1 128.5, 128.7, 131.4, 145.1, 153.0, 145.2, 152.8.

ESI mass spectrum: 324 [M+1$^+$], 325 [M+2$^+$].

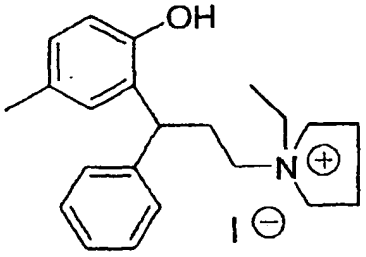
EXAMPLE 31 1-[3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylpyrrolidinium iodide



Methyl iodide (10 equivalents) was added to a solution of the free base 4-methyl-2-(1-phenyl-3-pyrrolidin-1-ylpropyl)phenol of Example 30 (0.3 g, 1.02 mmol) in acetone (4 mL). The reaction mixture is stirred overnight at room temperature. The solution is concentrated to initiate the precipitation of the resulting quaternary ammonium salt. The white precipitate is filtered, washed with diethyl ether and dried under vacuum to give a quaternized salt.

White crystals were obtained with a yield of 79%. The resulting compound was characterized:
^{1}H NMR (MeOH-d_4): δ 2.05-2.18 (m, 4H), 2.20 (s, 3H), 2.46-2.62 (m, 2H), 3.08 (s, 3H), 3.14-3.40 (m, 2H), 3.40-3.62(m, 4H), 4.40 (t, 1H, J=7.3 Hz), 6.68 (d, 1H, J=8Hz), 6.85 (d, 1H, J=8 Hz), 6.98 (d, 1H, J=1.5 Hz), 7.16-7.23 (m, 1H), 7.30 (t, 2H, J=7 Hz), 7.37-7.42 (m, 2H).
^{13}C NMR (MeOH-d_4): δ 19.3, 21.5, 28.2, 41.5, 46.8, 63.6, 64.5, 115.2, 126.5, 127.9, 128.0, 128.4, 128.5, 128.9, 129.2, 143.4, 152.5.
Elemental analysis, $C_{21}H_{28}INO$: Found(%): C 57.64, H 6.43, I 28.77, N 3.23, O 3.88; Theory(%): % C 57.67, H 6.45, I 29.02, N 3.20, O 3.66.
ESI mass spectrum for $C_{21}H_{28}NO^+$: 310.2.

EXAMPLE 32 1-Ethyl-1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]pyrrolidinium iodide



Ethyl iodide (10 equivalents) was added to a solution of the free base 4-methyl-2-(1-phenyl-3-pyrrolidin-1-ylpropyl)phenol of Example 30 (0.3 g, 1.02 mmol) in acetone (4 mL). The reaction mixture is stirred

overnight at room temperature. The solution is concentrated to initiate the precipitation of the resulting quaternary ammonium salt. The white precipitate is filtered, washed with diethyl ether and dried under vacuum to give a quaternized salt.

White crystals were obtained with a yield of 81%. The resulting compound was characterized:

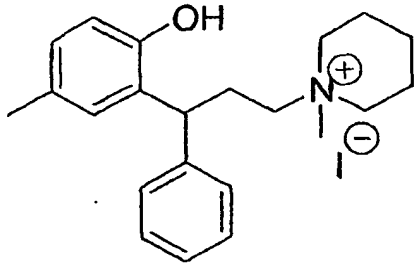
^{1}H NMR (MeOH-d_4): δ 1.24 (t, 3H, J=7 Hz), 2.0-2.18 (m, 4H), 2.20 (s, 3H), 2.40-2.63 (m, 2H), 3.08-3.25 (m, 2H), 3.35-3.60 (m, 6H), 4.38 (t, 1H, J=7.5 Hz), 6.70 (d, 1H, J=8 Hz), 6.85 (d, 1H, J=8 Hz), 7.0 (d, 1H, J=1.4 Hz), 7.16-7.23 (m, 1H), 7.30 (t, 2H, J=7 Hz), 7.37-7.42 (m, 2H).

^{13}C NMR (MeOH-d_4): δ 8.0, 19.5, 21.5, 28.0, 41.9, 54.7, 58.0, 64.5, 117.8, 126.4, 127.9, 128.1, 128.4, 128.7, 128.9, 129.2, 143.6, 152.8.

Elemental analysis, $C_{22}H_{30}INO$: Found(%): C 58.17, H 6.65, I 27.79, N 3.10, O 3.62; Theory(%): C 58.54, H 6.70, I 28.11, N 3.10, O 3.54.

ESI mass spectrum for $C_{22}H_{30}NO^+$: 324.2.

EXAMPLE 33 1-[3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylpiperidinium iodide



Methyl iodide (3.42 g, 1.5 mL, 0.024 mol) was added to a solution of the free base 4-methyl-2-(1-phenyl-3-piperidin-1-ylpropyl)phenol of Example 30 (0.3 g, 0.97 mmol) in a mixture of acetonitrile (6 mL) and acetone (2 mL). The reaction mixture was stirred overnight at room temperature. The solution was concentrated to initiate

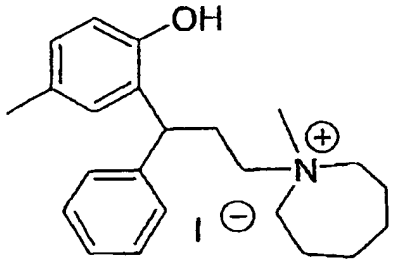
precipitation of the resulting quaternary ammonium salt. The white precipitate was filtered out, washed with chloroform and diethyl ether and dried under vacuum to give 0.397 g (90%) of the title compound.

Characterization of the obtained compound:

^{1}H NMR (MeOH-d_4): δ 1.57-1.84 (m, 6H), 2.19 (s, 3H), 2.46-2.64 (m, 2H), 3.06 (s, 3H), 3.14-3.4 (m, 6H), 4.39 (t, 1H, J=7.3Hz), 6.68 (d, 1H, J=8 Hz), 6.85 (dd, 1H, J=8 Hz, J=1.5 Hz), 7.0 (d, 1H, J=1.5 Hz), 7.18 (t, 1H, J=8Hz), 7.29 (t, 1H, J=7.4 Hz), 7.37-7.4 (m, 5H).

^{13}C NMR MeOH-d_4): δ 19.5, 19.7, 19.8, 20.7, 26.7, 41.5, 60.9, 61.2, 114.0, 115.1, 126.3, 127.9, 128.0, 128.4, 128.5, 128.9, 129.2, 143.4, 152.4.

EXAMPLE 34 1-[3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylazepanium iodide



Methyl iodide (10 equivalents) was added to a solution of the free base 2-(3-azepan-1-yl-1-phenylpropyl)-4-methylphenol of Example 30 (0.3 g, 1.02 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred overnight at room temperature. The solution was concentrated to initiate precipitation of the resulting quaternary ammonium salt. The white precipitate was filtered out, washed with diethyl ether and dried under vacuum to give a quaternized salt.

White crystals were obtained with a yield of 77%. The resulting compound was characterized:

^{1}H NMR (MeOH-d_4): δ 1.6-2.0 (m, 8H), 2.01 (s, 3H), 2.40-2.70 (m, 2H),), 3.10 (s, 3H), 3.15-3.60 (m, 6H), 4.38 (t,

1H, J=7 Hz), 6.68 (d, 1H, J=8Hz), 6.88 (d, 1H, J=8 Hz), 7.05 (s, 1H), 7.18-7.24 (m, 1H), 7.25-7.40 (m, 5H).
^{13}C NMR (MeOH-d_4): δ 20.8, 22.4, 27.5, 41.6, 50.2, 59.2, 63.8, 64.5, 64.8, 117.5, 126.3, 127.95, 128.03, 128.4, 128.6, 128.9, 129.2, 143.4, 152.5.
ESI mass spectrum for $C_{23}H_{32}NO^+$: 338.2.

The usefulness of the compounds according to the invention is further illustrated by the following examples.

EXAMPLE I Binding data

Muscarinic receptor subtype M_1-M_5 binding assays were carried out. Briefly, [3]H-methylscopolamine was allowed to bind to membranes from various recombinant mammalian cell lines, each with an over-expression of a particular receptor subtype. An equilibrium radioligand displacement assay was performed using the title compound of example 2, (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide (a quaternary ammonium compound according to the invention), and for comparison the following anticholinerigic agents: tolterodine, hydroxytolterodine, ipratropium, and atropine. The resulting K_i values, displayed in Table II, are averages of duplicate samples at each dose in an 11-point dose-response curve, using half-log intervals.

Table II K_i values (nM)

Receptor subtype	Displacing compound				
	(3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide	Tolterodine	Hydroxytolterodine	Ipratropium	Atropine
M_1	0.33	0.87	1.5	0.46	0.25
M_2	0.45	0.73	0.33	0.17	0.43
M_3	0.20	2.1	1.4	0.38	0.87
M_4	0.39	1.5	1.4	0.42	0.48
M_5	0.25	0.55	0.48	0.54	0.47

Thus, the title compound of example 2, (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide, according to the invention has high affinity and little or no selectivity for any of the muscarinic receptor M_1-M_5 subtypes. Obtained K_i values for (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide are in the same range as K_i values for tolterodine, hydroxytolterodine, ipratropium, and atropine.

EXAMPLE II Bronchodilatory effect of inhaled quaternary ammonium salts in Balb/c mice

Female BALB/c mice, weight range 19-22 g, were obtained from Charles River Laboratories (Kingston, NC). They received food and water *ad libitum*. All procedures in these studies were in compliance with the Animal Welfare Act Regulation, 9CFR Parts 1 and 2, Publication (NIH) 85-23, 1985.

Compounds for aerosol administration were prepared in sterile Dulbecco's Phosphate Buffered Saline.

Mice were placed in a carousel-style, nose only, exposure chamber and allowed to inhale aerosols for five minutes, using an ICN SPAG-2 nebulizer. This nebulizer generates a mean aerosol particle size of 1.3 microns at a rate of approximately 0.25 ml/minute.

Ten minutes, 4 hours, 8 hours, 24 hours, 36 hours or 48 hours later, the mice were moved to whole body plethysmograph chambers. Bronchoconstriction was induced in mice by administration of an 80 mg/ml methacholine (MC) aerosol into the plethysmograph chambers for 5 minutes. The mice were allowed to inhale an aerosol containing 80 mg/ml methacholine following inhalation treatment with vehicle, or 80 mg/ml methacholine following inhalation treatment with 0.072, 0.144, or 1.44 mg/ml of the title compound of example 2, i.e. (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide, or 80 mg/ml methacholine following inhalation treatment with 1.24 mg/ml ipratropium bromide. The average enhanced pause (lung resistance) was determined. In order to determine the baseline, saline aerosol (without methacholine) was also separately administered to the mice.

The results are shown in fig 1 (1.44 mg/ml of the title compound of example 2 and 1.24 mg/ml ipratropium bromide), fig 2 (0.144 mg/ml of the title compound of example 2), and fig 3 (0.072 mg/ml of the title compound of example 2).

Increasing doses of the title compound of example 2 produce increasing durations of action. In fig 1, inhalation of aerosols generated from a solution containing 1.44 mg/ml of the title compound of example 2 produced a complete block of methacholine-induced bronchoconstriction through 36 hours following administration. Ipratopium bromide (1.24 mg/ml) did not

display an equally sustained action. Inhalation of aerosols generated from solutions containing 0.144 mg/ml (fig 2) or 0.072 mg/ml (fig 3), respectively, of the title compound of example 2 prevented methacholine-induced bronchoconstriction through 24 or 8 hours, respectively, following administration.

EXAMPLE III Bronchodilatory effect of inhaled quaternary ammonium salts in Balb/c mice

Female BALB/c mice were obtained and fed as in example II. Compounds were prepared and administered to the mice (aerosol) as in example II.

Ten minutes, 30 minutes, 1 hour, 2 hours or 4 hours later, the mice were placed in plethysmograph chambers, and bronchoconstriction was induced in the mice by administration of an 80 mg/ml methacholine aerosol. The mice were allowed to inhale an aerosol containing 80 mg/ml methacholine following inhalation with vehicle, or 80 mg/ml methacholine following inhalation treatment with 1.46 mg/ml tolterodine, or 80 mg/ml methacholine following inhalation treatment with 1.44 mg/ml of the title compound of example 2, i.e. (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide.

The results are shown in fig 4. It is obvious from fig 4 that the title compound of example 2 has a pronounced effect on lung resistance. In addition, the bronchodilatory effects of the title compound of example 2 exhibit a prolonged duration.

EXAMPLE IV Bronchodilatory effect of inhaled quaternary ammonium salts in Balb/c mice

Female BALB/c mice were obtained and fed as in example II. Compounds were prepared and administered to the mice (aerosol) as in example II.

Ten minutes, 2 hours, 4 hours, 8 hours or 24 hours later, the mice were placed in plethysmograph chambers, and bronchoconstriction was induced in the mice by administration of an 80 mg/ml methacholine aerosol. The mice were allowed to inhale an aerosol containing 80 mg/ml methacholine following inhalation with vehicle, or 80 mg/ml methacholine following inhalation with 1.44 mg/ml of the title compound of example 2, i.e. (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide, or 80 mg/ml methacholine following inhalation with 1.24 mg/ml ipratropium bromide.

The results are shown in fig 5. It can be concluded that the bronchodilatory effects of the title compound of example 2 have a longer duration when compared to ipratropium bromide.

EXAMPLE V Pharmacokinetics of inhaled quaternary ammonium salts in Balb/c mice

Blood samples were taken from the mice in example II via cardiac puncture under isoflurane anesthesia at 2.5 minutes, 10 minutes, 30 minutes, 2 hours, 4 hours, 8 hours, or 12 hours after aerosol drug treatment.

The samples were collected in tubes containing EDTA and centrifuged at 12000 x g for four minutes. Plasma was removed and stored at -70 °C until assay.

Plasma samples were extracted via a liquid/liquid extraction technique. Plasma levels of the title compound of example 2 were determined by ESI-LC/MS/MS using a PE SCIEX API 4000 mass spectrometer in positive ion mode. Chromatographically, the analyte and the internal standard were resolved on a Phenomenex Phenyl-Hexyl column using an isocratic elution. The limit of quantitation was 24 pg/ml.

Plasma concentrations of the title compound of example 2 following aerosol exposure (inhalation) are summarized in table III and fig 6.

Table III Plasma concentration

Time	Plasma concentration ± std dev (pg/ml) following inhalation of various conc.		
	0.072 mg/ml	0.144 mg/ml	1.44 mg/ml
2.5 min	136 ± 38	264 ± 21	2675 ± 389
10 min	90 ± 1	162 ± 11	1395 ± 163
30 min	81 ± 8	112 ± 10	1120 ± 42
2 h	41 ± 6	55 ± 7	245 ± 3
4 h	14 ± 1	40 ± 3	157 ± 2
8 h	-	12 ± 1	80 ± 2
12 h	-	-	42 ± 2

The doses given to the lungs were proportional to the concentrations appearing in the plasma. Importantly, the systemic (plasma) exposure was very low, which indicates that the title compound of example 2 resides for a prolonged time in the lung. This correlates well with its long duration of action.

EXAMPLE VI (comparative) Pharmacokinetics of inhaled tolterodine in Balb/c mice

Female BALB/c mice were obtained and fed as in example II. Tolterodine L-tartrate for aerosol administration was prepared in sterile phosphate buffer solution at concentrations of 0.1, 0.5, and 1.0 mg/ml, and administered to the mice (aerosol) as in example II.

Blood samples were collected at 2.5 minutes, 15 minutes, 30 minutes, 1 hour or 2 hours after aerosol drug treatment. Blood samples were prepared as in example VI. Samples were analyzed using a PE SCIEX API 3000 mass spectrometer. Chromatographically, the analyte and the internal standard were resolved on a Zorbax ACE Phenyl column using a gradient elution. The limit of quantitation was 100pg/mL.

Figure 7 shows plasma concentrations of tolterodine following inhalation of nebulized solutions at 0.1, 0.5, or 1.0 mg/ml. Plasma levels for the 0.1 mg/ml concentration were at or below detection limits. Clearly, tolterodine is rapidly absorbed into the circulation. The plasma level of tolterodine is approximately one order of magnitude higher than the corresponding level of the the title compound of example 2 (example V, fig 6).

This demonstrates that while tolterodine is rapidly spread systemically, the compounds according to the invention have an increased duration of action, with implications locally (i.e. for treating asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, or rhinorrhea due to the common cold).

EXAMPLE VII Binding data

Muscarinic receptor subtype M_1-M_5 binding assays were performed. K_i values were determined for the title compounds of examples 3, 8, and 31-34 (all quaternary ammonium compounds according to the invention). The resulting K_i values are displayed in Table IV.

Table IV K_i values (nM)

Receptor subtype	Title compound of Example no					
	3	8	31	32	33	34
M_1	0.3	0.86	1.2	1.1	1.1	1
M_2	0.52	1.08	2.2	1.7	1.7	1
M_3	0.43	0.92	3.3	3.1	3.2	4.7
M_4	0.72	1.07	4.2	3.8	3.6	2.9
M_5	0.26	0.68	1.6	1.2	0.9	1.8

Thus, the title compounds of Example nos 3, 8, and 31-34 according to the invention have high affinity and little or no selectivity for any of the muscarinic receptor M_1-M_5 subtypes.

EXAMPLE VIII Bronchodilatory effect of inhaled quaternary ammonium salts in Balb/c mice

Bronchoconstriction was induced in BALB/c mice by administration of methacholine. The title compounds of Examples 3, 8, and 31-34 (all quaternary ammonium compounds according to the invention) were administered to the mice via inhalation of 1 mg/mL (free base equivalents (FBE)) of each compound. The resulting inhibition of methacholine-induced bronchoconstriction was determined at 10 min as well as 24 h and 48 h, or 36 h, after dosing. The results are displayed in the following Table V.

Table V

Title compound of example no (1 mg/mL FBE)	% inhibition of bronchoconstriction after 10 min	24 h	36 h	48 h
3	100		93	
8	82	60		15
31	100		0	
32	100		17	
33	100		0	
34	100		0	

EXAMPLE A

A 65 year old female with a history of chronic COPD with FEV_1 of 1.5 liters is treated with (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide in an aerosol formulation, 1 mg every 12 hr continuously for dyspnea. After two weeks of therapy, dyspnea tolerance is improved.

EXAMPLE B

A 50 year old male with a history of chronic COPD with FEV_1/FVC of 60% is treated with (3R)-3-(2-hydroxy-5-

methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide in an aerosol formulation, 2 mg every 8 hr continuously for dyspnea. After a week of treatment, the FEV_1/FVC ratio improves to about 65%.

EXAMPLE C

A 25 year old female with a history of asthma with a morning peak flow of less than 2 l/sec is treated with (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide powder, 0.1 mg every 8 hr continuously. Treatment improves the peak flow to 4-5 l/sec.

EXAMPLE D

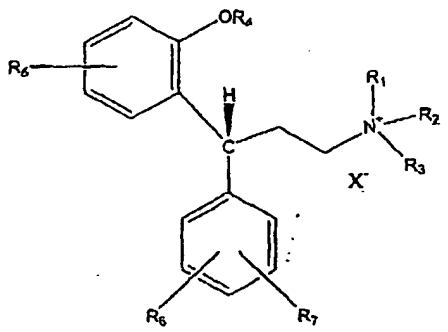
A 35 year old male with a history of severe asthma with a morning peak flow of 5 l/sec is treated with (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide powder, 6 mg once a day continuously. After a week of treatment, the peak flow improves to 9 l/sec.

EXAMPLE E

A 45 year old female with a history of severe asthma with a morning peak flow of less than 3 l/sec is treated with (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide in an aerosol formulation, 2 mg three times daily continuously. After a week of treatment the peak flow improves to 6 l/sec.

CLAIMS

1. A quaternary ammonium compound of the formula



and any stereoisomers thereof, wherein

R_1, R_2 and R_3 independently represent C_1-C_6 alkyl, optionally substituted with phenyl or hydroxyl, or both, and wherein any two of R_1, R_2 and R_3 may form a ring together with the quaternary ammonium nitrogen;

R_4 represents

-H,

$-CH_3$, or

$-CO-R_{4-1}$, wherein R_{4-1} represents

$-(C_1-C_4$ alkyl),

$-(C_1-C_4$ alkoxy), or

$-NR_{4-2}R_{4-3}$, wherein R_{4-2} and R_{4-3} independently represent -H or $-(C_1-C_4$ alkyl);

R_5, R_6 and R_7 independently represent

-H,

$-OCH_3$,

-OH,

$-CONH_2$,

$-SO_2NH_2$,

-F, -Cl, -Br, -I,

$-CF_3$, or

$-(C_1-C_4$ alkyl), optionally substituted with one or two

-OH,

-(C_1-C_4 alkoxy),

-COOH, or

-CO-O-(C_1-C_3 alkyl); and

X^- represents an anion of a pharmaceutically acceptable acid.

2. A quaternary ammonium compound according to claim 1, wherein the carbon stereocenter is (R).

3. A quaternary ammonium compound according to claim 1, wherein the carbon stereocenter is (S).

4. A quaternary ammonium compound according to claim 1, which is a mixture of stereoisomers.

5. A quaternary ammonium compound according to claim 1, wherein at least one of R_1, R_2 and R_3 represents C_1-C_3 alkyl.

6. A quaternary ammonium compound according to claim 5, wherein at least one of R_1, R_2 and R_3 represents isopropyl.

7. A quaternary ammonium compound according to claim 6, wherein at least two of R_1, R_2 and R_3 represents isopropyl.

8. A quaternary ammonium compound according to claim 5, wherein at least one of R_1, R_2 and R_3 represents methyl.

9. A quaternary ammonium compound according to claim 5, wherein at least one of R_1, R_2 and R_3 represents ethyl.

10. A quaternary ammonium compound according to claim 1, wherein R_1 and R_2 jointly form a ring together with the quaternary ammonium nitrogen.

11. A quaternary ammonium compound according to claim 10, wherein said ring comprises from 4 to 6 carbon atoms.

12. A quaternary ammonium compound according to claim 1, wherein R_4 represents -H, $-CH_3$, or $-CO-R_{4-1}$, wherein R_{4-1} represents C_1-C_4 alkyl.

13. A quaternary ammonium compound according to claim 12, wherein R_4 represents -H.

14. A quaternary ammonium compound according to claim 1, wherein R_5 represents –H, -Br, -Cl, $-CH_3$, or $-CH_2OH$.

15. A quaternary ammonium compound according to claim 14, wherein R_5 represents $-CH_3$.

16. A quaternary ammonium compound according to claim 1, wherein at least one of R_6 and R_7 represents -H.

17. A quaternary ammonium compound according to claim 1, wherein both R_6 and R_7 represent -H.

18. A quaternary ammonium compound according to claim 1, wherein X^- is selected from the group consisting of the anions of the following acids: tartaric, hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, nitric, citric, methanesulfonic, $CH_3-(CH_2)_n-COOH$ where n is 0 thru 4, $HOOC-(CH_2)_n-COOH$ where n is 1 thru 4, HOOC-CH=CH-COOH, and benzoic.

19. A quaternary ammonium compound according to claim 18, wherein X^- is selected from the group consisting of iodide, bromide, and chloride.

20. A quaternary ammonium compound according to claim 19, wherein X^- represents iodide.

21. A quaternary ammonium compound according to claim 19, wherein X^- represents chloride.

22. A quaternary ammonium compound according to claim 19, wherein X^- represents bromide.

23. A quaternary ammonium compound according to claim 1, which is selected from the group consisting of

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

(3R)-N-ethyl-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenyl-N-propylpropan-1-aminium iodide,

(3R)-N-benzyl-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropan-1-aminium iodide,

(3R)-N-(tert-butyl)-3-(2-hydroxy-5-methylphenyl)-N,N-dimethyl-3-phenylpropan-1-aminium bromide,

(3R)-3-[2-hydroxy-5-(hydroxymethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

(3S)-3-(2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

(3R)-3-(5-chloro-2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

(3R)-3-(5-bromo-2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

(3R)-3-[2-(acetyloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-[2-(isobutyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(4-fluorophenyl)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium bromide,

(3R)-3-[2-hydroxy-5-(trifluoromethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

(3R)-3-[2-(isobutyryloxy)-5-hydroxymethylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

(3R)-3-{2-(acetyloxy)-5-[(acetyloxy)methyl]phenyl}-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

2-{(1R)-3-[diisopropyl(methyl)ammonio]-1-phenylpropyl}-4-methylbenzenolate,

(3R)-N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-[2-(butyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium chloride,

5-hydroxy-N-[(3R)-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-N-isopropyl-N-methylpentan-1-aminium iodide,

(3R)-3-(2-hydroxy-4-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

3,3-bis(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium iodide,

(3R)-3-[5-(aminocarbonyl)-2-hydroxyphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

3,3-bis(2-methoxyphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium iodide,

1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylpyrrolidinium iodide,

1-ethyl-1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]pyrrolidinium iodide,

1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylpiperidinium iodide, and

1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylazepanium iodide.

24. A quaternary ammonium compound according to claim 23, which is selected from the group consisting of

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide, and

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium chloride.

25. A pharmaceutical composition comprising a therapeutically effective amount of a quaternary ammonium compound according to any one of claims 1-24, and a suitable pharmaceutical carrier therefor.

26. A quaternary ammonium compound according to any one of claims 1-24 for use as a medicament.

27. Use of a quaternary ammonium compound according to any one of claims 1-24 for the manufacture of a medicament for treating asthma.

28. Use of a quaternary ammonium compound according to any one of claims 1-24 for the manufacture of a medicament for treating chronic obstructive pulmonary disease (COPD).

29. Use of a quaternary ammonium compound according to any one of claims 1-24 for the manufacture of a medicament for treating rhinorrhea due to the common cold.

30. Use of a quaternary ammonium compound according to any one of claims 1-24 for the manufacture of a medicament for treating allergic rhinitis.

31. A method of treating asthma in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of a quaternary ammonium compound according to any one of claims 1-24.

32. A method of treating chronic obstructive pulmonary disease (COPD) in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of a quaternary ammonium compound according to any one of claims 1-24.

33. A method of treating allergic rhinitis in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of a quaternary ammonium compound according to any one of claims 1-24.

34. A method of treating rhinorrhea due to the common cold in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of a

quaternary ammonium compound according to any one of claims 1-24.

Drawings

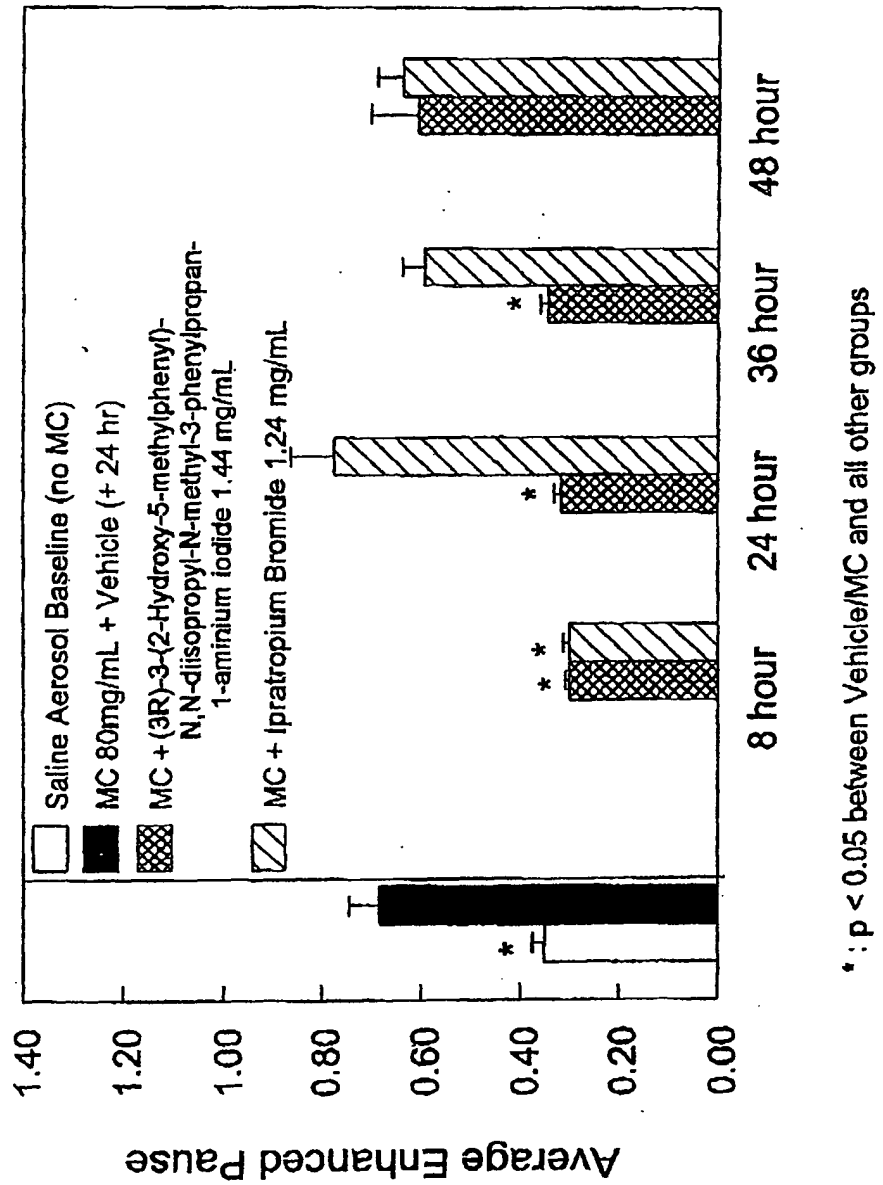


FIGURE 1

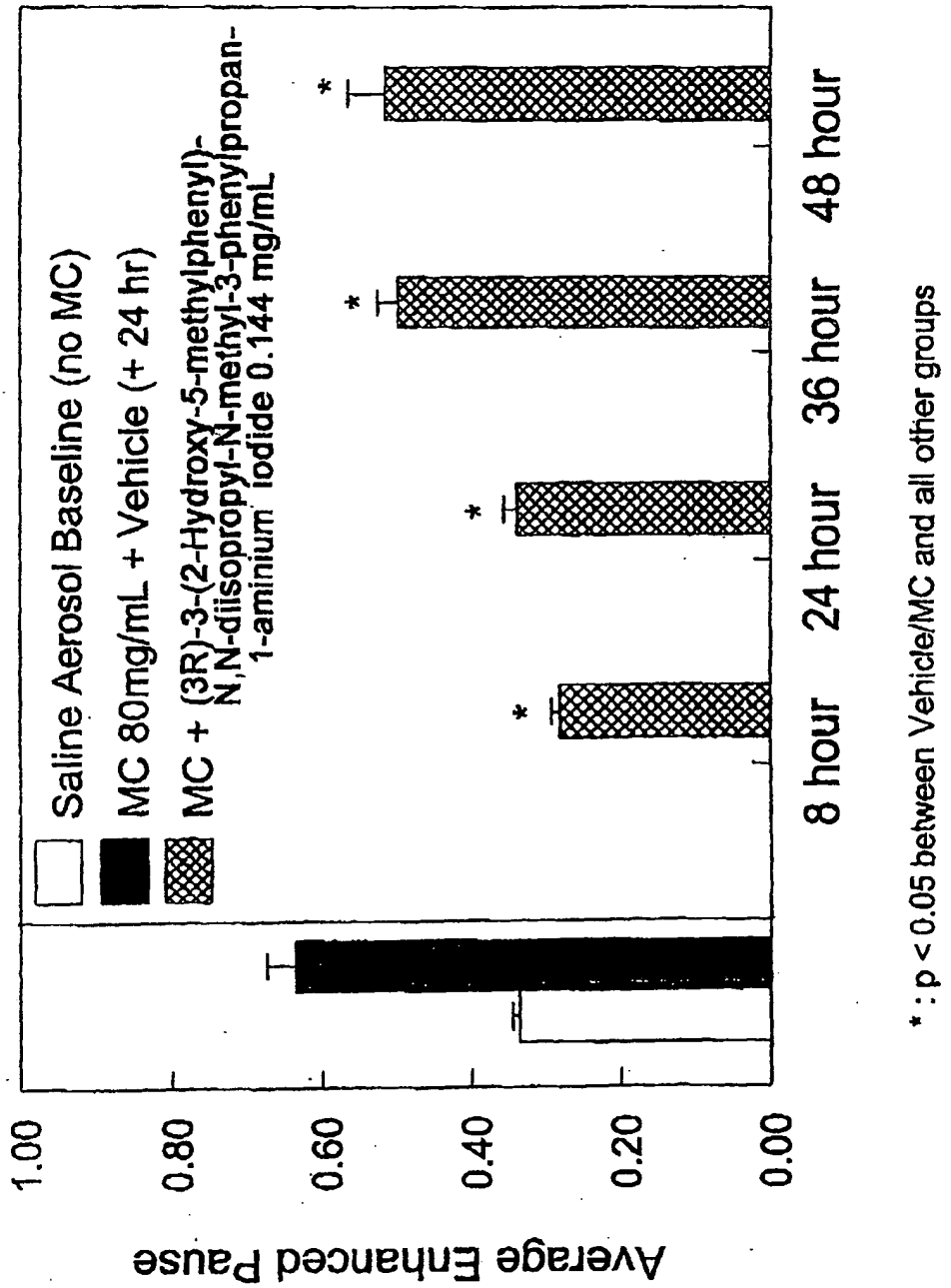

Saline Aerosol Baseline (no MC)
MC 80mg/mL + Vehicle (+ 24 hr)
MC + (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium Iodide 0.144 mg/mL
Average Enhanced Pause
1.00
0.80
0.60
0.40
0.20
0.00
8 hour
24 hour
36 hour
48 hour
* : p < 0.05 between Vehicle/MC and all other groups

FIGURE 2

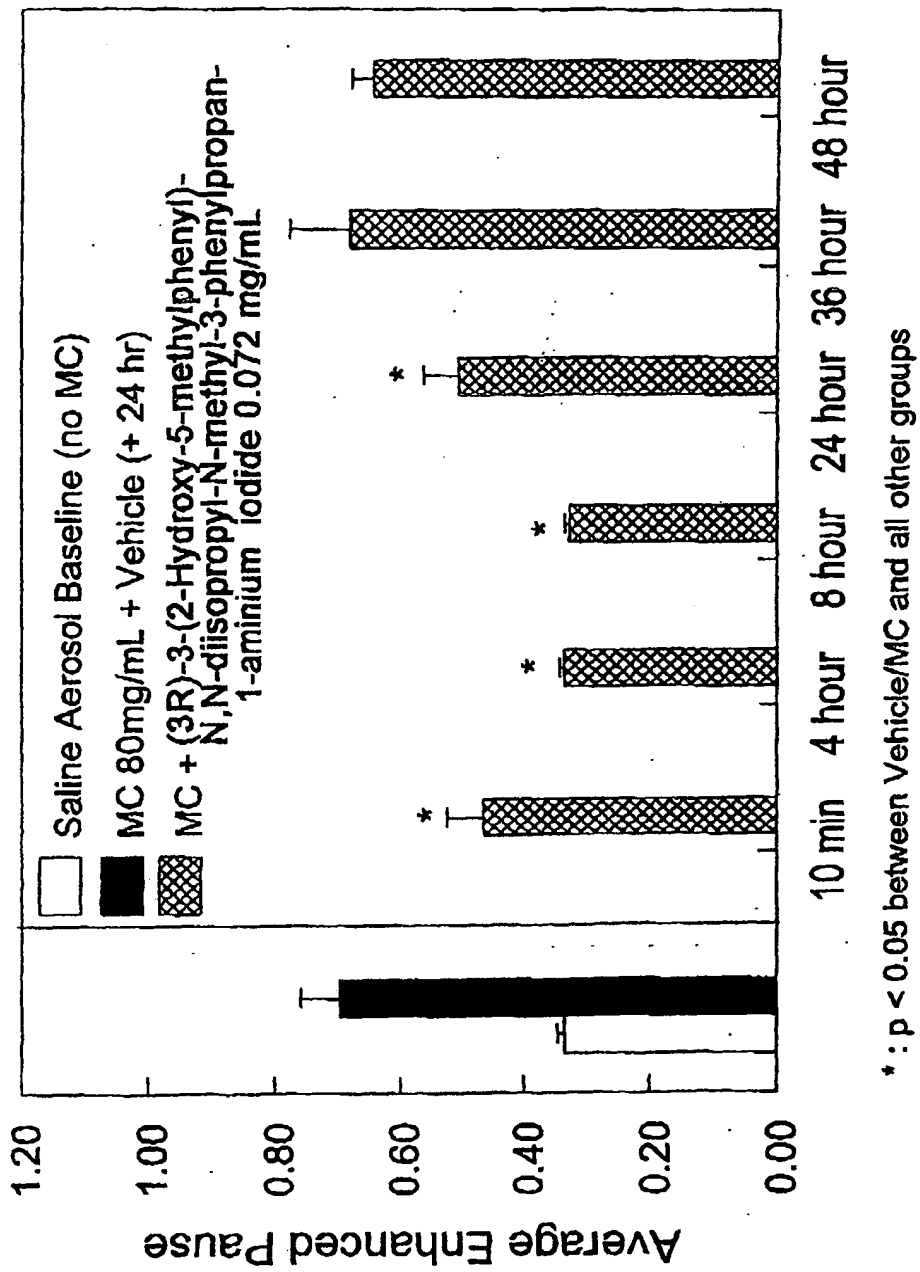

Saline Aerosol Baseline (no MC)
MC 80mg/mL + Vehicle (+ 24 hr)
MC + (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium Iodide 0.072 mg/mL
Average Enhanced Pause
1.20
1.00
0.80
0.60
0.40
0.20
0.00
10 min
4 hour
8 hour
24 hour
36 hour
48 hour
*
*
*
*
*: p < 0.05 between Vehicle/MC and all other groups

FIGURE 3

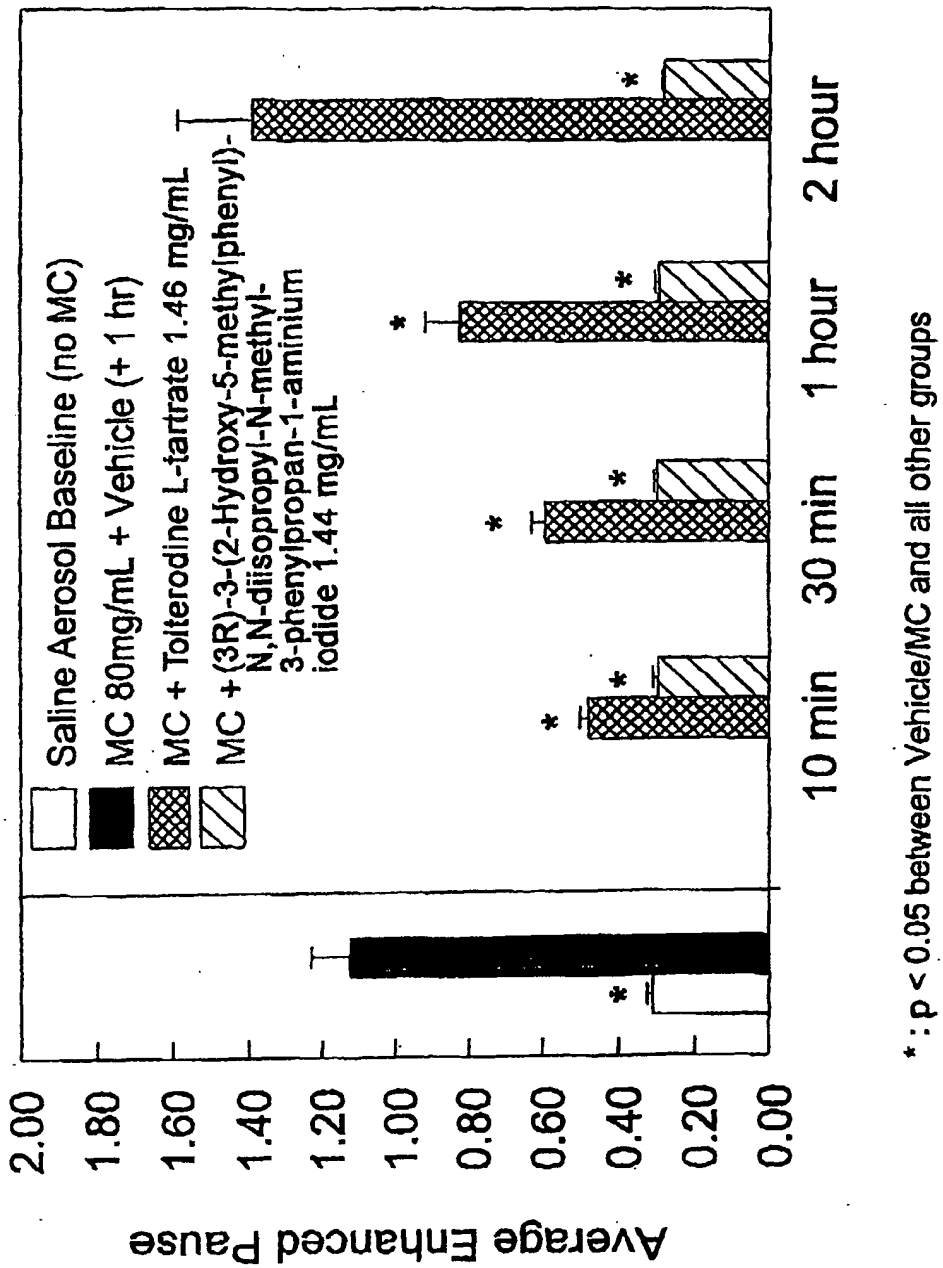


FIGURE 4

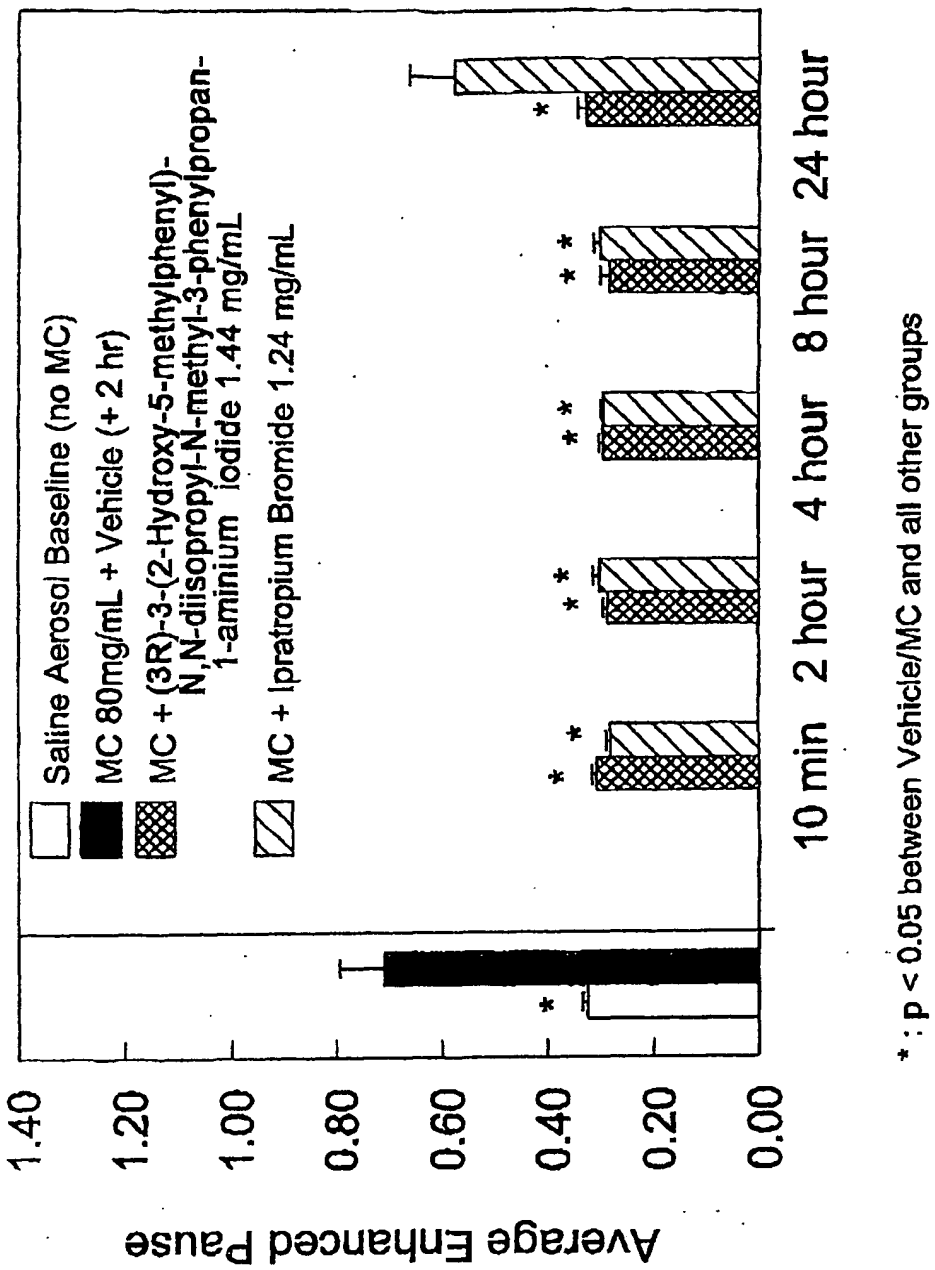


FIGURE 5

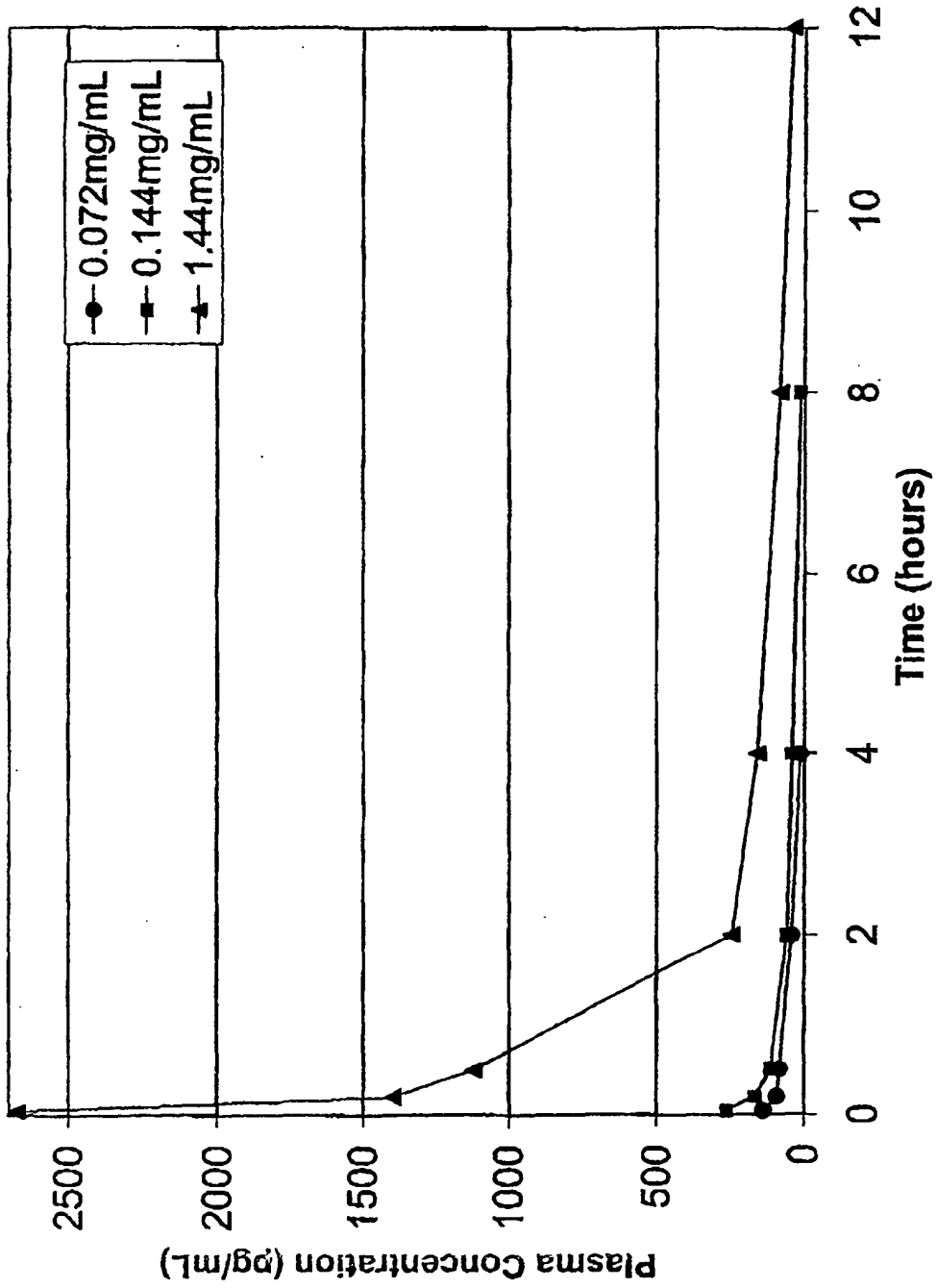


FIGURE 6

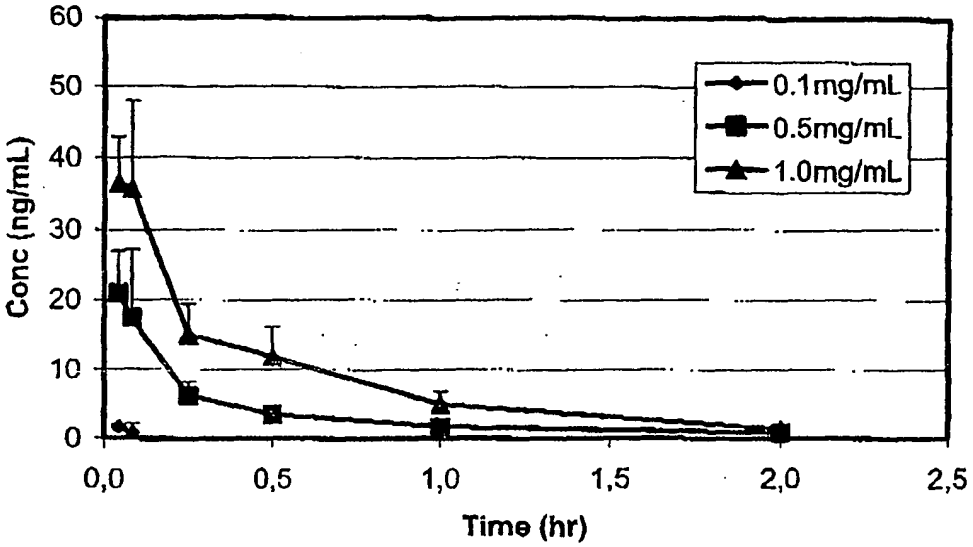

60
50
40
30
20
10
0
Conc (ng/mL)
0,0
0,5
1,0
1,5
2,0
2,5
Time (hr)
0.1mg/mL
0.5mg/mL
1.0mg/mL

FIGURE 7

INTERNATIONAL SEARCH REPORT

Interna ...lication No
PCT/US 02/34529

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C211/27 C07C211/29 C07C215/54 C07C215/66 C07C219/28
C07D295/02 C07C217/62 A61K31/14 A61K31/452 A61K31/40
A61P11/00

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 C07C C07D 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)
EPO-Internal, BEILSTEIN Data, 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.
A	US 2 592 191 A (WAYNE RUDDY ARLO) 8 April 1952 (1952-04-08) column 1, line 1 - line 11; claims	1-34
A	US 5 382 600 A (JOENSSON NILS A ET AL) 17 January 1995 (1995-01-17) cited in the application column 31 -column 36; claims; table 1	1-34
A	WEBER R W: "ROLE OF ANTICHOLINERGICS IN ASTHMA" ANNALS OF ALLERGY, AMERICAN COLLEGE OF ALLERGY AND IMMUNOLOGY,, US, vol. 65, November 1990 (1990-11), pages 348-360, XP000979858 ISSN: 0003-4738 the whole document	27-34

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 March 2003	02/04/2003

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	Bedel, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internati plication No
PCT/US 02/34529

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2592191 A	08-04-1952	NONE	
US 5382600 A	17-01-1995	AT 65990 T	15-08-1991
		AU 635493 B2	25-03-1993
		AU 2932989 A	11-08-1989
		CA 1340223 A1	15-12-1998
		DE 68900180 D1	12-09-1991
		DK 172590 A	19-07-1990
		EP 0325571 A1	26-07-1989
		EP 0354234 A1	14-02-1990
		ES 2029384 T3	01-08-1992
		FI 109900 B1	31-10-2002
		GR 3002854 T3	25-01-1993
		HK 64494 A	15-07-1994
		HU 58040 A2	28-01-1992
		HU 9400053 A3	30-01-1995
		JP 2664503 B2	15-10-1997
		JP 3503163 T	18-07-1991
		LU 90259 A9	16-09-1998
		NO 903085 A ,B,	11-07-1990
		WO 8906644 A1	27-07-1989

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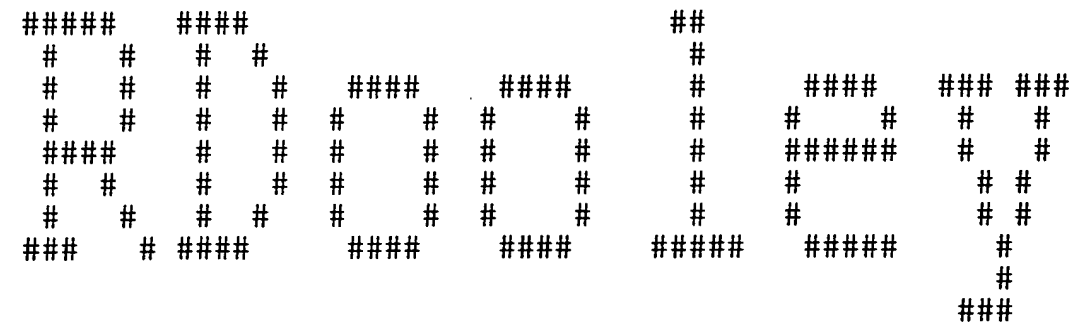

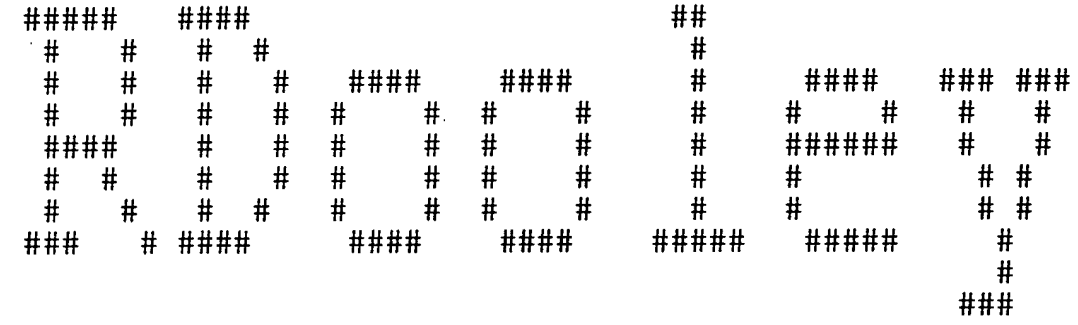

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Print Job Information:

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Time: 3:50:00 PM

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW HAMPSHIRE

Goss International Americas, Inc., Plaintiff, v. MAN Roland Inc. and MAN Roland Druckmaschinen AG, Defendants.	Civil Action No. C-03-513-SM
MAN Roland Inc. and MAN Roland Druckmaschinen AG, Counterclaim Plaintiffs, v. Goss International Americas, Inc. and Heidelberger Druckmaschinen AG, Counterclaim Defendants.	

PLAINTIFF GOSS INTERNATIONAL AMERICAS, INC.'S OPPOSITION TO DEFENDANTS' MOTION FOR SUMMARY JUDGMENT OF INVALIDITY UNDER 35 U.S.C. §§ 102 AND 112 (DOCKET ENTRY 146)

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TABLE OF AUTHORITIES

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Cases

INTRODUCTION

The differences between Goss's tubular blanket and gapless blanket cylinder printing press technology, on the one hand, and traditional flat blanket and gapped blanket cylinder technology, on the other hand, have been explained before in, for example, Goss's brief concerning MAN's previous written-description-related motion (the Goss brief is docket entry no. 116). The three photographs below show, from left to right, a flat blanket being installed, a Goss Sunday Press tubular blanket being installed, and a MAN Rotoman S tubular blanket being installed. (Additional photographs of tubular blankets and flat blankets are included in, for example, Goss's February 13, 2006, opposition to MAN's motion for summary judgment of non-infringement, from which these photographs were reproduced.)

As explained in the parties' summary judgment briefs on the infringement issue (and as shown on the right above), MAN's Rotoman S press uses gapless blanket cylinders and tubular blankets. MAN's defenses to the charges of willful patent infringement in this case center on the stripe or join that extends along the length of the Reeves tubular blanket used on MAN's accused

presses.[1] MAN argues that because the tubular blankets used on Goss's Sunday Press do not have such a stripe, that MAN should not be liable for patent infringement.

MAN has presented this argument via several different legal theories. First, MAN argues patent claim construction, asking the Court to rewrite Goss's patent claims to include new words and phrases like, "gapless," "continuous," and "devoid of any gap, seam, or splice" (*see* the parties' claim-construction briefs, docket entry nos. 142, 188, and 189).

Second, MAN argues non-infringement. For example, MAN's experts ask the Court to find that the stripe on the Reeves blanket changes its shape from tubular (Goss's invention) to flat (the previous technology, shown on the left above). Discussing the blanket shown in the photograph on the right above, MAN's expert testified as follows:

> Q. Okay, and the Reeves blanket that's used on the Rotoman S presses, is that blanket shaped like a tube?
>
> A. No.
>
> Q. It is not?
>
> A. It is not.
>
> Q. Your testimony to the jury is going to be that the Reeves blanket used on the Rotoman S presses is not shaped like a tube?
>
> A. That's my answer.

(Deposition of Roger Meadows, Exhibit 1 of this opposition, 124:7–16. *See also, e.g.*, Defendants' Non-Infringement Brief, docket entry no. 176).

Even if Goss's patent claims did include the "gapless" limitation that MAN argues the Court should add, MAN would still be a willful infringer. MAN's own 1994 patent (U.S. Patent

---

[1] MAN, however, has not presented to the Court a non-infringement argument to defend the other tubular blanket used on its presses, the MacDermid blanket. *See* Plaintiffs' Brief in support of Summary Judgment of Infringement ("Plaintiffs' Infringement Brief," docket entry no. 150), and Defendants' Brief in support of Summary Judgment for Non-infringement, ("Defendants' Non-Infringement Brief," docket entry no. 176).

No. 5,351,615), prosecuted by the same lawyer who later wrote the non-infringement opinions on which MAN is relying in this case, states the stripe or join changes nothing, that a blanket that has a stripe or join like the Reeves blanket still has, in the words of the MAN patent, a "continuous, gap-free outer surface." (Exhibit 2 of this opposition). That type of blanket is shown in fig. 3 of the MAN patent, below.

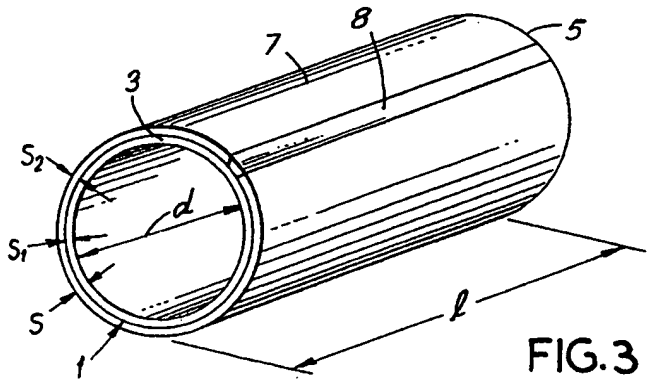

FIG.3

"The rubber layer 7 of the blanket has a continuous, gap-free outer surface, as illustrated in FIG. 3." (Ex. 2, col. 4, ll. 1-2)

Now, in this "Motion for Summary Judgment of Invalidity Under 35 U.S.C. §§ 102 and 112," MAN again returns to the stripe in the Reeves blanket. In MAN's words, "This motion concerns the portion of the patent claims that describe the tubular outer printing layer 40 of the of the tubular printing blanket 18" (Defendants' brief at 4).[2] MAN now argues that the Goss patents are invalid for lack of written description because during prosecution of its patent applications, Goss amended its patent claims to delete the word "gapless," changing the limitation

"a gapless cylindrical outer printing layer for transferring an ink pattern to a web," to

"an outer printing layer for transferring an ink pattern to a web"

[2] MAN's wrongly identifies the elements in the patents at suit, because 40 represents the outer surface of the tubular printing blanket, not the outer layer (which is labeled 66). *See, e.g.*, '734 patent at col. 5, l. 55 and col. 10, l. 4.

(December 11, 2000, amendment at 2).

As previously discussed in the context of the MAN's earlier written-description invalidity motion (*see, e.g.*, docket entry no. 116), "The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1330 (Fed. Cir. 2003). To satisfy the written-description requirement, an application must "reasonably convey[] to the artisan that the inventor had possession" of the claimed subject matter when the application was filed. *Lampi Corp. v. Am. Power Prod.*, Inc., 228 F.3d 1365, 1378 (Fed. Cir. 2000).

Thus, MAN's contention in this motion is that Goss's patent applications do not show that Jim Vrotacoe and the other Goss engineers invented what they claimed, *e.g.*,

> A tubular printing blanket for use on a blanket cylinder in an offset printing press comprising:
>
> a rigid cylindrical inner layer;
>
> an outer printing layer for transferring an ink pattern to a web; and
>
> an intermediate compressible layer between said inner and outer layers, the tubular printing blanket being radially expandable so as to enable the blanket to be axially mounted onto the blanket cylinder of the offset printing press.

('734 patent at col. 12, ll. 29-38).

MAN's contention is wrong. Jim Vrotacoe and the other Goss engineers did, of course, invent such a tubular blanket (even MAN does not argue otherwise), and they described it in their patent applications. And although MAN seeks summary judgment of patent invalidity, an issue on which MAN bears the burden of proof by clear and convincing evidence, MAN has presented no technical evidence or expert testimony in support of its contention that the Goss patent applications do not describe a tubular blanket with "an outer printing layer."

MAN's argument is not only unsupported, it is, as explained below, contradicted by the facts. The Court should deny MAN's motion.

MATERIAL FACTS

MAN does not supply a statement of particular, allegedly uncontested facts to support its motion. Nor, as noted above, does MAN supply any affidavits or technical testimony in support of its motion. The facts supporting this opposition are these, among others:

1. In 1989, the Goss inventors filed United States patent application no. 07/417,587 (Exhibit 3 of this opposition). The '587 application literally and expressly describes a tubular printing blanket with an outer printing layer, not a "gapless" outer layer:

> The tubular blanket has a cylindrical outer layer of incompressible material and a cylindrical layer of compressible material on an inner layer of rigid material.

(Ex. 3 at HWS 000162, emphasis added). (The word "cylindrical" is not a synonym for "gapless," but only indicates that the blanket is mounted on a cylinder; the inventors used the same word to describe the flat printing plate when mounted on the printing cylinder, *see* Ex. 3 at HWS 000167. The '587 application also literally and expressly describes a tubular blanket that, like the Reeves blanket used on the accused MAN Rotoman S presses, would be made with a stripe or join. The application states that the blanket:

> could be made in a flat planar piece of material which is then wrapped around sleeve 80 and adhered thereto. The opposite ends of the piece of material would abut each other.

(Ex. 3 at HWS 000179, emphasis added). MAN's own Reeves blanket is made in exactly this way.[3]

2. In April 1991, the '587 application was published as Canadian Patent Application Serial no. CA 2,026,954 and as European Patent Application no. 90117234.6.

3. In May 1991, the Goss inventors filed United States patent application no. 07/699,668. (Exhibit 5). The '668 application literally and expressly describes a tubular printing blanket with an outer printing layer, not a "gapless" outer layer:

> A blanket sleeve for an offset printing press comprises:
>
> (a) an elastic backing layer;
>
> (b) a compressible layer containing compressible thread, rubber cement, and microspheres; and,
>
> (c) an outer print layer.

(Ex. 5 at HWS 001482, emphasis added).

4. This claim of the '668 application was later rejected by the examiner for lack of written description under § 112, but not for the lack of the modifier "gapless." The examiner found no written description violation under § 112 for a claim lacking the "gapless" modifier, even though the examiner was clearly scrutinizing this exact claim for the written description requirement. Similarly, the examiner rejected some of the amendments made to the '100 and '734 applications in 2000 for lack of written description; however, the examiner did not reject the amendments that removed "gapless" from the claims. The defendants' arguments (with

[3] *See, e.g.*, Meadows Deposition, Ex. 1 at 7 (Q: "Would you agree that the Reeves and MacDermid blankets for the Rotoman S press are tubular in shape or shaped like tubes? A: What they're mounted on is, but the blanket itself is just like any flat blanket, wrapped around that in the case of the Reeves.").

respect to these amended claims) are in direct conflict with the findings of the examiners. (Defendant's Brief, at 11-13).

5. In April 1992, the Goss inventors filed United States patent application no. 07/864,680. (Exhibit 6). The '680 application literally and expressly describes a tubular printing blanket with an outer printing layer, not a "gapless" outer layer:

> The tubular blanket has a cylindrical outer layer of incompressible material and a cylindrical layer of compressible material on an inner layer of rigid material.

(Ex. 6 at HWS 000012, emphasis added). (Again, the word "cylindrical" is not a synonym for "gapless," but only indicates that the blanket is mounted on a cylinder; the inventors used the same word to describe the flat printing plate when mounted on the printing cylinder, *see* Ex. 6 at HWS 000021. When the '680 application was filed in April 1992, the '587 application had already been published, and one of ordinary skill in the art would therefore have already known what it described.

6. As MAN notes in its moving brief (at 7-8), the '734, '100, and '251 patents all have essentially the same specification as the '680 application. Each includes the description quoted in par. 5 above.

7. The specifications of the Goss patents state that the advantages of the new tubular-blanket technology as compared to traditional flat-blanket technology include reduced vibrations, higher operating speed, quick makeready times, and reduction in paper waste. Those advantages are achieved by tubular blankets regardless of whether they are completely uniform (like the Sunday Press blankets) or whether they have a stripe or join (like the Reeves blanket used on the MAN Rotoman S presses). *See, e.g.*, the December 28, 2005, "Supplemental Expert Report of Bernard Roth" (Ex. 7 to this opposition).

8. In summary: contrary to MAN's assertions, "one of ordinary skill in the art would not understand the printing blanket described in the patents-in-suit to necessarily have a gapless or continuous outer printing layer" (November 16, 2005, "Rebuttal Expert Report of Dr. Bernard Roth," Ex. 8 to this opposition, at 18). Thus, contrary to MAN's assertions, the inventions described in claim 1 of the '734 patent, claim 1 of the '100 patent, and claims 1 through 8 of the '251 patent are described in the specifications of those patents.

ARGUMENT

1. Goss's Specifications Literally and Expressly Describe An Outer Printing Layer, and Not A Gapless Outer Printing Layer As MAN Claims

As MAN's brief states, Goss's specifications for the '100, '734, and '251 patents are all essentially identical to the specification of U.S. Patent Application No. 07/864,680 ("the '680 application"), filed on May 7, 1992. (Defendants' Brief at 7-8).

MAN argues that the specification only describes a gapless outer layer. This is not correct. The '680 application literally and expressly describes a tubular printing blanket with an outer printing layer, not a "gapless" outer layer:

> The tubular blanket has a cylindrical outer layer of incompressible material and a cylindrical layer of compressible material on an inner layer of rigid material.

(Ex. 6 at HWS 000012, emphasis added).

This statement is *in haec verba* written-description support for the tubular printing blanket with an "outer layer" described in the claims of the '100, '734, and '251 patents. *See, e.g., Amgen Inc.* at 1332 n.8.

Moreover, as noted above, at the time the '680 application was filed, in view of the published '587 application, one of skill in the art would have understood the "tubular blanket" described in the '680 application to include a blanket with a stripe or join, that is, one:

> made in a flat planar piece of material which is then wrapped around sleeve 80 and adhered thereto. The opposite ends of the piece of material would abut each other.

(Exhibit 4 at HWS 000179, emphasis added).

Moreover, as Dr. Bernard Roth explained, one of skill in the art would recognize that such a tubular blanket solves the same problems in the same way as a tubular blanket that does not have a strip or join (Ex. 8 at 18). And as Dr. Roth noted, "one of ordinary skill in the art would not understand the printing blanket described in the patents-in-suit to necessarily have a gapless or continuous outer printing layer" *Id. Cf., e.g., Reiffin v. Microsoft*, 214 F.3d 1342, 1346 (Fed. Cir. 2000).

The specifications of the three Goss patents-in-suit thus include a written description of the "outer layer" element they claim. For this reason (and in any event because MAN has not presented clear and convincing evidence to the contrary, *see Invitrogen Corp. v. Clontech Labs.*, Inc., 429 F.3d 1052, 1072 (Fed. Cir. 2005)), MAN's motion should be denied.[4]

2. MAN's Written Description Of the Law of Written Description Is Wrong.

[4] Defendants also argue invalidity on §102 grounds, but this argument fails in the same way defendants' §112 argument fails because it is essentially the same argument. Defendants argue that the '251 cannot claim priority to any earlier applications, and is therefore invalidated by the earlier-filed applications, among other publications. However, this argument fails because the '251 claims are disclosed in the '587, '668, and '680 applications, and the '251 patent can claim a filing date earlier than (or identical to) the publication of defendants' examples of "prior art." (Defendants' Brief at 18-21).

In its brief, MAN argues that Goss's patents are invalid because, *in haec verba*, the specifications of the patents describe only a "gapless" outer layer, and the claims are not so limited. As explained above, MAN's argument is wrong on the facts, for the Goss patent specifications describe a tubular blanket with an outer layer that is not gapless.

But MAN is also wrong on the law. Jim Vrotacoe and the other Goss inventors were not obliged to set forth in their patent applications every possible version of their invention.[5] "It is a familiar principle of patent law that a claim need not be limited to a preferred embodiment." *Lampi Corp. v. American Power Prods.*, 228 F.3d 1365, 1378 (Fed. Cir. 2000). In other words, "that a claim may be broader than the specific embodiment disclosed in a specification is of no moment. . . . 35 U.S.C. § 112 requires disclosure of only one mode of practicing the invention." *In re Rasmussen*, 650 F.2d 1212, 1215 and 1215 n.7 (C.C.P.A. 1981).

MAN argues (as noted above, wrongly) that the specifications of the patents describe only a "gapless outer layer" tubular blanket, and that therefore it would violate § 112 for Goss to obtain patent protection for a tubular blanket without regard for whether the outer layer is "gapless." The flaw in MAN's legal argument—that an inventor is not limited to claiming exactly the embodiment—was explained by the Federal Circuit's predecessor court as follows:

> A hypothetical situation may make our point clear. If the original specification of a patent application on the scales of justice disclosed only a 1-pound "lead weight" as a counterbalance to determine the weight of a pound of flesh, we do not believe the applicant should be prevented, by the so-called "description requirement" of the first paragraph of § 112, or the prohibition against new matter of § 132, from later claiming the counterbalance as a "metal weight" or simply as a 1-pound "weight," although both "metal weight" and "weight" would indeed be progressively broader than "lead weight," including even such undisclosed, but obviously art-recognized equivalent,

[5] Of course, as noted above, the 1989 Goss '587 application does include an example of a blanket made exactly as the Reeves blanket for the MAN Rotoman S is made.

> "weight" as a pound of feathers. The broader claim language would be permitted because the description of the use and function of the lead weight as a scale counterbalance in the whole disclosure would immediately convey to any person skilled in the scale art the knowledge that the applicant invented a scale with a 1-pound counterbalance weight, regardless of its composition.

Rasmussen, 650 F.2d 1212, 1215. The *Rasmussen* court held that a claim including the general limitation "adheringly applied" was valid even though the specification included only a more specific description of the adhesion process, because "one skilled in the art who read Rasmussen's specification would understand that it is unimportant how the layers are adhered, so long as they are adhered." *Id.* at 1215.

The Federal Circuit explained this concept again more recently in *Ethicon Endo-Surgery v. U.S. Surgical*, 93 F.3d 1572 (Fed. Cir. 1996). The *Ethicon* case concerned a patent in which the specification described a surgical stapler with a lockout mechanism located "on the staple cartridge." The Court found that the patent office properly rejected a claim that described the lockout mechanism as being located instead "on the stapler," because there was no written description of a lockout mechanism in that location. However, the Court also found that a broader claim, one which did not specify the location of the lockout mechanism at all, to be proper.

> Such a claim would not be unsupported by the specification even though it would be literally infringed by undisclosed embodiments. The district court should not have imposed on claim 24 an additional limitation which it does not contain.

Id. at 1582 n.7.

MAN's citations to the *Gentry Gallery* and *Tronzo* cases are inapposite here. In *Gentry Gallery, Inc. v. The Berkline Corp.*, 134 F.3d 1473 (Fed. Cir. 1998), the question was whether a claim to a recliner in which the location of the reclining controls was not limited to being "on the console" (as opposed to elsewhere on the recliner) was proper. In that case, the Court found,

"the original disclosure clearly identifies the console as the only possible location for the controls." *Id.* at 1479. And moreover, the inventor had "admitted at trial that he did not consider placing the controls outside the console until he became aware that some of Gentry's competitors were so locating the controls." *Id.* [6] Similarly, in *Tronzo v. Biomet, Inc.*, 156 F.3d 1154 (Fed. Cir. 1998), patent claims to an artificial hip socket were found to be invalid because they were not limited to a cup of a particular shape, and the only embodiments described in the specification had that particular shape. The reason: as in *Gentry Gallery*, the specification relied on that particular shape as "an extremely important aspect" of the invention and the difference between the invention and the prior art. *See* 156 F.3d at 1159.[7] Those factors are not present here.

Even under MAN's misreading of the Goss patents' specifications (as noted above, the specifications literally describe a tubular blanket with an outer layer that is not limited to being "gapless"), this case is more similar to, for example, the Federal Circuit's later *Lampi* decision than to the earlier *Gentry Gallery* and *Tronzo* cases. Even though the patent specification at issue in *Lampi*, which involved a housing for a small night light that included two half-shells, repeatedly described the half-shells as being identical, and even though the patent drawings depicted only identical half-shells, the Court—applying the "familiar principle of patent law that claim need not be limited to a preferred embodiment"—ruled that the claims of the patent could properly include "half-shells that are not identical." 228 F.3d 1365, 1378 (Fed. Cir. 2000).

---

[6] Here, it is uncontested that Jim Vrotacoe and the other Goss inventors not only invented but in their 1989 application literally described a blanket with a stripe or join like the accused Reeves blanket. *See* Defendants' Non-Infringement Brief at 5. *See also* '587 application, Exhibit 4 at HWS 000167.

[7] Here, it is uncontested that the presence or absence of a strip or join on the tubular blanket had nothing to do with the differences between Goss's tubular blanket and the prior art, *e.g.* flat blankets.

CONCLUSION

The inventions set forth in the claims of the '734, '100, and '251 patents are literally and expressly described in those patents specifications, as they were in the 1991 '668 application and the 1989 '587 application, including the outer layer, which the specifications describe as follows:

> The tubular blanket has a cylindrical outer layer of incompressible material and a cylindrical layer of compressible material on an inner layer of rigid material.

(Exhibit 4 at HWS 000162, emphasis added).

For this reason, and in view of the other facts discussed above, MAN is wrong to argue that the patents describe only a "gapless" outer layer. MAN's motion should be denied.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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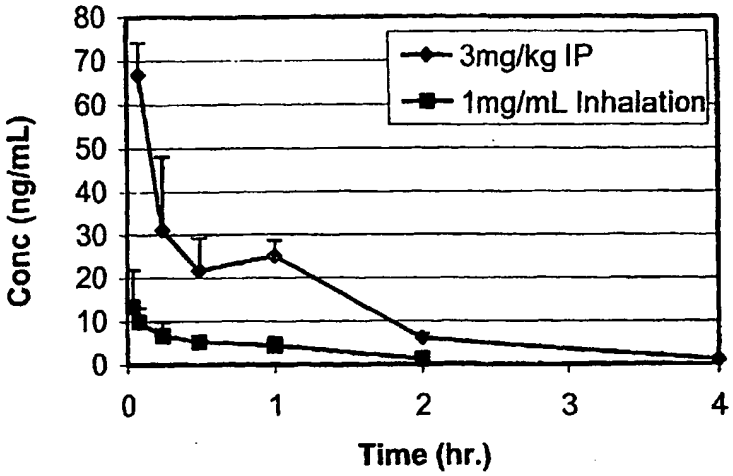
(54) Title: ANTIMUSCARINIC AEROSOL



(57) Abstract: The present invention concerns the use of antimuscarinic agents for the treatment of urinary disorders. The invention provides a method of treating urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a. treatment, a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, said administration being performed by inhalation or insufflation. Furthermore, the present invention provides a pharmaceutical composition for treating urinary disorder in a mammal, including man, which is in the form of an inhalable or insufflable preparation and comprises a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, together with an inhalably or insufflably acceptable carrier or diluent therefor. The invention also provides a novel use of an antimuscarinic agent, or solvate or prodrug thereof, for the manufacture of an inhalable or insufflable medicament for therapeutical treatment of urinary disorders.

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ANTIMUSCARINIC AEROSOL

This application claims the benefit of US Provisional Patent Application No 60/337,298, filed 5 November 2001, the entire disclosure of which is herein incorporated by reference.

Technical Field

The present invention is within the field of urology. More specifically, it is generally based on the use of antimuscarinic agents for the treatment of urinary disorders, said antimuscarinic agents being administered by inhalation or insufflation.

Background of the Invention

Urinary disorders and symptoms thereof include some or all of the following: urgency, frequency, incontinence, urine leakage, enuresis, dysuria, hesitancy, and difficulty of emptying bladder. In particular, urinary disorders include urinary incontinence, caused by e.g. unstable or overactive urinary bladder.

A substantial part (5-10%) of the adult population suffers from urinary incontinence, and the prevalence, particularly of so-called urge incontinence, increases with age. The symptoms of an unstable or overactive bladder comprise urge incontinence, urgency and urinary frequency. It is assumed that unstable or overactive bladder is caused by uncontrolled contractions of the bundles of smooth muscle fibres forming the muscular coat of the urinary bladder (the detrusor muscle) during the filling phase of the bladder. These contractions are mainly controlled by cholinergic muscarinic receptors, and the pharmacological treatment of unstable or

overactive bladder has been based on muscarinic receptor antagonists.

The reason why the bladder muscle contracts inappropriately is unclear in many cases. For some people it may be due to a problem with the nerve signals that run from the brain to the bladder. Sometimes minor nerve damage is caused by surgery or childbearing. This muscle squeezes or contracts more often than normal and at inappropriate times. Instead of staying at rest as urine fills the bladder, the detrusor contracts while the bladder is filling with urine. This causes a person to feel a sudden and sometimes overwhelming urge to urinate even when the bladder is not full.

US Patent 5,382,600 discloses 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl)-4-methylphenol, also known as N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, with the generic name of tolterodine, as being useful to treat urinary incontinence. H Postlind *et al*, Drug Metabolism and Disposition, 26(4): 289-293 (1998) discloses that tolterodine is a muscarinic receptor antagonist. It is presently being sold in a number of different countries for treatment of urinary incontinence under the name Detrol®, marketed by Pharmacia. When tolterodine is used to treat urinary incontinence it is administered perorally as a tablet. The major, active metabolite of tolterodine is the 5-hydroxymethyl derivative of tolterodine.

US Patent 5,559,269 and H Postlind *et al*, Drug Metabolism and Disposition, 26(4): 289-293 (1998) disclose hydroxytolterodine. US Patent 5,559,269 discloses this compound as being useful to treat urinary incontinence. Pharmacol. Toxicol., 81: 169-172 (1997) discloses that hydroxytolterodine has antimuscarinic activity. The international patent application WO 02/34245 discloses the use of tolterodine for treating asthma, COPD, and allergic rhinitis.

The international patent application WO 98/43942 discloses therapeutically active diarylpropylamines, which have favorable anticholinergic properties, and which can be used for the treatment of disorders related to urinary incontinence.

US Patent 6,124,354 discloses 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate and its use in treating urinary incontinence and irritable bowel syndrome (see Example 99). Can. J. Chem., 40: 1909-1916 (1962) refers to this compound as a potential antidote for treatment of anticholinesterase poisoning. J. Am. Chem. Soc., 69: 2902-2906 (1947), while not mentioning the diisopropylamino compound but a diethylamino analog, discloses that the diethylamino compound has antispasmolytic action against acetylcholine.

While efficiently relieving urinary incontinence in affected patients, the above-mentioned commercially available compounds do not provide their effects instantly upon administration thereof to the patient. Since urinary disorder symptoms often have a rapid onset, it is desirable to relieve the symptoms instantly.

The currently marketed administration form of tolterodine is film-coated tablets containing 1 mg, 2 mg or 4 mg of tolterodine L-tartrate for release in the gastrointestinal tract. Consumers constantly require alternative delivery forms, especially when the need for medicament treatment is urgent and/or when the patient has an active life-style.

Hence, known treatments are insufficient to certain groups of patients, which demand a more flexible treatment to meet their active way of life.

There is a need for new delivery forms of antimuscarinic agents for treatment of urinary disorders, which delivery forms possess properties such that the mentioned problems can be overcome.

Summary of the Invention

For these and other purposes, it is an object of the present invention to provide a method of treating urinary disorder in a mammal, including man, which method brings instant relief from symptoms arising from said urinary disorder.

It is also an object of the present invention to provide a method of treating urinary disorder in a mammal, including man, which method involves alternative delivery forms that are particularly suitable for urgent or acute treatment of symptoms.

It is an object of the present invention to provide a method of treating urinary disorder in a mammal, including man, which method is compatible with an active life-style.

It is a further object of the present invention to provide a pharmaceutical composition for treating urinary disorder in a mammal, including man, which can bring instant relief from symptoms arising from said urinary disorder.

It is also an object of the present invention to provide a pharmaceutical composition for treating urinary disorder in a mammal, including man, which is appropriate for alternative delivery forms being particularly suitable for urgent or acute treatment of symptoms.

It is an object of the present invention to provide a pharmaceutical composition for treating urinary disorder in a mammal, including man, use of which is compatible with an active life-style.

Another object of the present invention is to provide a novel use of an agent active against urinary disorder for the manufacture of a medicament for therapeutical treatment of urinary disorders, which medicament can bring instant relief from symptoms arising from said urinary disorder.

It is also an object of the present invention to provide a novel use of an agent active against urinary disorder for the manufacture of a medicament for therapeutical treatment of urinary disorders, which medicament is appropriate for alternative delivery forms that are particularly suitable for urgent or acute treatment of symptoms.

Yet another object of the present invention is to provide a novel use of an agent active against urinary disorder for the manufacture of a medicament for therapeutical treatment of urinary disorders, which medicament is compatible with an active life-style.

For these and other objects which will be evident from the following disclosure, the present invention provides a method of treating urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, said administration being performed by inhalation or insufflation.

The invention is based on the insight that antimuscarinic agents are rapidly distributed to the systemic circulation upon delivery via inhalation or insufflation, thus providing their effects instantly at target organs, such as the smooth muscles regulating emptying of the urinary bladder.

In one preferred embodiment of the method according to the invention, said disorder is unstable or overactive urinary bladder.

In a preferred embodiment of the method according to the invention, said disorder is urinary incontinence.

In another preferred embodiment of the method according to the invention, said antimuscarinic agent, or solvate or prodrug thereof, is administered as an aerosol formulation.

In yet another preferred embodiment of the method according to the invention, said antimuscarinic agent, or solvate or prodrug thereof, is administered as a powder formulation.

In a preferred embodiment of the method according to the invention, said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic esters, and inhalably or insufflably acceptable salts thereof.

In a more preferred embodiment of the method according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

In a more preferred embodiment of the method according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

In the most preferred embodiment of the method according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and tolterodine L-tartrate.

In a preferred embodiment of the method according to the invention, the administered amount of said antimuscarinic agent is from about 0.05 mg to about 12 mg.

In a more preferred embodiment of the method according to the invention, the administered amount of said antimuscarinic agent is from about 0.1 to about 6 mg.

In the most preferred embodiment of the method according to the invention, the administered amount of said antimuscarinic agent is from about 0.2 to about 5 mg.

Furthermore, the present invention provides a pharmaceutical composition for treating urinary disorder in a mammal, including man, which is in the form of an inhalable or insufflable preparation and comprises a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, together with an inhalably or insufflably acceptable carrier or diluent therefor.

In one preferred embodiment of the composition according to the invention, said disorder is unstable or overactive urinary bladder.

In a preferred embodiment of the composition according to the invention, said disorder is urinary incontinence.

In another preferred embodiment of the composition according to the invention, said composition is an aerosol formulation.

In yet another preferred embodiment of the composition according to the invention, said composition is a powder formulation.

In one preferred embodiment of the composition according to the invention, said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic esters, and inhalably or insufflably acceptable salts thereof.

In a more preferred embodiment of the composition according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

In a more preferred embodiment of the composition according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

In the most preferred embodiment of the composition according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and tolterodine L-tartrate.

In a preferred embodiment of the composition according to the invention, said antimuscarinic agent is present in an amount of from about 0.05 mg to about 12 mg, preferably from about 0.1 to about 6 mg, and more preferably from about 0.2 to about 5 mg.

The present invention also provides a novel use of an antimuscarinic agent, or solvate or prodrug thereof, for the manufacture of an inhalable or insufflable medicament for therapeutical treatment of urinary disorders.

In one preferred embodiment of the use according to the invention, said disorder is unstable or overactive urinary bladder.

In a preferred embodiment of the use according to the invention, said disorder is urinary incontinence.

In another preferred embodiment of the use according to the invention, said medicament is an aerosol formulation.

In yet another preferred embodiment of the use according to the invention, said medicament is a powder formulation.

In a preferred embodiment of the use according to the invention, said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic esters, and inhalably or insufflably acceptable salts thereof.

In a more preferred embodiment of the use according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-(diisopropylamino)ethyl-1-

phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

In a more preferred embodiment of the use according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

In the most preferred embodiment of the use according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and tolterodine L-tartrate.

Brief Description of the Drawings

Figure 1 is a diagram showing the plasma concentration (ng/ml)of tolterodine with time (hours) upon systemic and local administration (aerosol) in mice.

Figure 2 is a diagram showing the plasma concentration (ng/ml) of tolterodine with time (hours) upon local administration (aerosol) of various amounts in mice.

Figure 3 is a diagram showing the variation of serum concentration (nmol/l) of tolterodine and its active metabolite with time (hours) during 9 hours upon administration of tolterodine perorally through a 2 mg tablet in human patients.

Description of the Invention

The present invention involves the use of antimuscarinic agents to treat urinary disorders, such as unstable or overactive urinary bladder.

Overactive urinary bladder encompasses various urinary disorders, including overactive urinary bladder detrusor instability, detrusor hyperreflexia, urge incontinence, urgency and urinary frequency and LUTS (Lower Urinary Tract Symptoms giving obstructive urinary symptoms such as slow urination, dribbling at the end of urination, inability to urinate and/or the need to strain

to urinate at an acceptable rate or irritate symptoms such as frequency an/ or urgency).

Other conditions are also included, which give rise to urinary frequency, urgency and/or urge incontinence. Overactive bladder disorders also include nocturia and mixed incontinence. While overactive bladder is often associated with detrusor muscle instability, disorders of bladder function may also be due to neuropathy of the central nervous system (detrusor hyperreflexia) including spinal cord and brain lesions, such as multiple sclerosis and stroke. Overactive bladder symptoms may also result from, for example, male bladder outlet obstruction (usually due to prostatic hypertrophy), interstitial cystitis, local edema and irritation due to focal bladder cancer, radiation cystitis due to radiotherapy to the pelvis, and cystitis.

The method of the present invention is used to treat mammals, including man. It is preferred that the mammal is a human.

Upon traditional tablet administration of antimuscarinic agents to treat urinary disorders, the plasma concentration thereof increases rather slowly, peaking after 1-2 hours. The antimuscarinic agents are often metabolized by the liver following oral dosing. According to the present invention, administration of antimuscarinic agents to patients for treatment of urinary disorders can advantageously be performed via inhalation or insufflation. Thereby, the antimuscarinic agents instantly gain access to the systemic circulation and can affect target tissues, such as the smooth musculature surrounding the urinary tract.

The compositions according to the invention can be made up in solid or liquid form, such as powders, sterile solutions, suspensions or emulsions, and the like.

The antimuscarinic agents of the present invention are administered by inhalation or insufflation. The

inhalation or insufflation is preferably by either an aerosol or a powder.

The method and the antimuscarinic agents and compositions of the present invention are useful for the treatment of unstable or overactive urinary bladder, e.g. urinary incontinence.

The dosage of the specific antimuscarinic agent will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 4 mg per kg of body weight, administered singly or multiply in doses e.g. from about 0.05 mg to about 200 mg each. A clinically effective amount of antimuscarinic agents is from about 0.05 mg to about 12 mg. It is preferred that the effective amount is from about 0.1 to about 6 mg; it is more preferred that the effective amount is from about 0.2 to about 5 mg.

The dosage form for inhalation can be an aerosol. The minimum amount of an aerosol delivery is about 0.2 ml and the maximum aerosol delivery is about 5 ml. The concentration of the antimuscarinic agents may vary as long as the total amount of spray delivered is within the about 0.2 to about 5 ml amount and it delivers an effective amount. It is well known to those skilled in the art that if the concentration is higher, one gives a smaller dose to deliver the same effective amount.

The non-active ingredient or carrier can be just (sterile) water with the pH adjusted to where the active pharmaceutical agent is very soluble. It is preferred that the pH be at or near 7. Alternatively and preferably, the non-active carrier agent should be physiological saline with the pH adjusted appropriately. Aerosols for inhalation of various pharmaceutical agents are well known to those skilled in the art, including many aerosols for treating asthma.

Alternatively, the dosage form for inhalation can be a powder. Powders for inhalation of various pharmaceutical agents are well known to those skilled in the art, including many powders for treating asthma. When the dosage form is a powder, the antimuscarinic agent can be administered in pure form or diluted with an inert carrier. When an inert carrier is used, the antimuscarinic agent is compounded such that the total amount of powder delivered delivers an "effective amount" of the agent. The actual concentration of the agent may vary. If the concentration is lower, then more powder must be delivered; if the concentration is higher, less total material must be delivered to provide an effective amount of the agent.

The carriers may be of any inert material, organic or inorganic, suitable for administration via inhalation or insufflation, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavoring agents, buffers, and the like.

Various devices are on the market for administering powders for inhalation for asthma, and these devices are suitable for administering the antimuscarinic agents of the present invention.

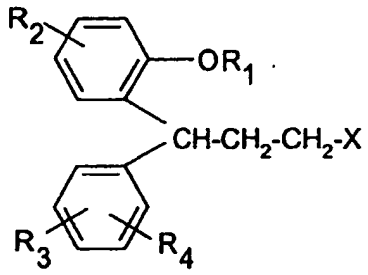
Pharmaceutically acceptable salts include salts of both inorganic and organic acids. The pharmaceutically acceptable salts are preferred over the corresponding free amines since they produce compounds that are more water soluble and more crystalline. The preferred pharmaceutically acceptable salts include salts of the following acids: tartaric, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, citric, methanesulfonic,

CH_3-$(CH_2)_n$-COOH where n is 0 through 4, HOOC-$(CH_2)_n$-COOH, where n is as defined above, HOOC-CH=CH-COOH, ϕ-COOH. For other acceptable salts, see Int. J. Pharm., 33: 201-217 (1986).

An exemplary class of antimuscarinic agents which may be used as active ingredients in the present invention comprises the arylcycloalkane carboxylic esters disclosed in US-6,124,354 (the entire disclosures of which are incorporated by reference herein).

An exemplary specific antimuscarinic agent is 2-[bis(1-methylethyl)amino]ethyl-1-phenylcyclopentanecarboxylate, also known as 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as metabolites, prodrug forms and pharmaceutically acceptable salts thereof.

Another exemplary class of antimuscarinic agents which may be used as active ingredients in the present invention comprises the 3,3-diphenylpropylamines disclosed in US-A-5,382,600, US-A-5,559,269 and US-A-5,686,464 (the entire disclosures of which are incorporated by reference herein) and having the general formula:



wherein R_1 signifies hydrogen or methyl; R_2, R_3 and R_4 independently signify hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen; and X represents a tertiary amino group $-NR_5,R_6$, wherein R_5 and R_6 signify non-aromatic hydrocarbyl groups, which may be the same or different, especially C_{1-6}-alkyl or

adamantyl, and which together contain at least three, preferably at least four carbon atoms, and each of which may carry a hydroxy substituent, and wherein R_5 and R_6 may form a ring together with the amine nitrogen, preferably a non-aromatic ring having no heteroatom other than the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

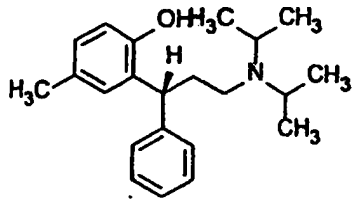
Exemplary specific compounds include tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, as well as the corresponding (S)-enantiomer, the racemate and the active 5-hydroxymethyl metabolites, solvates, prodrug forms and pharmaceutically acceptable salts thereof.

Useful analogues to the above compounds are disclosed in WO 98/43942 (the full disclosure of which is incorporated by reference herein).

Specifically, the compositions according to the present invention have proved to be very suitable for administering the above-mentioned drug tolterodine and would likewise be suitable for its related compounds, i.e. the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer; i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms and pharmacologically acceptable salts thereof.

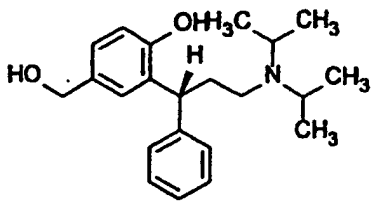
Tolterodine refers to 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol, also known as (R)-N,N-

diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, a compound of the formula:



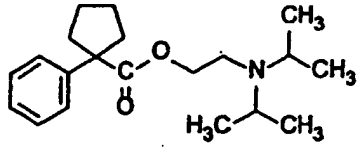
(R)-stereoisomer

Hydroxytolterodine refers to 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol, a compound of the formula:



(R)-stereoisomer

2-[bis(1-methylethyl)amino]ethyl-1-phenylcyclopentanecarboxylate, also known as 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, refers to a compound of the formula:



"Antimuscarinic agents" refer to muscarinic receptor antagonists. Examples of antimuscarinic agents include, but are not limited to, tolterodine, hydroxytolterodine, 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, propiverine, oxybutynin, trospium, darifenacin, temiverine, and ipratropium.

Propiverine is 1-methyl-4-piperidyl .alpha.,.alpha.-diphenyl-.alpha.-(n-propoxy)acetate and is disclosed in East German Patent 106,643 and in CAS 82-155841s (1975). Oxybutynin is 4-(diethylamino)-2-

butynylalphaphenylcyclohexaneglycolate and is disclosed in UK Patent 940,540. Trospium is 3alpha-hydroxyspiro[1alphaH,5alphaH-nortropane-8,1'pyrrolidinium]chloride benzilate and is disclosed in US Patent 3,480,623. Darifenacin is 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-alpha,alpha-diphenyl-, and is disclosed in US Patent 5,096,890. Temiverine is benzeneacetic acid, .alpha.-cyclohexyl-.alpha.-hydroxy-, 4-(diethylamino)-1,1-dimethyl-2-butynyl ester and is disclosed in US Patent 5,036,098. Ipratropium is 8-isopropylnoratropine methobromide and is disclosed in US Patent 3,505,337.

"Physiological saline" generally refers to a 0.9% aqueous sodium chloride solution.

"Pharmaceutically acceptable" refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

Analogously, "inhalably acceptable" and "insufflably acceptable", respectively, refer to properties and/or substance which are pharmaceutically acceptable and also suitable for use via inhalation and insufflation, respectively.

Examples

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various antimuscarinic agent and/or perform the various methods of the invention and are to be construed as merely illustrative, and not limitations of the preceding

disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

Example 1. Pharmacokinetic comparison of systemic and local (aerosol) administration, respectively, of tolterodine

Female BALB/c mice, weight range 19-22 g, were obtained from Charles River Laboratories (Kingston, NC). They received food and water *ad libitum*. All procedures in these studies were in compliance with the Animal Welfare Act Regulation, 9CFR Parts 1 and 2, Publication (NIH) 85-23, 1985.

Tolterodine L-tartrate, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-tartrate, for intraperitoneal administration was prepared in sterile 0.9% NaCl.

Tolterodine L-tartrate for aerosol administration was prepared in sterile phosphate buffer solution at a concentration of 1.0 mg/ml.

Mice were placed in a carousel-style, nose only, exposure chamber and allowed to inhale aerosols of tolterodine for five minutes, using an ICN SPAG-2 nebulizer. This nebulizer generates a mean aerosol particle size of 1.3 microns at a rate of approximately 0.25 ml/minute.

Thus, mice received tolterodine either by aerosol generated from a 1 mg/ml solution for five minutes or by intraperitoneal (i.p.) injection at a dose of 3 mg/kg. Blood samples were taken via cardiac puncture under isoflurane anesthesia at 5, 15, 30, 60, 120, and 240 minutes after i.p. treatment and at 2.5, 5, 15, 30, 60, and 120 minutes after aerosol drug treatment.

The samples were collected in tubes containing EDTA and centrifuged at 12000 x g for four minutes. Plasma was removed and stored at -70 °C until assay.

Plasma samples were extracted via a liquid/liquid extraction technique. Plasma levels for tolterodine were determined by ESI-LC/MS/MS using a PE SCIEX API 3000 mass spectrometer in positive ion mode. Chromatographically, the analyte and internal standard were resolved on a Zorbax ACE Phenyl column(2.1 x 50mm) using a gradient elution. The total analysis time was 4 minutes with a limit of quantitation of 100pg/mL.

Plasma concentrations of tolterodine following 3 mg/kg i.p. injection and following 1 mg/ml aerosol exposure (inhalation) are summarized in Figure 1.

Example 2. Aerosol administration of different amounts of tolterodine

Female BALB/c mice, weight range 19-22 g, were obtained from Charles River Laboratories (Kingston, NC). They received food and water *ad libitum*. All procedures in these studies were in compliance with the Animal Welfare Act Regulation, 9CFR Parts 1 and 2, Publication (NIH) 85-23, 1985.

Tolterodine L-tartrate for aerosol administration was prepared in sterile phosphate buffer solution at concentrations of 0.1, 0.5, and 1.0 mg/ml.

As described in Example 1, mice were exposed to aerosols of tolterodine generated from either 0.1, 0.5, or 1.0 mg/ml solutions. The duration of aerosol treatment was five minutes. Blood samples were collected via cardiac puncture at 2.5, 5, 15, 30, 60, and 120 minutes following the end of the drug nebulization period.

The samples from were collected in tubes containing EDTA and centrifuged at 12000 x g for four minutes. Plasma was removed and stored at -70 °C until assay.

Plasma samples were extracted and plasma levels for tolterodine were determined as described in Example 1.

Figure 2 shows plasma concentrations of tolterodine L-tartrate following inhalation of nebulized solutions at 0.1, 0.5, or 1.0 mg/mL. Plasma levels for the 0.1 mg/mL concentration were at or below detection limits. Clearly, tolterodine is rapidly absorbed into the circulation.

Example 3. Comparative pharmacokinetic study of oral administration of tolterodine

This example illustrates the systemic distribution in man of perorally administrated prior art tolterodine tablets.

In 30 human patients with overactive bladder, the pharmacokinetic effects were determined of a film-coated tablet containing 2 mg of tolterodine L-tartrate. Serum concentrations of tolterodine and its main 5-hydroxymethyl metabolite (below called 5-HM) were measured over time.

Blood samples were drawn immediately before dosing and after 0.5, 1, 2, 3, 6 and 9 hours, and the free (unbound) serum concentrations of tolterodine and its 5-HM metabolite were measured by gas chromatography/mass spectrometry. The unbound concentrations were calculated assuming a fraction unbound of 3.7% for tolterodine and of 36% for 5-HM as obtained from protein binding studies on human serum (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136).

Figure 3 shows the obtained variation with time of the sum of the unbound concentrations of tolterodine and 5-HM for the administration of a 2 mg tablet.

It is apparent that the patterns of blood concentrations of tolterodine and its active metabolite are altered upon aerosol administration thereof (examples 1 and 2, fig 1 and 2), when compared to prior art oral

administration (example 3, fig 3). Aerosol administration (fig 1 and 2) produces within a few minutes a distinct and instant rise in tolterodine plasma concentration, similar in pattern to what is seen upon intraperitoneal injection (fig 1). In contrast, oral administration (fig 3) results in slower uptake of tolterodine into the circulation, wherein a maximum blood concentration is reached in the range of one hour, and a concomitant prolonged presence of tolterodine in the circulation.

Claims

1. A method of treating urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, said administration being performed by inhalation or insufflation.

2. A method according to claim 1, wherein said disorder is unstable or overactive urinary bladder.

3. A method according to claim 1, wherein said disorder is urinary incontinence.

4. A method according to claim 1, wherein said antimuscarinic agent, or solvate or prodrug thereof, is administered as an aerosol formulation.

5. A method according to claim 1, wherein said antimuscarinic agent, or solvate or prodrug thereof, is administered as a powder formulation.

6. A method according to any one of claims 1-5, wherein said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic esters, and inhalably or insufflably acceptable salts thereof.

7. A method according to claim 6, wherein said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

8. A method according to claim 7, wherein said antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

9. A method according to claim 8, wherein said antimuscarinic agent is selected from the group consisting of tolterodine and tolterodine L-tartrate.

10. A method according to claim 1, wherein the administered amount of said antimuscarinic agent is from about 0.05 mg to about 12 mg.

11. A method according to claim 1, wherein the administered amount of said antimuscarinic agent is from about 0.1 to about 6 mg.

12. A method according to claim 1, wherein the administered amount of said antimuscarinic agent is from about 0.2 to about 5 mg.

13. A pharmaceutical composition for treating urinary disorder in a mammal, including man, which is in the form of an inhalable or insufflable preparation and comprises a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, together with an inhalably or insufflably acceptable carrier or diluent therefor.

14. A composition according to claim 13, wherein said disorder is unstable or overactive urinary bladder.

15. A composition according to claim 13, wherein said disorder is urinary incontinence.

16. A composition according to claim 13, which is an aerosol formulation.

17. A composition according to claim 13, which is a powder formulation.

18. A composition according to any one of claims 13-17, wherein said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic esters, and inhalably or insufflably acceptable salts thereof.

19. A composition according to claim 18, wherein said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-

(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

20. A composition according to claim 19, wherein said antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

21. A composition according to claim 20, wherein said antimuscarinic agent is selected from the group consisting of tolterodine and tolterodine L-tartrate.

22. A composition according to claim 13, wherein said antimuscarinic agent is present in an amount of from about 0.05 mg to about 12 mg.

23. A composition according to claim 13, wherein said antimuscarinic agent is present in an amount of from about 0.1 to about 6 mg.

24. A composition according to claim 13, wherein said antimuscarinic agent is present in an amount of from about 0.2 to about 5 mg.

25. Use of an antimuscarinic agent, or solvate or prodrug thereof, for the manufacture of an inhalable or insufflable medicament for therapeutical treatment of urinary disorders.

26. Use according to claim 25, wherein said disorder is unstable or overactive urinary bladder.

27. Use according to claim 25, wherein said disorder is urinary incontinence.

28. Use according to claim 25, wherein said medicament is an aerosol formulation.

29. Use according to claim 25, wherein said medicament is a powder formulation.

30. Use according to any one of claims 25-29, wherein said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic

esters, and inhalably or insufflably acceptable salts thereof.

31. Use according to claim 30, wherein said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

32. Use according to claim 31, wherein said antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

33. Use according to claim 32, wherein said antimuscarinic agent is selected from the group consisting of tolterodine and tolterodine L-tartrate.

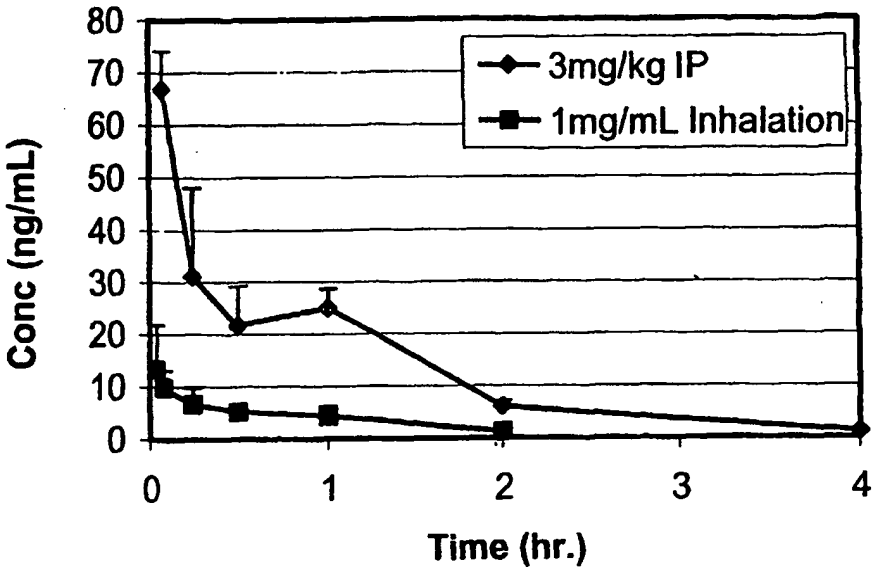


FIGURE 1

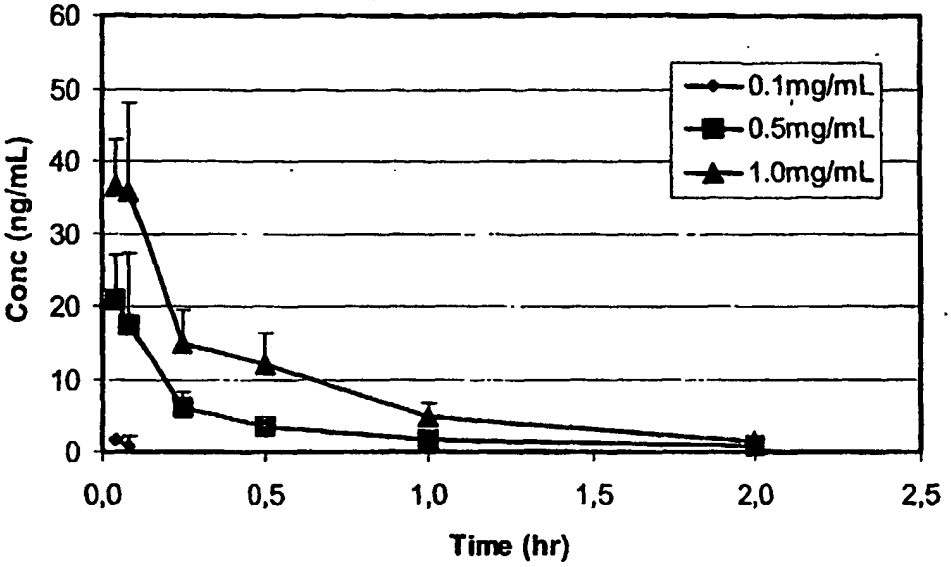


FIGURE 2

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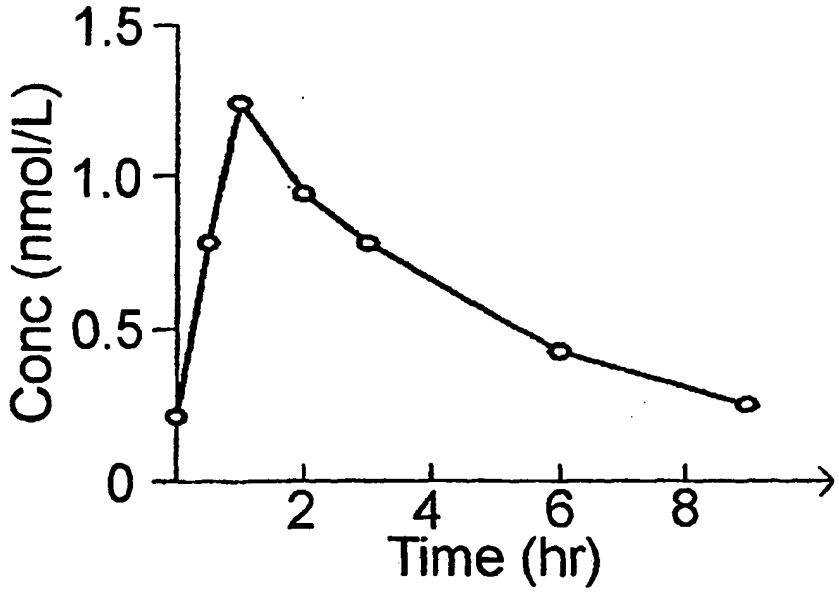

FIGURE 3

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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
26 February 2004

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.

(54) Title: ANTIMUSCARINIC AEROSOL

(57) Abstract: The present invention concerns the use of antimuscarinic agents for the treatment of urinary disorders. The invention provides a method of treating urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a. treatment, a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, said administration being performed by inhalation or insufflation.

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INTERNATIONAL SEARCH REPORT

Int Application No
PCT/US 02/35335

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/00 A61K31/137 A61K31/216 A61K9/12 A61P13/00
A61P13/10

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 A61K A61P

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)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 03 002059 A (BRIDGE PHARMA INC) 9 January 2003 (2003-01-09) abstract page 5, last paragraph; claims 1-15	1-6, 10-18, 22-30
P,X	WO 02 17907 A (SHERRATT AMANDA J ;THERAMAX INC (US); HOUDI ABDULGHANI A (US)) 7 March 2002 (2002-03-07) the whole document	1-5, 10-17, 22-29
P,X	WO 02 34245 A (SUNDQUIST STAFFAN ;PHARMACIA AB (SE); GILLBERG PER GORAN (SE); UPJ) 2 May 2002 (2002-05-02) the whole document	13-24

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the International search	Date of mailing of the international search report
3 July 2003	-4 11 2003

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	Hoff, P.

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INTERNATIONAL SEARCH REPORT

Int I Application No
PCT/US 02/35335

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 03067 A (ABERG GUNNAR) 29 January 1998 (1998-01-29) abstract page 4, paragraph 2; claims 1,2,4,6; examples	1-33
X	WO 94 11337 A (KABI PHARMACIA AB ;JOHANSSON ROLF ARNE (SE); MOSES PINCHAS (SE); N) 26 May 1994 (1994-05-26) cited in the application abstract page 6, line 36 - page 7, line 3 page 7, line 24 - line 28; claims; examples	1-33
X	WO 96 23492 A (SEPRACOR INC) 8 August 1996 (1996-08-08) abstract; claims 1-3,7,8; examples	1-5, 10-17, 22-29
X	US 5 736 577 A (MCCULLOUGH JOHN R ET AL) 7 April 1998 (1998-04-07) abstract column 2, line 55 - line 59 column 3, line 48 - line 52; claims 1,4; examples	1-5, 10-17, 22-29
X	"MARTINDALE, The complete drug reference" 2000, PHARMACEUTICAL PRESS , XP002246330 page 453 - page 454 page 754 - page 755 page 757	13-17, 22-24
A	EP 0 325 571 A (KABIVITRUM AB) 26 July 1989 (1989-07-26) cited in the application abstract page 6, line 59 - line 63; claims; example 22	1-33

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

.....ational application No.
PCT/US 02/35335

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-7, 10-19, 22-31 (all partially), 8, 9, 20, 21, 32, 33

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: -

Present claims 1-5,10-17,22-29 relate to a compound defined by reference to a desirable characteristic or property, namely "antimuscarinic agent".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Furthermore, present claims 1-6,13-18,25-30 relate to an extremely large number of possible compounds (in terms of 3,3-diphenylpropylamines, arylcycloalkane carboxylic esters, prodrug). Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. Again, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search for the first invention has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds tolterodine and hydroxytolterodine, with due regard to the general idea underlying the present invention.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5),

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-7(partially),8,9,10-19(partially),20, 21,22-31(partially),32,33

Use of the antimuscarinic agents tolterodine and hydroxytolterodine for treating urinary disorders by inhalation or insufflation and composition thereof

---

2. claims: 1-7(partailly),10-19(partially),22-31(partially)

Use of the antimuscarinic agent 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate for treating urinary disorders by inhalation or insufflation and composition thereof

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INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/US 02/35335

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03002059 A	09-01-2003	US 2003027856 A1	06-02-2003
		WO 03002059 A2	09-01-2003
WO 0217907 A	07-03-2002	US 2002161044 A1	31-10-2002
		AU 8839501 A	13-03-2002
		EP 1333825 A1	13-08-2003
		WO 0217907 A1	07-03-2002
		US 2003191183 A1	09-10-2003
WO 0234245 A	02-05-2002	AU 1296202 A	06-05-2002
		CA 2422901 A1	02-05-2002
		EP 1330241 A2	30-07-2003
		WO 0234245 A2	02-05-2002
		US 2002161054 A1	31-10-2002
WO 9803067 A	29-01-1998	AU 728395 B2	11-01-2001
		AU 3725997 A	10-02-1998
		CA 2259012 A1	29-01-1998
		EP 0924983 A1	30-06-1999
		JP 2000515525 T	21-11-2000
		WO 9803067 A1	29-01-1998
		US 6310103 B1	30-10-2001
WO 9411337 A	26-05-1994	AT 164828 T	15-04-1998
		AU 672458 B2	03-10-1996
		AU 5438094 A	08-06-1994
		CA 2148827 A1	26-05-1994
		DE 69317898 D1	14-05-1998
		DE 69317898 T2	15-10-1998
		DK 667852 T3	11-01-1999
		EP 0667852 A1	23-08-1995
		ES 2117155 T3	01-08-1998
		FI 952179 A	05-05-1995
		HK 1006349 A1	19-02-1999
		HU 72742 A2	28-05-1996
		JP 3343256 B2	11-11-2002
		JP 8503208 T	09-04-1996
		NO 951775 A	05-05-1995
		WO 9411337 A1	26-05-1994
		US 5559269 A	24-09-1996
		US 5686464 A	11-11-1997
WO 9623492 A	08-08-1996	US 5532278 A	02-07-1996
		US 5677346 A	14-10-1997
		AT 196252 T	15-09-2000
		AU 706741 B2	24-06-1999
		AU 4966496 A	21-08-1996
		BR 9607001 A	28-10-1997
		CA 2211400 A1	08-08-1996
		CZ 9702421 A3	17-12-1997
		DE 69610290 D1	19-10-2000
		DE 69610290 T2	29-03-2001
		DK 806948 T3	18-12-2000
		EP 0806948 A1	19-11-1997
		ES 2150663 T3	01-12-2000
		FI 973163 A	30-09-1997
		GR 3034974 T3	28-02-2001
		HU 9800794 A2	28-07-1998

INTERNATIONAL SEARCH REPORT

Inter ıl Application No
PCT/US 02/35335

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9623492 A		JP 11511730 T	12-10-1999
		NO 973516 A	07-08-1997
		NZ 303372 A	28-01-1999
		PL 321498 A1	08-12-1997
		PT 806948 T	28-02-2001
		RU 2181589 C2	27-04-2002
		SK 103597 A3	10-03-1999
		WO 9623492 A1	08-08-1996
		US 5736577 A	07-04-1998
US 5736577 A	07-04-1998	US 5532278 A	02-07-1996
		AU 732568 B2	26-04-2001
		AU 3513797 A	21-01-1998
		BR 9710031 A	10-08-1999
		CA 2257121 A1	08-01-1998
		CZ 9804283 A3	16-06-1999
		EP 0914113 A1	12-05-1999
		HU 9903839 A2	28-03-2000
		JP 2000513724 T	17-10-2000
		KR 2000022194 A	25-04-2000
		NO 985896 A	16-12-1998
		NZ 333282 A	23-06-2000
		PL 330752 A1	24-05-1999
		RU 2195276 C2	27-12-2002
		SK 178698 A3	10-09-1999
		WO 9800126 A1	08-01-1998
		AT 196252 T	15-09-2000
		AU 706741 B2	24-06-1999
		AU 4966496 A	21-08-1996
		BR 9607001 A	28-10-1997
		CA 2211400 A1	08-08-1996
		CZ 9702421 A3	17-12-1997
		DE 69610290 D1	19-10-2000
		DE 69610290 T2	29-03-2001
		DK 806948 T3	18-12-2000
		EP 0806948 A1	19-11-1997
		ES 2150663 T3	01-12-2000
		FI 973163 A	30-09-1997
		GR 3034974 T3	28-02-2001
		HU 9800794 A2	28-07-1998
		JP 11511730 T	12-10-1999
		NO 973516 A	07-08-1997
		NZ 303372 A	28-01-1999
		PL 321498 A1	08-12-1997
		PT 806948 T	28-02-2001
		RU 2181589 C2	27-04-2002
		SK 103597 A3	10-03-1999
		WO 9623492 A1	08-08-1996
		US 5677346 A	14-10-1997
EP 0325571 A	26-07-1989	AT 65990 T	15-08-1991
		AU 635493 B2	25-03-1993
		AU 2932989 A	11-08-1989
		CA 1340223 C	15-12-1998
		DE 68900180 D1	12-09-1991
		DK 172590 A	19-07-1990
		EP 0325571 A1	26-07-1989
		EP 0354234 A1	14-02-1990

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0325571 A		ES 2029384 T3	01-08-1992
		FI 109900 B1	31-10-2002
		GR 3002854 T3	25-01-1993
		HK 64494 A	15-07-1994
		HU 58040 A2	28-01-1992
		HU 9400053 A3	30-01-1995
		JP 2664503 B2	15-10-1997
		JP 3503163 T	18-07-1991
		LU 90259 A9	16-09-1998
		NO 903085 A ,B,	11-07-1990
		WO 8906644 A1	27-07-1989
		US 5382600 A	17-01-1995

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(54) Title: MULTI-STAGE ORAL DRUG CONTROLLED-RELEASE SYSTEM

(57) Abstract: The present invention relates to, as a novel oral drug delivery system for control of drug release, a preparation for maintaining drug concentration in blood at a certain level for a prolonged time by allowing the drug to be released by a constant rate through stepwise control of drug release upon the administration of the preparation.

MULTI-STAGE ORAL DRUG CONTROLLED-RELEASE SYSTEM

Technical Field

The present invention relates to, as a novel oral drug delivery system for controlling drug release, a preparation for maintaining drug concentration in blood at a certain level for prolonged time by allowing the drug to be released by a constant rate through stepwise control of drug release upon the administration of the preparation.

Background Art

Administration forms capable of controlling drug release become an important part of medication in terms of improved treatment effect, reduction of side effects and patient's convenience. Such controlled-release of drug is accomplished through designing of a system comprising the drug. Controlled-release of drug brings many therapeutic advantages, and the most important point is that blood level of drug can be maintained for long time while minimizing fluctuation of the blood level. Accordingly, allowing drug to be released at a constant rate from a preparation is the most important aspect in controlled-release preparation, and in particular, an amount of drug equivalent to that eliminated from the body should be released from the preparation and continuously absorbed while passing through the gastrointestinal tract.

Controlled-release preparations developed so far can be divided into three types, i.e. a type in which drug-containing particles (granules) are coated, matrix type mainly based on polymers, and a type based on osmotic pressure, and among them, the matrix form tablet has been interested greatly as a drug delivery system for the advantage of easy manufacture. When compared with tablets, because of the size and resultant increase of surface area, granules lead to relatively fast disintegration, resulting

in the disadvantage of a short drug-release time in a body.

Most matrix preparations release a drug via diffusion, and regarding with the matrix preparations, various techniques such as introducing water-insoluble coating layer on matrix particles in which drug is dispersed have been developed. In case components of coating layer and the matrix are insoluble in body fluid, diffusion of drug is controlled by the components of coating layer or matrix. Drug release from such preparation occurs by concentration gradient of drug introduced by water penetrated to the preparation. Such type of release shows a tendency of decline in the release rate at the last stage due to the gradual reduction of concentration gradient and the gradual increase of diffusion distance. Accordingly, release rate of drug cannot be maintained at a constant level but gradually reduces as a function of time, finally failing to maintain constant blood level of drug.

Such simple matrix tablets just extend the period of drug release, and exhibit inherent limit of releasing drug by first order kinetics or at a rate of (time) $^{0.5}$. To maintain constant release rate, attempts to modify the previous matrix formulations have been made. Representative methods are to reduce initial drug release rate by introduction of a coating layer, to induce zero-order release rate by morphological approach to preparation, and to combine said two methods. Another approach is method of maintaining constant release rate by allowing diffusion distance to be reduced as a function of time through using erodible and swelling polymer as a main component of matrix.

Majority of the complements to the matrix preparation via coating were attempted for special object besides the control of release rate, e.g. enteric coated tablet or delayed release of drug in colon. As the best example of morphological approach to preparation, a method of regulating release area by introducing hydrophilic or

hydrophobic layer on both sides of drug-containing layer and a method of exposing constant area of the coated tablet can be enumerated.

Matrix formulation mainly consists of a drug and a biocompatible polymer, and in particular, in controlled-release preparation, polymer acts a very important role. Polymer matrix with the characteristic of swelling and erosion consists of swelling layer, diffusion layer and erosion layer, and has the advantage that drug release rate can be regulated at a fixed level based on the moving rates of swelling layer and erosion layer. However, also in case of using erosive polymer, release area deceases with time and this leads to typical matrix release mechanism pattern where release rate decreases with reduction of release area. To correct such drug release pattern, coating layer and a factor capable of controlling swelling were introduced. USP 6,156,343 retarded swelling and initial release by use of polyvinyl alcohol as material for matrix core, and by addition of a salt and introduction of a coating layer.

However, besides the simple erodible polymeric matrix system, non-erodible preparation with coating layer comprising water-insoluble polymer such as lacquer is still defective for time-dependent reduction of drug release, and osmotic preparation is disadvantageous for complicacy of the system and cost problem.

To overcome the declination of drug release with time, DE 1,767,765 developed multi-layer tablets, layers with different concentration of drug, and DE 2,651,176 designed a tablet in which drug concentration can increase from the outer layer towards the center. However, like osmotic preparation, the multi-layer tablet also has some disadvantages, necessity for special facility and complicate manufacture.

USP 4,252,786 designed a preparation in which the core of water-insoluble swelling polymer swells with penetration of water to lead to burst of coating layer.

Such pulsitile drug release is desirable for improving bioavailability of a drug whose first pass effect can be saturated, and it was revealed that drug release from the preparation is less sensitive to pH value of GI tract. Such preparation can freely control the delay of initial drug release, yet, drug release after the burst of the coating layer, still, depends on concentration gradient of drug.

USP 4,610,870 (Jain *et al.*) disclosed a coated tablet showing zero-order release rate. The core of this tablet includes hydroxypropylmethylcellulose and/or methylcellulose, one or more non-swellable binders and/or wax binders, one or more inert fillers or excipients, and one or more lubricant.

USP 4,252,786 by Weiss *et al.* resolved the rapid initial-release problem of swelling and erodible formulation by coating the swelling matrix core with a hydrophobic film coating layer capable of burst. Drug release in this preparation occurs via diffusion through initial non-damaged coating layer, and core expands by continuous penetration of external fluid, leading to burst of the coating layer. Thereafter, the swelling matrix core controls the drug release. Overall drug release is continuous based on such control of initial release, and zero-order release can be achieved.

Though said two patents resolved the problem of non-linear drug release that can occur in swelling and erodible matrix tablet by introducing a coating layer, it is still only simple coated tablet, therefore has failed in overcoming the feature and basic limitations of swelling and erodible matrix. Further, in case of a drug with high water-solubility, it is not effective for prolonged release over 24 hr.

USP Nos. 4,309,404 and 4,248,857 (DeNeale *et al.*) used

carboxypolymethylene as substance for core and introduced seal coating and sugar coating thereon, and USP No. 4,309,405 (Guley *et al.*) disclosed the similar formulation with the above one, using a combination of hydroxypropylmethylcellulose or hydroxypropylcellulose and hydrophobic polymer as core substance. These two formulations demonstrated zero-order release pattern over 12 hr, yet only after rapid initial drug release for 1 hr.

USP No. 4,610,870 discloses a coated tablet showing zero-order release pattern over 8 to 12 hr, and the coating layer of this tablet inhibits the rapid initial release while being gradually disappeared by swelling of the core layer, and then, drug is released with erosion of the core.

USP No. 5,464,633 introduced compressed layer instead of coating layer to swelling and erodible core matrix tablet in order to modify drug release rate, thereby preventing rapid initial drug release, and at the same time, endowed sustained release effect over prolonged time. In case of such multi-layer tablet, to remove inconvenience of coating for coated tablet, compressed layer was introduced, yet, for formation of compressed layered tablet, special facility and complicate calculation of release area were necessary.

USP No. 6,083,532 compensated for pH dependent behavior of drug solubility by using a combination of pH dependent substance and pH-independent polymer as a constituent of core matrix. Such release-modifying attempts were to make the release uninfluenced by individual patient's physiological condition, and applied as means for maximizing drug action. Such preparations can be applied to only specific group of drugs with specific pH-dependency, and as external fluid penetrates continuously into inside of the matrix, it sensitively reacts to pH within the gastrointestinal tract, thus it is difficult to expect continuously steady drug release.

USP No. 4,610,870 used a mixture of hydroxypropylmethylcellulose and methylcellulose as a gel-forming substance, and introduced a coating layer consisting of hydrophilic and hydrophobic materials on the core tablet. Based on this attempt, a preparation was designed to release procaine hydrochloride by zero-order over 8 to 12 hr.

USP No. 6,068,859 discloses controlled-release preparation of azithromycin where, in order to control time-dependent release of drug, the drug was dispersed and embedded in core matrix comprising four kinds of hydro-colloidal gel-forming substance and drug release was induced by erosion of the matrix, and when needed, a coating layer was introduced. As another method, a mixture of coated particles and particles without coating layer was introduced into a single capsule or tablet to allow drug to be released via release channel formed through the uncoated particles. Such preparations were attempted to achieve a comprehensive continuousness by combining each portions with different characteristics such as multi-particulate system, yet control on each part and mixing ratio thereof is necessary, so large amount of time and effort is required.

WO 99/47128 relates to tablet or capsule as biphasic sustained release delivery system, where particles comprising hydrophilic drug and hydrophobic polymer are dispersed in hydrophilic polymer. This system is applied to drugs with high water-solubility, such as metformin hydrochloride, to lead to increased release time and increased transit time in upper gastrointestinal tract by swelling of the preparation. Though the sustained release is effectively accomplished by controlling drug diffusion via adequate application of discontinuous phase of hydrophilic and hydrophobic substance, still, depends on concentration gradient. Therefore, it shows disadvantage of dumping effect due to rapid initial release and time-dependent reduction of release rate.

Therefore, it exhibits sustained release effect for about 10 hr in case of drug with high water-solubility, yet represents typical release profile for a matrix tablet, and thus not effective in terms of long term drug release for more than 24 hr and release rate control.

The conventional techniques as described above experienced difficulty in releasing drug at constant rate for prolonged time due to substantial problems such as time-dependent reduction of drug release area and increase of diffusion distance. In case of preparation based on osmotic pressure, zero-order release can be induced, but it has problem of complicated manufacturing process and high manufacturing cost.

The present invention makes it the object to provide an oral drug controlled-release preparation with minimized solubility-limit for drug to apply and improved stability, which can release drug at a constant rate for a long time without the disadvantages such as complicate manufacturing process and high manufacturing cost as in osmotic preparation or substantial problems such as time-dependent reduction of drug release area and increase of diffusion distance

Disclosure of the Invention

The present invention relates to, as a novel oral drug delivery system for control of drug release, a preparation for maintaining drug concentration in blood at a certain level for a prolonged time by allowing the drug to be released by a constant rate through stepwise control of drug release upon the administration of the preparation. More specifically, the present invention relates to controlled-release oral preparation characterized by stepwise release of granules from matrix and of drug from the granules, comprising

(1) granules comprising a drug and a carrier material in size of 0.1 ~ 1 mm, said carrier material is hydrophobic material in case of a drug with water-solubility of 1 mg/ml or more, while hydrophilic material in case of a drug with water-solubility of less than 1 mg/ml;

(2) a matrix in which said granules are embedded, comprising swelling and erodible polymer(s) and swelling-regulating material(s); and

(3) a release-modifying layer comprising hydrophobic release-modifying polymer, hydrophilic release-modifying polymer, pH-dependent release-modifying polymer or a mixture thereof.

In general, the term "very soluble" is applied to what has water-solubility of 1 mg/ml or more and there is no upper limit of the solubility. The preparation in the present invention can be applied to any drug whose water-solubility is 1 mg/ml or more, accordingly, can also be applied to a drug with water-solubility of about 1 g/ml.

The preparation of the present invention is also applied to a drug with water-solubility of less than 1 mg/ml besides "very soluble" drug and there is no lower limit of the solubility. The preparation of the present invention can be applied to any drug with water-solubility of less than 1 mg/ml, accordingly, can be applied to a drug whose water-solubility is about 0.1 ng/ml.

It is preferred for the preparation of the present invention that 50 to 100% of the drug is present in granules, and the remaining exists within the erodible and swelling matrix or the release-modifying layer, or within the matrix and release-modifying layer in directly dispersed form.

The coated swelling-matrix oral preparation for control of drug release, according to the present invention, consists of three components: (1) Granules containing a drug; (2) swelling and erodible matrix where the drug-containing granules are embedded; and (3) a coating layer surrounding the matrix. Considering the drug release mechanism, coating layer provides initial lag-time for a certain amount of time. This is for enteric preparation or for release at specific site in the body. Further, coating layer functions in inhibiting dumping effect of drug release and in raising drug stability under storage. When said controlled-release preparation is exposed in the body fluid, coating layer disappears with swelling of inner matrix after the certain amount of time, leading to active swelling and erosion of the matrix. Swelling and erosion of the matrix leads to controlled-release of granules embedded in matrix and then drug is released in controlled way from the granules. In case of conventional swelling matrix system, direct release of drug from inner matrix leads to tendency of time-dependent decrease of drug release rate, while in case of the system according to the present invention, drug within the granules is directly released into matrix, and at the same time, drug-containing granules are continuously released and drug is released from the granules, i.e. multi-stage controlled-release, accordingly, drug release area increases with time due to cumulated granules to compensate the reduction of release rate according to reduction of surface area of erodible matrix itself, ultimately leading to drug release at constant rate.

The first constitution of the preparation according to the present invention is granules comprising a drug and a carrier material, wherein the size of said granules is 0.1 ~ 1 mm, said carrier material is hydrophobic material in case of drug with water-solubility of 1 mg/ml or more, and hydrophilic material in case of drug with water-

solubility of less than 1 mg/ml.

In the preparation of the present invention, it is preferred that in case drug has a water-solubility within range from 1 mg/ml to 100 mg/ml, the drug-containing granules are prepared by wet granulation, and in case the drug has water-solubility of 100 mg/ml or more, the drug-containing granules are prepared into granules by dispersing the drug in hydrophobic fusible materials forming the granules.

Additionally, when water-solubility of the drug is less than 1 mg/ml, it is preferred to prepare the drug-containing granules according to solid dispersion method.

In case of drug with water-solubility of 1 mg/ml or more, it is preferred for said hydrophobic material forming the granules to be at least one selected from the group consisting of fatty acids, fatty acid esters, fatty acid alcohols, fatty acid mono-, di-, tri-glycerides, waxes, hydrogenated castor oil, hydrogenated vegetable oil and as like. Examples of the fatty acid alcohols include cetostearyl alcohol, stearyl alcohol, lauryl alcohol, myristyl alcohol and as like. Examples of the fatty acid esters include glyceryl monostearate, glycerol monooleate, acetylated monoglyceride, tristearin, tripalmitin, cetyl ester wax, glyceryl palmitostearate, glyceryl behanate (Compritol 888 ATO™) and as like. Examples of the waxes include beeswax, carnauba wax, glyco wax, castor wax and as like.

In case of drug with water-solubility of less than 1 mg/ml, for the preparation of the present invention, it is preferable that said hydrophilic carrier material forming granules is at least one selected from the group consisting of polyalkylene glycol and carboxyvinyl hydrophilic polymer. As specific example, polyethyleneglycol with

molecular weight of 1,000-6,000, carbomer (Carbopol™), calcium carboxymethylcellulose and sodium carboxymethylcellulose can be enumerated.

The granules of the preparation according to the present invention can further comprise other additives and excipients. As example, lactose, starch, mannitol, saccharose, glucose, sorbitol, dibasic calcium phosphate dihydrate, anhydrous dibasic calcium phosphate, microcrystalline cellulose (Avicel™), gelatin, polyvinylpyrrolidone and salt can be enumerated. The granules can contain at least one of the above additives. The granules can further contain, if necessary, cross-linked sodium carboxymethylcellulose or cross-linked polyvinylpyrrolidone, which accelerates disintegration of granules, and to correct pH dependence of drug, can contain inorganic acid and its conjugate base, or organic acid (such as citric acid and tartaric acid) and its conjugate base. The granules prepared as described above are the part that finally controls release and absorption of drug. In case of hydrophilic drugs, the control is achieved by diffusion through hydrophobic substance forming the granules, while in hydrophobic drugs, hydrophilic substance forming the granules, hydration environment established around the granules and increased surface area improve wettability of drug to increase the water-solubility thereof.

The second constitution of the preparation according to the present invention is matrix having said granule embedded therein, which comprising swelling and erodible polymer(s) and swelling-regulating material(s).

As the swelling and erodible polymer forming the matrix, for the formation of hydrogel matrix, at least one selected from the group consisting of

hydroxyalkylcellulose, hydroxypropylalkylcellulose, polyalkylene oxide, sodium alginate, povidone, polyvinyl alcohol and sodium carboxymethylcellulose can be used. In particular, it is preferred to use at least one selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, polyethylene oxide, sodium alginate, povidone polyvinyl alcohol and sodium carboxymethyl cellulose.

In addition, the matrix can further include adjuvant for formation of the swelling and erodible matrix, and at least one selected from the group consisting of cross-linked sodium carboxymethylcellulose or cross-linked polyvinylpyrrolidone, lactose, starch, mannitol, saccharose, glucose, sorbitol, dibasic calcium phosphate dihydrate, anhydrous dibasic calcium phosphate, microcrystalline cellulose (Avicel™), gelatin, polyvinylpyrrolidone, magnesium stearate, stearic acid, sodium stearate, talc, sodium benzoate, boric acid and colloidal silica, can be used. Also, the matrix can contain a portion of drug to be contained in granules.

Swelling-regulating material among said matrix components is used to control the degree and velocity of swelling of the polymer, and as the swelling-regulating material, cross-linked sodium carboxymethylcellulose or cross-linked polyvinylpyrrolidone, or a mixture thereof can be used. The swelling-regulating material is preferred to be used in a content of 1 to 10% by weight to the total weight of matrix. The swelling and erodible polymer forming the core matrix provides, via swelling, hydration environment around the granules dispersed within the matrix. In particular, it acts a role of raising drug solubility in case of granules comprising hydrophobic drug. Further, it carries out function, secondary drug release control, by controlling the release of granules from the surface by erosion.

The third constitution of the preparation according to the present invention is release-modifying layer, and comprises at least one selected from the group consisting of hydrophobic release-modifying polymer, hydrophilic release-modifying polymer and pH-dependent release-modifying polymer.

In said release-modifying layer, the term "modifying" means that drug release from the preparation is again controlled by this layer, that is, release-modifying layer.

Hydrophobic release-modifying polymer as adequate material for forming the coating layer includes ethylcellulose, shellac and ammonio methacrylate copolymer (Eudragit RS™ or Eudragit RL™) and at least one of them can be used.

As adequate material for forming the coating layer, hydrophilic release-modifying polymer can be selected from the group consisting of hydroxyalkylcellulose and hydoxypropylalkylcellulose and at least one of them can be used, and preferably, selected from the group consisting of hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxybutylcellulose, hydroxypentylcellulose, hydroxypropylmethylcellulose, hydroxypropylbutylcellulose and hydroxypropylpentylcellulose.

As material suitable for the formation of the coating layer, pH-dependent release-modifying polymer includes generally used enteric polymer. Specifically, it is possible to enumerate as follows: hydroxyalkylcellulose phthalate, hydroxyalkylmethylcellulose phthalate, cellulose acetyl phthalate, sodium cellulose acetate phthalate, cellulose ester phthalate, cellulose ether phthalate and anionic

copolymer of methacrylic acid and methyl or ethyl methacrylate. At least one selected from the group consisting of them can be used. As example for the anionic copolymer of methacrylic acid and methyl or ethyl methacrylate, Eudragit L and S can be enumerated.

Said release modifying layer can further includes plasticizer and, for example, it can be selected from the group consisting of castor oil, hydrogenated castor oil, fatty acid, substituted triglycerides and glyceride, polyethylene glycol of molecular weight within range of 300 to 50,000 and its derivatives. Such release modifying layer, i.e. coating layer, acts a role of primary drug release control and functions in modifying zero-order release rate of the matrix core. Using of pH dependent or hydrophobic polymer coating enables target-oriented system. For the coating layer, hydrophobic, hydrophilic and pH dependent polymers are used individually or in a combination of them. Coating solution includes plasticizer in a ratio of 5 to 50% by weight of the coating substance.

It is preferred for said release modifying layer to be 1 to 20% by weight to total weight of matrix. For the preparation of coating solution, water or organic solvent is used and as suitable organic solvent, methanol, ethanol, isopropanol, acetone, chloroform, dichloromethane and a mixture thereof can be used.

The oral drug controlled-release system of the present invention comprises granules containing effective amount of drug, swelling and erodible polymer matrix in which the granules are embedded, and a coating layer surrounding the core matrix consisting of the granules and matrix. It is preferred that granules containing the drug

reach 50 to 80% by weight to total weight of the preparation.

In the preparation according to the present invention, examples of the applicable drug is as follows:

therapeutic agents for aconuresis of oxybutynin, tolterodine and therapeutically equivalent salts thereof;

calcium channel blockers of nifedipine, verapamil, isradipin, nilvadipin, flunarizine, nimodipine, diltiazem, nicardipine, nisoldipin, felodipin, amlodipin, cinarizin and pendilin and pharmaceutically acceptable derivatives thereof;

beta-adrenergic antagonists of propranolol, metoprolol and pharmaceutically acceptable derivatives thereof;

angiotensin-converting enzyme inhibitors of captopril, enalapril, ramipril, fosinopril, altiopril, benazepril, libenzapril, alacepril, cilazapril, cilazaprilat, perindopril, zofedopril, lisinopril, imidapril, spirapril, rentiapril, delapril, alindapril, indalapril, quinalapril and therapeutically equivalent salts thereof;

non-steroidal anti-inflammatory agents of ketorolac, ketoprofen, benoxaprofen, caprofen, flubiprofen, fenoprofen, suprofen, fenbufen, ibuprofen, indoprofen, naproxen, miroprofen, oxaprozine, pranoprofen, pirprofen, thiaprofenic acid, fluprofen, alminoprofen, bucloxic acid, alclofenac acematacin, aspirin, indomethacin, ibufenac, isoxepac, profenac, fentiazac, clidanac, oxpinac, sulindac, tolmetin, zomepirac, zidometacin, tenclofenac, tiopinac, mefenamic acid, flufenamic acid, niflumic acid, meclofenamic acid, tolfenamic acid, diflufenisal, isoxicam, sudoxicam and therapeutically equivalent salts thereof;

therapeutic agents for respiratory disorders of theophylline, salbutamol, aminophylline, dextromethorphan, pseudoephedrine and therapeutically equivalent salts thereof;

analgesics of tramadol, acetaminophen, morphine, hydromorphone, oxycodone, propoxyphene and therapeutically equivalent salts thereof;

psychoneural drugs of fluoxetine, paroxetine, buspirone, bupropion, carmabazepine, carvidopa, levodopa, methylphenidate, trazodone, valproic acid, amitriptyline, carbamazepine, ergoloid, haloperidol, lorazepam and therapeutically equivalent salts thereof;

antibiotics of azithromycin dihydrate, cepha antibiotics, clarithromycin, doxycycline, nitrofurantonin and therapeutically equivalent salts thereof;

antihyperlipidemic agent of bezafibrate, fenofibrate, ethofibrate, lovastatin and therapeutically equivalent salts thereof;

antidiabetic agent of glyburide, glipizide, metformin and therapeutically equivalent salts thereof; and

cyclobenzaprin, favotidin, nizatidine, propafenone, clonazepam, hyoscyamine, diphenhydramine, olistat, doxazosin and therapeutically equivalent salts thereof.

It is preferable for the granules to be prepared by wet granulation, in case of water-soluble drug. For example, a drug, substance forming the granules as described above and at least one kind of additives are mixed and combined by adding binder solution comprising hydrophilic polymer and water or organic solvent such as denatured anhydrous ethanol as granulating fluid. Granulating fluid is added until wet mixture is formed and then the wet mixture is passed through 6~18 mesh sieve. This is dried in an oven at 24 to 60°C for 12 to 24 hr. The dried granules are screened with 10~24 mesh sieve.

In case a drug has water-solubility of 50 mg/ml or more, for effective release-

delay, drug particles can be covered with hydrophobic substance by melt-granulation. At a temperature of at least melting point of delivery system component, drug and other additives are mixed, dispersed and slowly cooled to obtain solid body of the delivery system, and granules are obtained by pulverization and screening.

In case of hydrophobic drug, it is preferable that drug, granule component described above and at least one additive are admixed, melted at melting point of the granule component to obtain solid dispersion. For example, granule-forming additives are added to the formed solid dispersion until granules are formed. The granules are screened through 6~18 mesh sieve, and then dried in an oven at 24 to 60°C for 12 to 24 hr. The dried granules are screened with 10~24 mesh sieve. Granules prepared as described above are mixed with swelling and erodible polymer and at least one additive forming matrix. Lubricant is added to the mixture and the final mixture is prepared into compressed tablet of core matrix without coating layer. Coating layer is formed by using hydrophobic polymer, hydrophilic polymer and enteric or pH dependent substance, individually or in a mixture. At least one polymer for the formation of coating layer and plasticizer is made ready in a form dispersed in water or organic solvent and then the dispersion solution is sprayed on the core matrix prepared as above. Coated tablet is finally dried in an oven at 40 to 50°C. For stability and color of preparation, seal coating can be conducted. In order to allow drug concentration to rapidly reach effective blood level, 1 to 20% of drug can be directly contained within the coating layer.

Drug release through the multi-stage controlled-release system according to the present invention is controlled via three steps.

At the first step, coating layer, i.e. release-modifying layer exhibits intentional release-delaying effect over a certain amount of time. In case of coating layer consisting of hydrophilic polymer alone, overall release profile is not influenced and release pattern of the core matrix itself is maintained, leading to maintenance of zero-order release profile over an 8 to 24 hr or more periods. In case hydrophilic or enteric polymer is used along with hydrophobic polymer, after release-delay over a certain amount of time is maintained, external fluid is penetrated through pores formed by dissolution of hydrophilic or enteric polymer and hydrophilic plasticizer and the penetrated fluid starts to swell the core matrix. Swelling pressure of the core matrix causes disappearing of coating layer and zero-order release of drug occurs. When coated with enteric polymer, below pH 4.0, there is no release, then at pH 4.0 or more, release starts with loss of the coating layer.

At the second step, swelling of the core matrix actively undergoes upon the disintegration and dissolution of the coating layer, and leads to establishment of hydration environment around the granules embedded in the matrix. As erosion of matrix component starts from the surface of the swelling matrix, granules are to be released by a constant rate.

It is preferred for the preparations of the present invention that, by erosion of the surface of matrix, 0 to 20% of total granules is released over 0 to 4 hr, 0 to 50% is released over 0 to 8 hr, 0 to 70% is released over 0 to 16hr, and 0 to 100% is released over 0 to 24 hr.

At the third step, finally, drug is released by diffusion through pores formed

within the granules and by osmotic pressure difference against the external fluid.

Drug release pattern of core matrix itself maintains zero-order release, and introducing of coating layer brings delay over a certain amount of time to lead to intentional appearance of biphasic zero-order release pattern. Release rate can be controlled in various ways by ratio of granules component forming the system and amount of granules, amount of swelling polymer and ratio of swelling matrix to granules, and ratio and amount of hydrophobic, hydrophilic or enteric polymer forming the coating layer.

The system prepared according to the present invention is oral multi-stage controlled-release system and suitable for designing oral drug delivery system taken once or twice a day which exhibits controlled-release for a long time and on specific target for the drug's therapeutic purpose. Drug is released from granules that are released from matrix by swelling and erosion, and cumulated released-granules allow surface area for drug release to be maintained at a constant level. Thus, this compensates the decrease of drug release rate according to reduction of surface area by erosion of matrix, leading to prolonged drug release at constant rate. Maintaining of zero-order release rate enables blood level of drug to be kept at a steady level for a long time.

Best Mode for Carrying Out the Invention

The Examples given below are just to explain the present invention and, in any case, they should not be regarded as limiting the scope of the present invention, and in view of the detailed description of invention and the patent claims, the Examples and

their equivalents are obvious to persons skilled in the art.

Examples 1~5. Preparations of core matrix tablet containing oxybutynin

Oxybutynin, glyceryl behanate, solubilizer, binder, release-regulating agent and inert diluents were mixed for 10 min at dry state. The mixture, after water was added, was granulated for 5 min. The granules thus formed were screened through 18-mesh sieve and dried in an oven at 24 to 40°C for 12 to 24 hr. The dried granules were screened with 20-mesh sieve. Hydroxypropylmethylcellulose, binders, swelling-regulating agent and diluents were added to the screened granules, and then they were mixed for 10 min. Finally, lubricant was added to them, and then they were mixed for 5 min. The mixture was compressed to prepare tablets. The following Table 1 represents the ingredients of the core matrix tablet.

Table 1. Compositions of core matrix tablet containing oxybutynin

Ingredient (mg)	Example 1	Example 2	Example 3	Example 4	Example 5
Oxybutynin hydrochloride	5	5	5	5	5
Glyceryl behanate	10	10	20	15	15
Dibasic calcium phosphate dihydrate	35.9	45.9	55.9	56.85	28.425
Lactose	-	-	-	-	28.425
Sodium chloride	-	-	-	17.63	17.63
Sodium lauryl sulfate	0.1	0.1	0.1	0.15	0.15
Povidone	6	6	6	9	9
Cross-linked sodium carboxymethylcellulose	-	-	-	-	15
Hydroxypropylmethyl cellulose	40	30	20	45	30
Magnesium stearate	3	3	3	1.5	1.5
Total	100	100	100	150	150

Experimental Example 1. Dissolution test for the preparations of Examples 1~5

Release profile of core matrix tablet prepared in said Examples 1-5 was determined by USP dissolution test method under conditions of simulated intestinal fluid (fluid II, pH 6.8), paddle type II and 50 rpm/900 ml and dissolution level according to time was measured. The result was represented by dissolution percentage as function of time in Table 2.

Table 2. Dissolution percentage (%)

Time (hr)	Example 1	Example 2	Example 3	Example 4	Example 5
0	0.00	0.00	0.00	0.00	0.00
1	11.03	14.47	10.51	4.78	15.27
2	10.74	18.56	15.51	10.29	32.75
3	13.53	20.30	14.81	16.01	41.93
4	14.18	25.22	20.77	20.00	48.53
6	17.07	31.54	28.14	30.65	58.80
8	24.04	40.52	37.91	38.86	62.73
10	29.81	48.68	45.35	46.23	68.64
12	36.70	58.42	43.76	53.48	72.06
24	68.74	84.54	72.98	91.73	93.01

Based on the dissolution test result for the controlled-release preparation of the present invention obtained in Examples 1-5, it was confirmed that various controlled-release patterns of oxybutynin could be obtained by the core matrix tablet itself, and the release rate could be controlled by regulating the content of swelling and erodible polymer and glyceryl behanate. Example 4 represents zero-order release pattern over 24 hr, and Example 5 shows that the release pattern can be affected by the content of swelling-regulating material contained in the matrix.

Examples 6 and 7. Preparations of core matrix tablet containing oxybutynin

Oxybutynin, glyceryl behanate, solubilizer, binder, release-regulating agent and inert diluents were mixed for 10 min at dry state. The mixture; after water was added, was granulated for 5 min. The granules thus formed were screened through 18-mesh sieve and dried in an oven at 24 to 40°C for 12 to 24 hr. The dried granules were screened with 20-mesh sieve. Polyethylene oxide, binders, swelling-regulating agent and diluents were added to the screened granules, and then they were mixed for 10 min. Finally, lubricant was added to them, and then they were mixed for 5 min. The mixture was compressed to prepare tablets. The following Table 3 represents the ingredients of the core matrix tablet.

Table 3. Compositions of core matrix tablet containing oxybutynin

Ingredient (mg)	Example 6	Example 7
Oxybutynin hydrochloride	5	5
Hydrogenated castor oil	5	15
Dibasic calcium phosphate dihydrate	65	55
Sodium chloride	17.85	17.85
Sodium lauryl sulfate	0.15	0.15
Povidone	9	9
Polyethylene oxide	45	45
Magnesium stearate	3	3
Total	150	150

Experimental Example 2. Dissolution test for the preparations of Examples 6 and 7

Release profiles of the core matrix tablets prepared in said Examples 6 and 7 were determined by USP dissolution test apparatus under conditions of simulated intestinal fluid (fluid II, pH 6.8), paddle type II and 50 rpm/900 ml and dissolution level according to time was measured. The result was represented by dissolution percentage as function of time in Table 4.

Table 4. Dissolution percentage (%)

Time (hr)	Example 6	Example 7
0	0.00	0.00
1	5.57	3.11
2	10.26	4.98
3	10.75	6.44
4	15.67	8.75
6	24.20	14.86
8	60.99	49.38
18	67.38	59.29
20	67.72	62.02
24	71.30	66.00

Examples 8-10. Coating of core matrix tablet containing oxybutynin

The core matrix tablet prepared in said Example 2 was coated with a mixture of hydrophilic release-modifying polymer and hydrophobic release-modifying polymer, i.e. hydroxypropylmethylcellulose and ethylcellulose. Coating solution was prepared according to the composition given in Table 5. Spray coating was carried out in pan coater, and then the products were dried in oven at 40 to 50°C for 12 to 24 hr.

Table 5. Coating Solution Composition

Components (%)	Example 8	Example 9	Example 10
Hydroxypropylmethylcellulose	5.4	4.8	4.2
Ethylcellulose	0.6	1.2	1.8
Castor oil	0.7	0.7	0.7
Ethanol	46.7	46.7	46.7
Methylene chloride	46.7	46.7	46.7
Coating %*	3	3	3

*Coating degree to the weight of uncoated core matrix tablet is represented by %.

Experimental Example 3. Dissolution test for the preparations of Examples 8~10

Release profiles of the coated core matrix tablets prepared in said Examples 8-

10 were determined by USP dissolution test apparatus under conditions of pH 4.0 solution, paddle type II and 50 rpm/900 ml and time-dependent dissolution level was measured. The result was represented by dissolution percentage as function of time in Table 6.

Table 6. Dissolution percentage (%)

Time (hr)	Example 8	Example 9	Example 10
0	0.00	0.00	0.00
1	6.16	6.07	3.74
2	11.53	10.67	7.07
3	17.28	16.01	10.59
4	24.66	19.82	13.69
6	34.47	27.63	20.04
8	45.13	34.60	27.23
10	54.51	41.98	31.46
12	63.67	50.11	37.56
24	100.72	85.25	69.06

The dissolution test results for the coated core matrix of Examples 8 to 10 reveal that drug release rate of core matrix showing zero-order release pattern can be regulated by relative content of hydrophobic release-modifying substance contained in the coating layer.

Examples 11 and 12. Coating of core matrix tablet containing oxybutynin

The core matrix tablets prepared by said Examples 4 and 5 were coated with a mixture of hydrophobic release-modifying polymer and pore-forming substance, i.e. ethylcellulose and polyethyleneglycol (MW 300). Coating solution was prepared according to the composition given in Table 7. Spray coating was carried out in pan coater, and then the products were dried in oven at 40 to 50°C for 12 to 24 hr.

Table7. Coating Solution Composition

Components (%)	Example 11	Example 12
Ethylcellulose	7.0	7.0
Polyethylene glycol (MW: 300)	2.8	2.8
Ethanol	90.2	90.2
Coating %*	1.0	1.0

*Degree of coating to the weight of uncoated core matrix tablet is represented by %.

Experimental Example 4. Dissolution test for the preparations of Examples 11 and 12

Release profiles of the coated core matrix tablet prepared in said Examples 11 and 12 were determined by USP dissolution test apparatus under conditions of simulated intestinal fluid (Fluid II, pH 6.8), paddle type II and 50 rpm/900 ml and time-dependent dissolution level was measured. The result was represented by dissolution percentage as function of time in Table 8.

Table 8. Dissolution percentage (%)

Time (hr)	Example 11	Example 12
0	0.00	0.00
1	0.00	4.67
2	1.68	17.61
3	3.45	19.41
4	5.89	27.70
6	10.55	34.38
18	35.79	64.76
20	41.92	72.18
22	49.87	79.45
24	55.24	99.32

The dissolution test result for the coated core matrix of Examples 11 and 12 demonstrates that the depth of coating and the content of hydrophilic release-modifying polymer, that is, pore-forming material can modify the drug release rate of core matrix

showing zero-order release pattern.

Examples 13~15. Coated core matrix tablet containing oxybutynin

Preparation process for matrix core is the same as in Examples 1-5. Example 13 includes within granules citric acid, substance for regulating pH-surrounding granules, instead of sodium chloride, and includes swelling-regulating material to control the swelling pressure and the swelling speed of matrix. In case of Examples 14 and 15, swelling-regulating material exists in both granules and matrix. As coating substance, shellac was used, and the compositions of the coating solution and the core matrix are represented in the following Table 9.

Table 9. Compositions of core matrix tablet containing oxybutynin and coating solution

	Ingredient (mg)	Example 13	Example 14	Example 15
Core Matrix	Oxybutynin hydrochloride	5	5	5
	Glyceryl behanate	15	15	15
	Dibasic calcium phosphate dihydrate	28.425	28.425	28.425
	Lactose	31.925	41.925	41.925
	Sodium chloride	-	17.35	17.35
	Citric acid	17.5	-	-
	Sodium lauryl sulfate	0.15	0.15	0.15
	Povidone	9	9	9
	Cross-linked sodium carboxymethylcellulose	1.5	1.65	1.65
	Hydroxypropylmethylcellulose	30	30	30
	Magnesium stearate	1.5	1.5	1.5
	Moisture*	q.s.	q.s.	q.s.
	Total	150	150	150
Coating solution	Shellac(OPAGLOSGS-2-0401)	50%	50%	50%
	Ethanol	50%	50%	50%
	Coating%+	5	1	5

*Removed during treatment process.

+ Degree of coating to the weight of uncoated core matrix tablet is represented by %.

Experimental Example 5. Dissolution test for the preparations of Examples 13 and 14

Release profiles of the coated core matrix tablets prepared in said Examples 13 and 14 were determined by USP dissolution test apparatus under conditions of simulated intestinal fluid (Fluid II, pH 6.8), paddle type II and 50 rpm/900 ml and time-dependent dissolution level was measured. The result was represented by dissolution percentage as function of time in Table 10.

Table 10. Dissolution percentage (%)

Time (hr)	Example 13	Example 14
0	0.00	0.00
1	1.20	3.96
2	3.28	9.72
3	22.85	24.45
4	30.15	32.45
6	43.64	40.94
19	79.36	86.58
20	81.34	90.45
22	84.22	93.63
24	87.00	98.03

The dissolution test result for the coated core matrix tablets of Examples 13 and 14 shows that achieving release-delay effect over a certain amount of time by controlling depth of shellac coating leads to biphasic release pattern. The release-delay and the rapid drug release after the period can be induced by regulating the content of swelling-regulating material contained in the core matrix.

Experimental Example 6. Dissolution test for the preparations of Examples 13~15

Release profiles of the coated core matrix tablets prepared in said Examples 13

to 15 were determined by USP dissolution test method (paddle type II, 50 rpm/900 ml). According to the simulated GI method (Gastrointestinal method), the test was conducted in simulated stomach fluid (Fluid I, pH 1.2) for 2 hr and then under simulated intestinal fluid (Fluid II, pH 6.8), time-dependent dissolution level over 24 hr was measured. The result was represented by dissolution percentage as function of time in Table 11.

Table 11. Dissolution percentage (%)

Time (hr)	Example 13	Example 14	Example 15
0	0.00	0.00	0.00
0.5	1.97	10.29	4.78
1	7.02	24.50	10.03
1.5	15.34	33.90	20.96
2	20.54	44.03	28.13
3	28.87	51.67	41.58
4	35.30	55.25	40.00
6	46.86	62.19	47.18
18	73.23	89.89	85.36
20	76.85	92.43	85.02
22	81.44	94.67	86.37
24	83.50	96.41	91.26

Examples 16-18. Coated core matrix tablet containing oxybutynin

Preparation process of matrix core is the same as in Examples 1-5. Example 16 includes swelling-regulating material within granules and matrix to control swelling pressure and swelling speed of matrix. In case of Examples 17 and 18, the content of swelling and erodible polymer within the matrix was increased or reduced, respectively. As coating substance, a mixture of 1:1 ratio of enteric polymer, i. e. hydroxy-propylmethylcellulose phthalate, and shellac was used. Compositions of the coating solution and core matrix are represented in Table 12.

Table 12. Compositions of core matrix tablet containing oxybutynin and coating solution

	Ingredient (mg)	Example 16	Example 17	Example 18
Core Matrix	Oxybutynin hydrochloride	5	5	5
	Glyceryl behanate	15	15	15
	Dibasic calcium phosphate dihydrate	28.425	28.425	28.425
	Lactose	41.925	41.925	26.925
	Sodium chloride	17.35	17.35	17.35
	Citric acid	-	-	-
	Sodium lauryl sulfate	0.15	0.15	0.15
	Povidone	9	16.5	9
	Cross-linked sodium carboxymethylcellulose	1.65	1.65	1.65
	Hydroxypropylmethyl cellulose	30	22.5	45
	Magnesium stearate	1.5	1.5	1.5
	Moisture*	q.s.	q.s.	q.s.
	Total	150 mg	150 mg	150 mg
Coating solution	Shellac (OPAGLOS GS-2-0401)	2.68%	2.68%	2.68%
	Hydroxypropylmethyl cellulose phthalate	2.68%	2.68%	2.68%
	Methylene chloride	48.66%	48.66%	48.66%
	Ethanol	45.99%	45.99%	45.99%
	Coating%+	4	4	4

*Removed during treatment process.

+ Degree of coating to the weight of the uncoated core matrix tablet is represented by %.

Experimental Example 7. Dissolution test for the preparations of Examples 16~18

Release profiles of the coated core matrix tablets prepared in said Examples 16 to 18 were determined by USP dissolution test method (paddle type II, 50 rpm/900 ml), and according to the simulated GI method (Gastrointestinal method). The test was conducted in simulated stomach fluid (Fluid I, pH 1.2) for 2 hr and then under simulated intestinal fluid (Fluid II, pH 6.8), time-dependent dissolution level over 24 hr was measured. The result was represented by dissolution percentage as function of time in

Table 13.

Table 13. Dissolution percentage (%)

Time (hr)	Example 16	Example 17	Example 18
0	0.00	0.00	0.00
0.5	0.00	0.00	0.00
1	0.00	0.00	0.00
1.5	0.00	0.00	0.00
2	0.00	0.00	0.00
3	5.01	0.00	0.00
4	8.55	2.29	3.31
6	18.51	14.52	11.09
8	28.50	32.33	19.86
18	73.27	77.65	51.32
20	75.66	82.15	55.05
22	78.63	81.52	55.15
24	81.87	83.72	58.58

The dissolution test result for the coated core matrix of Examples 14 to 16 represents that pH-dependent release of drug could be corrected by introducing substance with pH dependency into the coating layer, and that drug release was inhibited during the stay in stomach for 2-3 hr and, thereafter, exhibited zero-order release pattern up to 24 hr.

Example 19. Coated core matrix tablet containing Ketorolac

Ketorolac tromethamine, glyceryl behanate, solubilizer, binder, release-regulating material and inert diluents were mixed for 10 min at dry state. The mixture, after water was added, was granulated for 5 min. The granules thus formed were screened through 18-mesh sieve and dried in an oven at 24 to 40°C for 12 to 24 hr. The dried granules were screened with 20-mesh sieve. Hydroxypropylmethyl cellulose, binders, swelling-regulating agent and diluents were added to the screened

granules, and then they were mixed for 10 min. Finally, lubricant was added to them, and then they were mixed for 5 min. The mixture was compressed to prepare tablets. Thus prepared core matrix tablets were spray coated in pan coater and dried in oven at 40 to 50°C for 12 to 24 hr. The following Table 14 represents the ingredients of the core matrix tablet and composition of the coating solution.

Table 14. Composition of the core matrix tablet and the coating solution

	Ingredient (mg)	Example 19
Core Matrix	Ketorolac tromethamine	10
	Glyceryl behanate	30
	Dibasic calcium phosphate dihydrate	39.35
	Sodium chloride	15
	Sodium lauryl sulfate	0.15
	Povidone	9
	Hydroxypropylmethylcellulose	45
	Magnesium stearate	1.5
	Moisture*	q.s.
	Total	150
Coating solution	Hydroxypropylmethylcellulose	9.6%
	Ethyl cellulose	2.4%
	Methylene chloride	93.4%
	Ethanol	93.4%
	Castor oil	1.2%
	Coating%+	10

*Removed during treatment process.

+ Degree of coating to the weight of the uncoated core matrix tablet is represented by %.

Experimental Example 8. Dissolution test for the preparations of Example 19

Release profile of the coated core matrix tablet prepared in said Example 17 was determined by USP dissolution test method under condition of simulated intestinal fluid (Fluid II, pH 6.8), paddle type II and 50 rpm/900 ml, and time-dependent dissolution level was measured. The result was represented by dissolution percentage

as function of time in Table 15.

Table 15. Dissolution percentage (%)

Time (hr)	Example 19
0	0.00
1	20.61
2	33.43
3	44.80
4	54.33
6	70.26
8	83.40
12	96.17

Ketorolac was released from the coated core matrix tablets of Example 19 at a constant rate up to 12 hr, and the release rate could be regulated by the content of swelling material within the matrix and by the coating depth.

Example 20. Coated core matrix tablet containing enalapril maleate

Therapeutic composition containing enalapril maleate according to the present invention is prepared as follows. First, enalapril maleate, glyceryl behanate, solubilizer, binder, release-regulating substance and inert diluents were mixed for 10 min at dry state. The mixture, after water was added, was granulated for 5 min. Granules thus formed was screened through 18-mesh sieve and dried in an oven at 24 to 40°C for 12 to 24 hr. The dried granules were screened with 20-mesh sieve. Hydroxypropylmethylcellulose, binders, swelling-regulating agent and diluents were added to the screened granules, and then they were mixed for 10 min. Finally, magnesium stearate was added to them, and then they were mixed for 5 min. The mixture was compressed to prepare tablets. Thus-prepared core matrix tablets were spray coated in pan coater and dried in oven at 40 to 50°C for 12 to 24 hr. The

following Table 16 represents the ingredients of the core matrix tablet and composition of the coating solution.

Table 16. Compositions of core matrix tablet and coating solution

	Ingredient (mg)	Example 20
Core Matrix	Enalapril maleate	10
	Glyceryl behanate	30
	Dibasic calcium phosphate dihydrate	39.35
	Sodium chloride	15
	Sodium lauryl sulfate	0.15
	Povidone	9
	Hydroxypropylmethylcellulose	45
	Magnesium stearate	1.5
	Moisture*	q.s.
	Total	150
Coating solution	Hydroxypropylmethylcellulose	9.6%
	Ethyl cellulose	2.4%
	Methylene chloride	93.4%
	Ethanol	93.4%
	Castor oil	1.2%
	Coating%+	10

*Removed during treatment process

+Degree of coating to the weight of the uncoated core matrix tablet is represented by %.

Experimental Example 9. Dissolution test for the preparations of Example 18

Release profile of the coated core matrix tablet prepared in said Example 18 was determined by USP dissolution test method under conditions of simulated intestinal fluid (Fluid II, pH 6.8), paddle type II and 50 rpm/900 ml, and time-dependent dissolution level was measured. The result was represented by dissolution percentage as function of time in Table 17.

Table 17. Dissolution percentage (%)

Time (hr)	Example 18
0	0.00
1	20.61
2	33.43
3	44.80
4	54.33
6	70.26
8	83.40
12	96.17

Example 21. Coated core matrix tablet containing captopril

Therapeutic composition containing captopril according to the present invention is prepared as follows. First, captopril, glyceryl behanate, solubilizer, binder, release-regulating substance and inert diluents were mixed for 10 min at dry state. The mixture, after water was added, was granulated for 5 min. Granules thus formed was screened through 18-mesh sieve and dried in an oven at 24 to 40°C for 12 to 24 hr. The dried granules were screened with 20-mesh sieve. Hydroxypropylmethylcellulose, binders, swelling-regulating agent and diluents were added to the screened granules, and then they were mixed for 10 min. Finally, magnesium stearate was added to them, and then they were mixed for 5 min. The mixture was compressed to prepare tablets. Thus prepared core matrix tablets were spray coated in pan coater and dried in oven at 40 to 50°C for 12 to 24 hr. Ingredients of the core matrix tablet and composition of the coating solution are shown in Table 18.

Table 18. Compositions of core matrix tablet and coating solution

	Ingredient (mg)	Example 21
Core Matrix	Captopril	25
	Glyceryl behanate	62.5
	Dibasic calcium phosphate dihydrate	5
	Povidone	5
	Hydroxypropylmethylcellulose	150
	Magnesium stearate	2.5
	Moisture*	q.s.
	Total	250
Coating solution	Hydroxypropylmethylcellulose	9.6%
	Ethyl cellulose	2.4%
	Methylene chloride	93.4%
	Ethanol	93.4%
	Castor oil	1.2%
	Coating%+	10

*Removed during treatment process

+Degree of coating to the weight of the uncoated core matrix tablet is represented by %.

Experimental Example 10. Dissolution test for the preparations of Example 21

Release profile of the coated core matrix tablet prepared in said Example 19 was determined by USP dissolution test method under conditions of simulated intestinal fluid (Fluid II, pH 6.8), paddle type II and 50 rpm/900 ml, and time-dependent dissolution level was measured. The result was represented by dissolution percentage as function of time in Table 19.

Table 19. Dissolution percentage (%)

Time (hr)	Example 21
0	0.00
1	13.64
2	23.51
3	33.40
4	38.77
8	61.48
19	80.67
20	82.13
22	84.19
24	90.79

Example 22. Preparation of core matrix tablets containing diltiazem

Therapeutic composition containing diltiazem according to the present invention is prepared as follows. First, diltiazem hydrochloride, glyceryl behanate, solubilizer, binder, release-regulating substance and inert diluents were mixed for 10 min at dry state. The mixture, after water was added, was granulated for 5 min. Granules thus formed was screened through 18-mesh sieve and dried in an oven at 24 to 40°C for 12 to 24 hr. The dried granules were screened with 20-mesh sieve. Hydroxypropylmethylcellulose, binders, swelling-regulating agent and diluents were added to the screened granules, and then they were mixed for 10 min. Finally, magnesium stearate was added to them, and then they were mixed for 5 min. The mixture was compressed to prepare tablets. Ingredients of the core matrix tablet are shown in Table 20.

Table 20. Compositions of core matrix tablet containing diltiazem

	Ingredient (mg)	Example 22
Core Matrix	Diltiazem hydrochloride	90
	Glyceryl behanate	40
	Dibasic calcium phosphate dihydrate	90
	Sodium chloride	45
	Sodium lauryl sulfate	1
	Povidone	10
	Hydroxypropylmethylcellulose	120
	Magnesium stearate	4
	Moisture*	q.s.
	Total	400

*Removed during treatment process

Experimental Example 11. Dissolution test for the preparations of Example 22

Release profile of the coated core matrix tablet prepared in said Example 22 was determined by USP dissolution test method under conditions of simulated intestinal fluid (Fluid II, pH 6.8), paddle type II and 50 rpm/900 ml, and time-dependent dissolution level was measured. The result was represented by dissolution percentage as function of time in Table 21.

Table 21. Dissolution percentage (%)

Time (hr)	Example 22
0	0.00
1	13.40
2	20.94
3	27.56
4	33.58
6	45.12
8	55.18
10	64.38
12	72.01
16	90.50
20	100.72

Example 23. Preparation of core matrix tablets containing theophylline

Therapeutic composition containing theophylline according to the present invention is prepared as follows. First, theophylline hydrochloride, glyceryl behanate, solubilizer, binder, release-regulating substance and inert diluents were mixed for 10 min at dry state. The mixture, after water was added, was granulated for 5 min. Granules thus formed was screened through 18-mesh sieve and dried in an oven at 24 to 40°C for 12 to 24 hr. The dried granules were screened with 20-mesh sieve. Hydroxypropylmethylcellulose, binders, swelling-regulating agent and diluents were added to the screened granules, and then they were mixed for 10 min. Finally, magnesium stearate was added to them, and then they were mixed for 5 min. The mixture was compressed to prepare tablets. Ingredients of the core matrix tablet are shown in Table 22.

Table 22. Composition of core matrix tablet containing theophylline

	Ingredient (mg)	Example 23
Core Matrix	Theophylline	200
	Glyceryl behanate	80
	Dibasic calcium phosphate dihydrate	380
	Sodium chloride	90
	Sodium lauryl sulfate	2
	Povidone	20
	Hydroxypropylmethylcellulose	120
	Magnesium stearate	8
	Moisture*	q.s.
	Total	900

*Removed during treatment process

Experimental Example 12. Dissolution test for the preparations of Example 23

Release profile of the coated core matrix tablet prepared in said Example 23 was determined by USP dissolution test method under conditions of simulated intestinal

fluid (Fluid II, pH 6.8), paddle type II and 50 rpm/900 ml, and time-dependent dissolution level was measured. The result was represented by dissolution percentage as function of time in Table 23.

Table 23. Dissolution percentage (%)

Time (hr)	Example 23
0	0.00
1	11.83
2	17.60
3	22.65
4	26.87
6	35.11
8	41.73
10	47.61
12	50.37
24	72.19

The present invention can provide a constant release rate over an 8 to 24 hr or more period by allowing drug to be released from granules released from matrix, as well as directly from inside of the matrix, and by regulating the release rate of the granules by the content of swelling-regulating material within the matrix. Further, the present invention minimized solubility-limit of drug by applying a suitable manufacturing method and components of the granules in consideration of water-solubility of drug.

Industrial Applicability

The present invention provides oral drug controlled-release preparation with sustained-release effect proper to the characteristics of drug action, as well as with improved stability, by inducing zero-order release through effectively allowing drug release area to be maintained at a fixed level and through introducing a release-modifying layer.

CLAIMS

1. A controlled-release oral preparation characterized in that release of granules from matrix and drug release from the granules are conducted in stepwise way, wherein the preparation comprises:

(1) granules comprising a drug and a carrier material in size of 0.1 ~ 1 mm, said carrier material is hydrophobic material in case of drug with water-solubility of 1 mg/ml or more and said carrier material is hydrophilic material in case of drug with water-solubility of less than 1 mg/ml;

(2) a matrix in which said granules are embedded, comprising swelling and erodible polymer and swelling-regulating material; and

(3) a release-modifying layer comprising hydrophobic release-modifying polymer, hydrophilic release-modifying polymer, pH-dependent release-modifying polymer or a mixture thereof.

2. The controlled-release oral preparation in Claim 1, wherein 50 to 100% of the drug is present within the granules, and the remaining drug exists within the matrix or the release-modifying layer, or within the matrix and the release-modifying layer in directly dispersed form.

3. The controlled-release oral preparation in Claim 1, wherein the drug has a water-solubility within range from 1 mg/ml to 100 mg/ml, and the granules containing the drug is prepared by wet granulation.

4. The controlled-release oral preparation in Claim 1, wherein the drug has a water-solubility of at least 100 mg/ml, and the granules containing the drug is prepared in

granular form by dispersing the drug in fusion of granules components.

5. The controlled-release oral preparation in Claim 1, wherein the drug has a water-solubility of less than 1 mg/ml, and the granules containing the drug is prepared by solid dispersion method.

6. The controlled-release oral preparation in Claim 1, wherein the hydrophobic material is at least one selected from the group consisting of fatty acids, fatty acid esters, fatty acid alcohols, fatty acid mono-, di-, tri-glycerides, waxes, hydrogenated castor oil and hydrogenated vegetable oil.

7. The controlled-release oral preparation in Claim 6, wherein the fatty acid alcohol is at least one selected from the group consisting of cetostearyl alcohol, stearyl alcohol, lauryl alcohol and myristyl alcohol; fatty acid ester is at least one selected from the group consisting of glyceryl monostearate, glycerol monooleate, acetylated monoglyceride, tristearin, tripalmitin, cetyl ester wax, glyceryl palmitostearate and glyceryl behanate; and wax is at least one selected from the group consisting of beeswax, carnauba wax, glyco wax and castor wax.

8. The controlled-release oral preparation in Claim 1, wherein the hydrophilic material is at least one selected from the group consisting of polyalkylene glycol and carboxyvinyl hydrophilic polymer, and the drug is solid-dispersed in said hydrophilic polymer.

9. The controlled-release oral preparation in Claim 1, wherein the swelling and erodible

polymer is at least one selected from the group consisting of hydroxypropyl cellulose, hydroxypropylmethylcellulose, polyethylene oxide, sodium alginate, povidone, polyvinyl alcohol and sodium carboxymethylcellulose.

10. The controlled-release oral preparation in Claim 1, wherein said swelling-regulating material is at least one selected from the group consisting of cross-linked sodium carboxymethylcellulose and cross-linked polyvinylpyrrolidone.

11. The controlled-release oral preparation in Claim 1, wherein said hydrophobic release-modifying polymer used for the formation of release-modifying layer, is at least one selected from the group consisting of ethylcellulose, shellac and ammonio methacrylate copolymer; said hydrophilic release-modifying polymer is at least one selected from the group consisting of hydroxyalkylcellulose and hydroxypropylalkylcellulose; and said pH-dependent release-modifying polymer is at least one selected from the group consisting of hydroxyalkylcellulose phthalate, hydroxyalkylmethylcellulose phthalate, cellulose acetyl phthalate, sodium cellulose acetate phthalate, cellulose ester phthalate, cellulose ether phthalate, and anionic copolymer of methacrylic acid with methyl or ethyl methacrylate.

12. The controlled-release oral preparation in Claim 1, wherein said release-modifying layer is 1 to 20% by weight to total weight of matrix, and the granules containing the drug reach 50 to 80% by weight to total weight of the preparation.

13. The controlled-release oral preparation in Claim 1, wherein the drug is selected from the following group:

therapeutic agents for aconuresis of oxybutynin, tolterodine and therapeutically equivalent salts thereof;

calcium channel blockers of nifedipine, verapamil, isradipin, nilvadipin, flunarizine, nimodipine, diltiazem, nicardipine, nisoldipin, felodipin, amlodipin, cinarizin and pendilin and pharmaceutically acceptable derivatives thereof;

beta-adrenergic antagonists of propranolol, metoprolol and pharmaceutically acceptable derivatives thereof;

angiotensin-converting enzyme inhibitors of captopril, enalapril, ramipril, fosinopril, altiopril, benazepril, libenzapril, alacepril, cilazapril, cilazaprilat, perindopril, zofedopril, lisinopril, imidapril, spirapril, rentiapril, delapril, alindapril, indalapril, quinalapril and therapeutically equivalent salts thereof;

non-steroidal anti-inflammatory agents of ketorolac, ketoprofen, benoxaprofen, caprofen, flubiprofen, fenoprofen, suprofen, fenbufen, ibuprofen, indoprofen, naproxen, miroprofen, oxaprozine, pranoprofen, pirprofen, thiaprofenic acid, fluprofen, alminoprofen, bucloxic acid, alclofenac acematacin, aspirin, indomethacin, ibufenac, isoxepac, profenac, fentiazac, clidanac, oxpinac, sulindac, tolmetin, zomepirac, zidometacin, tenclofenac, tiopinac, mefenamic acid, flufenamic acid, niflumic acid, meclofenamic acid, tolfenamic acid, diflufenisal, isoxicam, sudoxicam and therapeutically equivalent salts thereof;

therapeutic agents for respiratory disorders of theophylline, salbutamol, aminophylline, dextromethorphan, pseudoephedrine and therapeutically equivalent salts thereof;

analgesics of tramadol, acetaminophen, morphine, hydromorphone, oxycodone, propoxyphene and therapeutically equivalent salts thereof;

psychoneural drugs of fluoxetine, paroxetine, buspirone, carmabazepine, carvidopa, levodopa, methylphenidate, trazodone, valproic acid, amitriptyline, carbamazepine,

ergoloid, haloperidol, lorazepam and therapeutically equivalent salts thereof;

antibiotics of azithromycin dihydrate, cepha antibiotics, clarithromycin, doxycycline, nitrofurantonin and therapeutically equivalent salts thereof;

antihyperlipidemic agent of bezafibrate, fenofibrate, ethofibrate, lovastatin and therapeutically equivalent salts thereof;

antidiabetic agent of glyburide, glipizide, metformin and therapeutically equivalent salts thereof; and

cyclobenzaprin, favotidin, nizatidine, propafenone, clonazepam, hyoscyamine, diphenhydramine, olistat, doxazosin and therapeutically equivalent salts thereof.

14. The controlled-release oral preparation in Claim 1, wherein the drug is released in zero-order over at least 8 to 24 hr upon the administration of the preparation.

15. The controlled-release oral preparation in Claim 1, wherein by erosion of the surface of matrix, 0 to 20% of total granules is released over 0 to 4 hr, 0 to 50% is released over 0 to 8 hr, 0 to 70% is released over 0 to 16hr, and 0 to 100% is released over 0 to 24 hr.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR03/00200

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 9/16

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:A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean patents and applications for inventions since 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search terms used)
CAPLUS(STN), PROMT(STN), SCISEARCH(STN), INVESTEXT(STN), INSPEC(STN), COMPENDEX(STN), PASCAL(STN), CABA(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Aoki, S et al, "Preparation of a novel type of controlled-release carrier and evaluation of drug release from the matrix tablet and its physical-proprerties", International Journal of Pharmaceutics, USA, 1992, Vol.85, No.1-3, pp.29-38	1-14
A	US 6294195 B1(Purdue Pharma L.P.) 25 SEP 2001 see the whole document	1-14
A	US 5273760 A (Euroceltique, S.A,.) 28 DEC 1993 see the whole document	1-14
A	US 5582837 A (Depomed, Inc.,) 10 DEC 1996 see the whole document	1-14
A	US 5811126 A (Euro-Celtique, S.A.,) 22 SEP 1998 see the claims	1-14

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6294195 B1	25.09.2001	JP 11124327 A2	11.05.1995
		JP 3267561 B2	08.03.2002
		EP 1243269 A3	09.01.2003
		EP 1243269 A2	02.09.2002
		KR 252188 B1	01.05.2000
US 5273760 A	28.12.1993	EP 636370 B1	21.10.1998
		EP 636370 A1	01.02.1995
		AU 716793 B2	09.03.2000
		JP 7206679 A2	08.08.1995
US 5582837 A	10.12.1996	WO 9318755 A1	30.09.1993
		JP 7507059 T2	03.08.1995
		EP 632720 B1	11.11.1998
		EP 632720 A1	11.01.1995
		AU 3811493 A1	21.10.1993
US 5811126 A	22.09.1998	WO 9712605 A1	10.04.1997
		JP 10502390 T2	03.03.1998
		EP 797435 A1	01.10.1997
		AU 7143796 A1	28.04.1997

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

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(81) Bestimmungsstaaten *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, 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, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Bestimmungsstaaten *(regional)*: ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:
— *mit internationalem Recherchenbericht*
— *vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen*

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) **Title:** COMBINATION OF SELECTED OPIOIDS WITH OTHER ACTIVE SUBSTANCES FOR USE IN THE THERAPY OF URINARY INCONTINENCE

(54) **Bezeichnung:** KOMBINATION AUSGEWÄHLTER OPIOIDE MIT ANDEREN WIRKSTOFFEN ZUR THERAPIE DER HARNINKONTINENZ

(57) **Abstract:** The invention relates to the use of a combination of the compounds of group A, especially opioids, with the compounds of group B for producing a drug for the treatment of urinary urgency or urinary incontinence. The invention also relates to corresponding drugs and to a method for treating urinary urgency or urinary incontinence.

(57) **Zusammenfassung:** Die Erfindung betrifft die Verwendung einer Kombination von Verbindungen der Gruppe A, insbesondere Opioiden, und Verbindungen der Gruppe B zur Herstellung eines Arzneimittels zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz sowie entsprechende Arzneimittel und Verfahren zur Behandlung von vermehrtem Harndrang bzw. Haminkontinenz sowie entsprechende Arzneimittel und Verfahren zur Behandlung von vermehrtem Harndrang bzw. Haminkontinenz.

WO 03/099268 A1

Patentanmeldung der Grünenthal GmbH, D-52078 Aachen
(eigenes Zeichen: G 3132)

Kombination ausgewählter Opioide mit anderen Wirkstoffen zur Therapie der Harninkontinenz

Die Erfindung betrifft die Verwendung einer Kombination von Verbindungen der Gruppe A, insbesondere Opioiden, und Verbindungen der Gruppe B, zur Herstellung eines Arzneimittels zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz sowie entsprechende Arzneimittel und Verfahren zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz.

Harninkontinenz ist der unwillkürliche Harnabgang. Dieser tritt unkontrolliert auf, wenn der Druck innerhalb der Harnblase den Druck übersteigt, der zum Schließen des Harnleiters notwendig ist. Ursachen können zum einen ein erhöhter interner Blasendruck (z. B. durch Detrusorinstabilität) mit der Folge der Dranginkontinenz und zum anderen ein erniedrigter Sphinkterdruck (z. B. nach Geburt oder chirurgischen Eingriffen) mit der Folge der Streßinkontinenz sein. Der Detrusor ist die grob gebündelte mehrschichtige Blasenwandmuskulatur, deren Kontraktion zur Harnentleerung führt, der Sphinkter der Schließmuskel der Harnröhre. Es treten Mischformen dieser Inkontinenzarten sowie die sogenannte Überfluß-inkontinenz (z. B. bei benigner Prostatahyperplasie) oder Reflexinkontinenz (z. B. nach Rückenmarksschädigungen) auf. Näheres dazu findet sich bei Chutka, D. S. und Takahashi, P. Y., 1998, Drugs 560: 587-595.

Harndrang ist der auf Harnentleerung (Miktion) abzielende Zustand vermehrter Blasenmuskelspannung bei Annäherung an die Blasenkapazität (bzw. bei deren Überschreitung). Dabei wirkt diese Anspannung als Miktionsreiz. Unter einem vermehrten Harndrang versteht man dabei insbe-

sondere das Auftreten vorzeitigen oder gehäuften manchmal sogar schmerzhaften Harndrangs bis hin zum sog. Harnzwang. Das führt in der Folge zu einer deutlich häufigeren Miktion. Ursachen können u.a. Harnblasenentzündungen und neurogene Blasenstörungen sowie auch Blasentuberkulose sein. Es sind aber noch nicht alle Ursachen geklärt.

Vermehrter Harndrang wie auch Harninkontinenz werden als extrem unangenehm empfunden und es besteht ein deutlicher Bedarf bei von diesen Indikationen betroffenen Personen, eine möglichst langfristige Verbesserung zu erreichen.

Üblicherweise werden vermehrter Harndrang und insbesondere Harninkontinenz medikamentös mit Substanzen behandelt, die an den Reflexen des unteren Harntraktes beteiligt sind (Wein, A. J., 1998, Urology 51 (Suppl. 21): 43 – 47). Meistens sind dies Medikamente, die eine hemmende Wirkung auf den Detrusormuskel, der für den inneren Blasendruck verantwortlich ist, haben. Diese Medikamente sind z. B. Parasympatholytika wie Oxybutynin, Propiverin oder Tolterodin, trizyklische Antidepressiva wie Imipramin oder Muskelrelaxantien wie Flavoxat. Andere Medikamente, die insbesondere den Widerstand der Harnröhre oder des Blasenhalses erhöhen, zeigen Affinitäten zu α-Adrenorezeptoren wie Ephedrin, zu β-Adrenorezeptoren wie Clenbutarol oder sind Hormone wie Östradiol.

Einen genauen Einblick in die verwendeten Therapeutika und Therapiemethoden, insbesondere bezüglich der Antimuskarinika und anderer peripher wirkender Stoffe, gibt hier der Übersichtsartikel von K.E. Andersson et al. „The pharmacological treatment of urinary incontinence",. BJU International (1999), 84, 923 – 947.

Auch bestimmte Diarylmethylpiperazine und –piperidine sind für diese Indikation in der WO 93/15062 beschrieben. Ebenso wurde für Tramadol ein positiver Effekt auf die Blasenfunktion in einem Rattenmodell

rhythmischer Blasenkontraktionen nachgewiesen (Nippon-Shinyaku, WO 98/46216). Weiterhin gibt es in der Literatur Untersuchungen zur Charakterisierung der opioiden Nebenwirkung Harnretention, woraus sich einige Hinweise auf die Beeinflussung der Blasenfunktionen durch schwache Opioide wie Diphenoxylat (Fowler et al., 1987 J. Urol 138:735-738) und Meperidin (Doyle and Briscoe, 1976 Br J Urol 48:329-335), durch gemischte Opioidagonisten / -antagonisten wie Buprenorphin (Malinovsky et al., 1998 Anesth Analg 87:456-461; Drenger and Magora, 1989 Anesth Analg 69:348-353), Pentazocin (Shimizu et al. (2000) Br. J. Pharmacol. 131 (3): 610 – 616) und Nalbuphin (Malinovsky et al., 1998, a.a.O), sowie durch starke Opioide wie Morphin (Malinovsky et al., 1998 a.a.O; Kontani und Kawabata, (1988); Jpn J Pharmacol. Sep;48(1):31) und Fentanyl (Malinovsky et al., 1998 a.a.O) ergeben. Allerdings erfolgten diese Untersuchungen zumeist in analgetisch wirksamen Konzentrationen.

Bei den hier in Frage kommenden Indikationen ist zu beachten, daß es sich im allgemeinen um sehr langfristige medikamentöse Anwendungen handelt und sich die Betroffenen im Gegensatz zu vielen Situationen, in denen Analgetika eingesetzt werden, einer sehr unangenehmen, aber nicht unaushaltbaren Situation gegenüber sehen. Daher ist hier - noch mehr als bei Analgetika - darauf zu achten, Nebenwirkungen zu vermeiden, will der Betroffene nicht ein Übel gegen das andere tauschen. Auch sind bei einer dauerhaften Harninkontinenzbehandlung auch analgetische Wirkungen weitgehend unerwünscht.

Aufgabe der vorliegenden Erfindung war es daher, Stoffe oder Stoffkombinationen aufzufinden, die zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz hilfreich sind und bei den wirksamen Dosen bevorzugt gleichzeitig geringere Nebenwirkungen und/oder analgetische Wirkungen zeigen als aus dem Stand der Technik bekannt, insbesondere einen synergistischen Effekt zur Behandlung der Harninkontinenz zeigen.

Überraschenderweise wurde nun gefunden, daß eine Kombination aus Verbindungen der Gruppe A, die Opioide und andere zentralwirkende Substanzen, die mit Opioid-Rezeptoren wechselwirken und deren Effekte durch Naloxon antagonisiert werden können, oder insbesondere Substanzen, die über einen Opiat-Rezeptor, insbesondere den μ-Rezeptor, wirken, umfaßt, und Verbindungen der Gruppe B, die Muskarinantagonisten, und andere überwiegend peripher wirkende, in der Harninkontinenz bekanntermaßen wirksame Substanzen umfaßt, eine hervorragende Wirkung auf die Blasenfunktion besitzen. Weiter erwiesen sich diese Kombinationen - deutlich über das Erwartete hinaus - bereits bei sehr geringen Dosen als so wirksam, daß die kombinierten Wirkstoffe niedrig dosiert eingesetzt werden konnten. Dadurch ist zu erwarten, daß sonst bei höheren notwendigen Dosierungen auftretende Nebenwirkungen deutlich zurückgehen werden, während die therapeutische Wirkung durch diese Kombination aus peripherem, überwiegend direkt auf die Blase oder Blasenmuskulatur wirkendem, antimuskarinem Effekt und zentralem Opioid-Effekt bzw. μ-Rezeptor-Effekt voll erhalten bleibt.

Dementsprechend ist Erfindungsgegenstand die Verwendung einer Wirkstoffkombination aus wenigstens einer der **Verbindungen A** und wenigstens einer der **Verbindungen B**, mit **Verbindung A** ausgewählt aus:

Gruppe a) enthaltend:

Tramadol, O-Demethyltramadol, oder O-desmethyl-N-mono-desmethyl-tramadol als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder

Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe b) enthaltend:

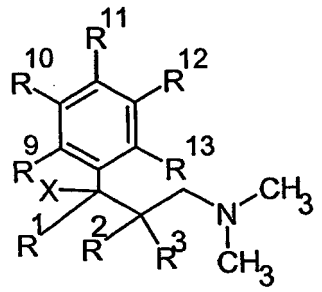
- Codein
- Dextropropxyphen
- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)
- Tilidin
- Tramadol
- Viminol
- Butorphanol
- Dextromoramid
- Dezocin
- Diacetylmorphin (Heroin)
- Hydrocodon
- Hydromorphon
- Ketobemidon
- Levomethadon
- Levomethadyl-Acetate (l-α-Acetylmethadol (LAAM))
- Levorphanol
- Morphin
- Nalorphin
- Oxycodon
- Pentazocin
- Piritramide

- Alfentanil
- Buprenorphin
- Etorphin
- Fentanyl
- Remifentanil
- Sufentanil

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe c) enthaltend:

1-Phenyl-3-dimethylamino-propanverbindungen gemäß allgemeiner **Formel I**



I

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^2 und R^3 jeweils unabhängig voneinander ausgewählt sind aus H oder C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^2 und R^3 zusammen einen gesättigten C_{4-7}-Cycloalkylrest bilden, unsubstituiert oder ein- oder mehrfach substituiert,

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert;

$PO(O\text{-}C_{1\text{-}4}\text{-Alkyl})_2$, $CO(OC_{1\text{-}5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1\text{-}3}\text{-Alkyl})$, $CO(C_{1\text{-}5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1\text{-}3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} $C_{1\text{-}4}$-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; $C_{1\text{-}6}$-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

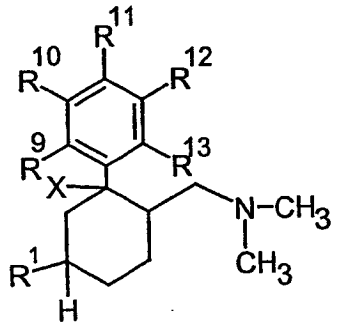
oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe d) enthaltend:

substituierte 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel II**



II

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, Benzyl, CF_3, OH, OCH_2-C_6H_5, O-C_{1-4}-Alkyl, Cl oder F und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder

ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert;
Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

oder

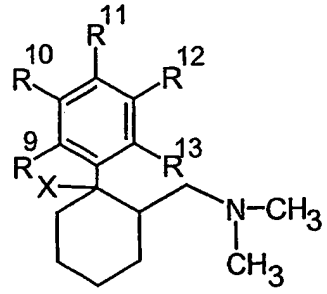
R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,
als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form

der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und/oder

Gruppe e) enthaltend:

6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel III**



III

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt

oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

mit der Maßgabe, daß, wenn R^9, R^{11} und R^{13} H entsprechen, und einer von R^{10} oder R^{12} H und der andere OCH_3 entspricht, X nicht OH sein darf,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und mit wenigstens einer der **Verbindungen B**, ausgewählt aus:

den Antimuskarinika: Atropin, Oxybutinin, Propiverin, Propanthelin, Emepronium, Trospium, Tolterodin, Darifenacin und α,α-Diphenylessigsäure-4-(N-methyl-piperidyl)-ester, sowie Duloxetin, Imipramin und Desmopressin,

sowie

Venlafaxin, Fesoterodin, Solifenacin (YM905), Resiniferatoxin, Cizolirtine, Nitro-Flurbiprofen, HCT1026,

Talnetant, TAK-637, SL 251039, R 450, Rec 15/3079, (-)-DDMS, NS-8 und/oder DRP-001

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

zur Herstellung eines Arzneimittels zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz.

Überraschenderweise hatte sich herausgestellt, daß die Kombination der genannten Substanzen bestimmte physiologische Parameter, die bei vermehrtem Harndrang bzw. Harninkontinenz von Bedeutung sind, deutlich positiv beeinflußen. Jede einzelne dieser Veränderungen kann eine deutliche Erleichterung im symptomatischen Bild von betroffener Patienten bedeuten.

Die Verbindungen der Gruppe B wirken überwiegend peripher in der Harninkontinenz. Dabei ist Venlafaxin ein selektiver Noradrenalin Reuptake Inhibitor mit Wirksamkeit in der Stressinkontinenz (Bae J.H. et al., BJU International 2001, 88, 771, 775). Fesoterodin ist ein von Schwarz Pharma entwickelter mACh Antagonist. Solifenacin (YM905) ist ein von Yamanouchi entwickelter mACh Antagonist. Resiniferatoxin ist ein von Afferon, Mundipharma und ICOS entwickelter VR1-Agonist (allerdings insbesondere zur lokalen Anwendung). Cizolirtine ist eine im Europäischen Patent EP 289 380 B1 beschriebene Verbindung (2-[phenyl(1-methyl-1H-pyrazole-5-yl)methoxy]-N,N-dimethylethanamine, die auch als 5-[alpha -(2-

dimethylaminoethoxy)benzyl]-1-methyl-1H-pyrazole oder 5-{[N,N-dimethylaminoethoxy)phenyl]methyl}-1-methyl-1H-pyrazole) bezeichnet werden kann) mit bisher unbekanntem Wirkmechanismus, die von der Firma Esteve (ES) klinisch in der Haminkontinenz untersucht wird. Nitro-Flurbiprofen und HCT-1026 sind zwei von NicOx entwickelte auf NO + COX wirkende Stoffe. Talnetant ist ein von Glaxo Smith Kline entwickelter NK Antagonist. TAK-637 ist ein von Takeda entwickelter NK Antagonist. SL 251039 ist ein von Sanofi entwickelter a_1AR Agonist. R 450 ist ein von Roche entwickelter a_1AR Agonist. Rec 15/3079 ist ein von Recordati entwickelter $5HT_{1A}$-Antagonist. (-)-DDMS ist eine von Sepracor entwickelte Substanz, die auf NA + D wirkt. NS-8 ist eine von Nippon Shinyaku entwickelte Substanz, die auf PCA wirkt. DRP-001 ist eine von Sosei für die Dranginkontionenz entwickelte Substanz mit unbekanntem Wirkmechanismus.

Im Sinne dieser Erfindung versteht man unter Alkyl- bzw. Cykloalkyl-Resten gesättigte und ungesättigte (aber nicht aromatische), verzweigte, unverzweigte und cyclische Kohlenwasserstoffe, die unsubstituiert oder ein- oder mehrfach substituiert sein können. Dabei steht C_{1-2}-Alkyl für C1- oder C2-Alkyl, C_{1-3}-Alkyl für C1-, C2- oder C3-Alkyl, C_{1-4}-Alkyl für C1-, C2-, C3- oder C4-Alkyl, C_{1-5}-Alkyl für C1-, C2-, C3-, C4- oder C5-Alkyl, C_{1-6}-Alkyl für C1-, C2-, C3-, C4-, C5- oder C6-Alkyl, C_{1-7}-Alkyl für C1-, C2-, C3-, C4-, C5-, C6- oder C7-Alkyl, C_{1-8}-Alkyl für C1-, C2-, C3-, C4-, C5-, C6-, C7- oder C8-Alkyl, C_{1-10}-Alkyl für C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8,- C9- oder C10-Alkyl und C_{1-18}-Alkyl für C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8,- C9-, C10-, C11-, C12-, C13-, C14-, C15-, C16-, C17- oder C18-Alkyl. Weiter steht C_{3-4}-Cycloalkyl für C3- oder C4-Cycloalkyl, C_{3-5}-Cycloalkyl für C3-, C4- oder C5-Cycloalkyl, C_{3-6}-Cycloalkyl für C3-, C4-, C5- oder C6-Cycloalkyl, C_{3-7}-Cycloalkyl für C3-, C4-, C5-, C6- oder C7-Cycloalkyl, C_{3-8}-Cycloalkyl für C3-, C4-, C5-, C6-, C7- oder C8-Cycloalkyl, C_{4-5}-Cycloalkyl für C4- oder C5-Cycloalkyl, C_{4-6}-Cycloalkyl für C4-, C5- oder C6-Cycloalkyl, C_{4-7}-Cycloalkyl für C4-, C5-, C6- oder C7-Cycloalkyl, C_{5-6}-Cycloalkyl für C5- oder C6-

Cycloalkyl und C_{5-7}-Cycloalkyl für C5-, C6- oder C7-Cycloalkyl. In Bezug auf Cycloalkyl umfaßt der Begriff auch gesättigte Cycloalkyle, in denen ein oder 2 Kohlenstoffatome durch ein Heteroatom, S, N oder O ersetzt sind. Unter den Begriff Cycloalkyl fallen aber insbesondere auch ein- oder mehrfach, vorzugsweise einfach, ungesättigte Cycloalkyle ohne Heteroatom im Ring, solange das Cycloalkyl kein aromatisches System darstellt. Vorzugsweise sind die Alkyl- bzw. Cykloalkyl-Reste Methyl, Ethyl, Vinyl (Ethenyl), Propyl, Allyl (2-Propenyl), 1-Propinyl, Methylethyl, Butyl, 1-Methylpropyl, 2-Methylpropyl, 1,1-Dimethylethyl, Pentyl, 1,1-Dimethylpropyl, 1,2-Dimethylpropyl, 2,2-Dimethylpropyl, Hexyl, 1-Methylpentyl, Cyclopropyl, 2-Methylcyclopropyl, Cyclopropylmethyl, Cyclobutyl, Cyclopentyl, Cyclopentylmethyl, Cyclohexyl, Cycloheptyl, Cyclooctyl, aber auch Adamantyl, CHF_2, CF_3 oder CH_2OH sowie Pyrazolinon, Oxopyrazolinon, [1,4]Dioxan oder Dioxolan.

Dabei versteht man im Zusammenhang mit Alkyl und Cycloalkyl – solange dies nicht ausdrücklich anders definiert ist - unter dem Begriff substituiert im Sinne dieser Erfindung die Substitution mindestens eines (gegebenenfalls auch mehrerer) Wasserstoffreste(s) durch F, Cl, Br, I, NH_2, SH oder OH, wobei unter „mehrfach substituiert" bzw. „substituiert" bei mehrfacher Substitution zu verstehen ist, daß die Substitution sowohl an verschiedenen als auch an gleichen Atomen mehrfach mit den gleichen oder verschiedenen Substituenten erfolgt, beispielsweise dreifach am gleichen C-Atom wie im Falle von CF_3 oder an verschiedenen Stellen wie im Falle von -CH(OH)-CH=CH-$CHCl_2$. Besonders bevorzugte Substituenten sind hier F, Cl und OH. In Bezug auf Cycloalkyl kann der Wasserstoffrest auch durch OC_{1-3}-Alkyl oder C_{1-3}-Alkyl (jeweils ein- oder mehrfach substituiert oder unsubstituiert), insbesondere Methyl, Ethyl, n-Propyl, i-Propyl, CF_3, Methoxy oder Ethoxy, ersetzt sein.

Unter dem Begriff $(CH_2)_{3-6}$ ist -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-CH_2- und CH_2-CH_2-CH_2-CH_2-CH_2-CH_2- zu verstehen, unter

$(CH_2)_{1-4}$ ist $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$ und $-CH_2-CH_2-CH_2-CH_2-$ zu verstehen, unter $(CH_2)_{4-5}$ ist $-CH_2-CH_2-CH_2-CH_2-$ und $-CH_2-CH_2-CH_2-CH_2-CH_2-$ zu verstehen, etc.

Unter einem Aryl-Rest werden Ringsysteme mit mindestens einem armomatischen Ring aber ohne Heteroatome in auch nur einem der Ringe verstanden. Beispiele sind Phenyl-, Naphthyl-, Fluoranthenyl-, Fluorenyl-, Tetralinyl- oder Indanyl, insbesondere 9H-Fluorenyl- oder Anthracenyl-Reste, die unsubstituiert oder einfach oder mehrfach substituiert sein können.

Unter einem Heteroaryl-Rest werden heterocyclische Ringsysteme mit mindestens einem ungesättigten Ring verstanden, die ein oder mehrere Heteroatome aus der Gruppe Stickstoff, Sauerstoff und/oder Schwefel enthalten und auch einfach oder mehrfach substituiert sein können. Beispielhaft seien aus der Gruppe der Heteroaryle Furan, Benzofuran, Thiophen, Benzothiophen, Pyrrol, Pyridin, Pyrimidin, Pyrazin, Chinolin, Isochinolin, Phthalazin, Benzo-1,2,5 thiadiazol, Benzothiazol, Indol, Benzotriazol, Benzodioxolan, Benzodioxan, Carbazol, Indol und Chinazolin aufgeführt.

Dabei versteht man im Zusammenhang mit Aryl und Heteroaryl unter substituiert die Substitution des Aryls oder Heteroaryls mit R^{23}, OR^{23} einem Halogen, vorzugsweise F und/oder Cl, einem CF_3, einem CN, einem NO_2, einem $NR^{24}R^{25}$, einem C_{1-6}-Alkyl (gesättigt), einem C_{1-6}-Alkoxy, einem C_{3-8}-Cycloalkoxy, einem C_{3-8}-Cycloalkyl oder einem C_{2-6}-Alkylen.

Dabei steht der Rest R^{23} für H, einen C_{1-10}-Alkyl-, vorzugsweise einen C_{1-6}-Alkyl-, einen Aryl- oder Heteroaryl- oder für einen über eine C_{1-3}-Alkylen-Gruppe gebundenen Aryl- oder Heteroaryl-Rest, wobei diese Aryl

und Heteroarylreste nicht selbst mit Aryl- oder Heteroaryl-Resten substituiert sein dürfen,

die Reste R^{24} und R^{25}, gleich oder verschieden, für H, einen C_{1-10}-Alkyl-, vorzugsweise einen C_{1-6}-Alkyl-, einen Aryl-, einen Heteroaryl- oder einen über eine C_{1-3}-Alkylen-Gruppe gebundenen Aryl- oder Heteroaryl-Rest bedeuten, wobei diese Aryl und Heteroarylreste nicht selbst mit Aryl- oder Heteroaryl-Resten substituiert sein dürfen,

oder die Reste R^{24} und R^{25} bedeuten zusammen $CH_2CH_2OCH_2CH_2$, $CH_2CH_2NR^{26}CH_2CH_2$ oder $(CH_2)_{3-6}$, und

der Rest R^{26} für H, einen C_{1-10}-Alkyl-, vorzugsweise einen C_{1-6}-Alkyl-, einen Aryl-, oder Heteroaryl- Rest oder für einen über eine C_{1-3}-Alkylen-Gruppe gebundenen Aryl- oder Heteroaryl-Rest, wobei diese Aryl und Heteroarylreste nicht selbst mit Aryl- oder Heteroaryl-Resten substituiert sein dürfen.

Unter dem Begriff Salz ist jegliche Form des erfindungsgemäßen Wirkstoffes zu verstehen, in dem dieser eine ionische Form annimmt bzw. geladen ist und mit einem Gegenion (einem Kation oder Anion) gekoppelt ist bzw. sich in Lösung befindet. Darunter sind auch Komplexe des Wirkstoffes mit anderen Molekülen und Ionen zu verstehen, insbesondere Komplexe, die über ionische Wechselwirkungen komplexiert sind.

Unter dem Begriff des physiologisch verträglichen Salzes mit Kationen oder Basen versteht man im Sinne dieser Erfindung Salze mindestens einer der erfindungsgemäßen Verbindungen - meist einer (deprotonierten) Säure - als Anion mit mindestens einem, vorzugsweise anorganischen, Kation, die physiologisch – insbesondere bei Anwendung im Menschen und/oder

Säugetier – verträglich sind. Besonders bevorzugt sind die Salze der Alkali- und Erdalkalimetalle aber auch mit NH_4^+, insbesondere aber (Mono-) oder (Di-) Natrium-, (Mono-) oder (Di-) Kalium-, Magnesium- oder Calzium-Salze.

Unter dem Begriff des physiologisch verträglichen Salzes mit Anionen oder Säuren versteht man im Sinne dieser Erfindung Salze mindestens einer der erfindungsgemäßen Verbindungen – meist, beispielsweise am Stickstoff, protoniert - als Kation mit mindestens einem Anion, die physiologisch – insbesondere bei Anwendung im Menschen und/oder Säugetier – veträglich sind. Insbesondere versteht man darunter im Sinne dieser Erfindung das mit einer physiologisch verträglichen Säure gebildete Salz, nämlich Salze des jeweiligen Wirkstoffes mit anorganischen bzw. organischen Säuren, die physiologisch - insbesondere bei Anwendung im Menschen und/oder Säugetier - verträglich sind. Beispiele für physiologisch verträgliche Salze bestimmter Säuren sind Salze der: Salzsäure, Bromwasserstoffsäure, Schwefelsäure, Methansulfonsäure, Ameisensäure, Essigsäure, Oxalsäure, Bernsteinsäure, Apfelsäure, Weinsäure, Mandelsäure, Fumarsäure, Milchsäure, Zitronensäure, Glutaminsäure, 1,1-Dioxo-1,2-dihydro1b6-benzo[d]isothiazol-3-on (Saccharinsäure), Monomethylsebacinsäure, 5-Oxo-prolin, Hexan-1-sulfonsäure, Nicotinsäure, 2-, 3- oder 4-Aminobenzoesäure, 2,4,6-Trimethyl-benzoesäure, a-Liponsäure, Acetylglycin, Acetylsalicylsäure, Hippursäure und/oder Asparaginsäure. Besonders bevorzugt ist das Hydrochlorid-Salz.

Geeignete Salze im Sinne dieser Erfindung und in jeder beschriebenen Verwendung und jedem der beschriebenen Arzneimittel sind Salze des jeweiligen Wirkstoffes mit anorganischen bzw. organischen Säuren und/oder einem Zuckeraustauschstoff wie Saccharin, Cyclamat oder Acesulfam. Besonders bevorzugt ist jedoch das Hydrochlorid.

Verbindungen der **Gruppe c)** und deren Herstellung sind aus der DE 44 26 245 A1 bzw. der US 6,248,737 bekannt. Verbindungen der **Gruppe d)** und **e)** und deren Herstellung sind aus der DE 195 25 137 A1 bzw. US 5,733,936 bzw. US RE37355E bekannt.

In einer bevorzugten Ausführungsform gilt für die erfindungsgemäße Verwendung, daß die **Verbindung A in Gruppe a)** ausgewählt ist aus:

Tramadol, (+)-Tramadol, (+)-O-Demethyltramadol oder (+)-O-desmethyl-N-mono-desmethyl-tramadol,
vorzugsweise Tramadol oder (+)-Tramadol,
insbesondere (+)-Tramadol.

In einer bevorzugten Ausführungsform gilt für die erfindungsgemäße Verwendung, daß die **Verbindung A** in **Gruppe b)** ausgewählt ist aus:

- Codein
- Dextropropxyphen
- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)
- Tilidin
- Viminol
- Butorphanol
- Dezocin
- Nalorphin
- Pentazocin
- Buprenorphin

, vorzugsweise

- Codein
- Dextropropxyphen
- Dihydrocodein
- Meptazinol
- Nalbuphin
- Tilidin
- Buprenorphin

In einer bevorzugten Ausführungsform gilt für die erfindungsgemäße Verwendung, daß die **Verbindung A** in **Gruppe c)** ausgewählt ist aus Verbindungen gemäß **Formel I** für die gilt:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F, $OC(O)CH_3$ oder H,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise CH_3, C_2H_5, C_4H_9 oder t-Butyl, insbesondere CH_3 oder C_2H_5,

und/oder

R^2 und R^3 unabhängig voneinander ausgewählt sind aus

H, C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise H, CH_3, C_2H_5, i-Propyl oder t-Butyl, insbesondere H oder CH_3, vorzugsweise R^3 = H,

oder

R^2 und R^3 zusammen einen C_{5-6}-Cycloalkylrest bilden, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, vorzugsweise gesättigt und unsubstituiert, insbesondere Cyclohexyl.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OCH_3 oder SCH_3

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

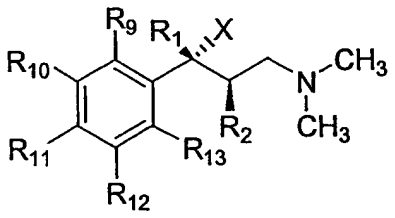
oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7.

Dabei ist es für Verbindungen der **Gruppe c)** besonders bevorzugt, wenn gilt, daß Verbindungen der **Formel I** mit R^3 = H in Form der Diastereomeren mit der relativen Konfiguration Ia



Ia

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer verwendet werden

und/oder

daß die Verbindungen der **Formel I** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer verwendet werden.

Dabei ist es besonders bevorzugt, wenn **Verbindung A** ausgewählt aus folgender Gruppe verwendet wird:

- (2RS,3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3,4-Dichlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Difluoromethyl-phenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-1-Dimethylamino-2-methyl-3-(3-methylsulfanyl-phenyl)-pentan-3-ol,
- (3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-4,4-dimethyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (1RS,2RS)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phe-nol,
- (+)-(1R,2R)-Essigsäure-3-dimethylamino-1-ethyl-1-(3-methoxy-phenyl)-2-methyl-propylester,
- (1RS)-1-(1-Dimethylaminomethyl-cyclohexyl)-1-(3-methoxy-

phenyl)-propan-1-ol,
- (2RS, 3RS)-3-(4-Chlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (2RS,3RS)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol und
- (+)-(2R,3R)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol,

vorzugsweise als Hydrochlorid.

In einer bevorzugten Ausführungsform gilt für die erfindungsgemäße Verwendung, daß die **Verbindung A** in **Gruppe d)** ausgewählt ist aus Verbindungen gemäß **Formel II** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere OH,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, CF_3, OH, O-C_{1-4}-Alkyl, Cl oder F, vorzugsweise OH, CF_3 oder CH_3,

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden,

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

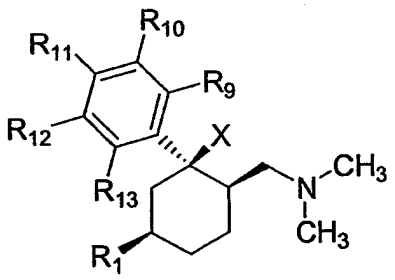
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

Dabei ist es für Verbindungen der **Gruppe d)** besonders bevorzugt, wenn gilt, daß Verbindungen der **Formel II** in Form der Diastereomeren mit der relativen Konfiguration IIa



IIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer verwendet werden,

und/oder

daß die Verbindungen der **Formel II** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer verwendet werden.

Dabei ist es besonders bevorzugt, wenn **Verbindung A** ausgewählt aus folgender Gruppe verwendet wird:

- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,3R,6R)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-hydroxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3SR,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,2R,5S)-3-(2-Dimethylaminomethyl-1-hydroxy-5-methyl-cyclohexyl)-phenol oder
- (1RS,2RS,5RS)-3-(2-Dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

In einer bevorzugten Ausführungsform gilt für die erfindungsgemäße Verwendung, daß die **Verbindung A** in **Gruppe e)** ausgewählt ist aus Verbindungen gemäß **Formel III** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere F oder H.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere dadurch gekennzeichnet, daß,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

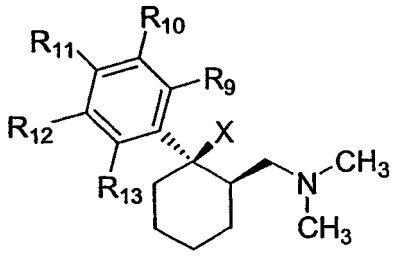
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

Dabei ist es für Verbindungen der **Gruppe e)** besonders bevorzugt, wenn gilt, daß Verbindungen der **Formel III** in Form ihrer Diastereomeren mit der relativen Konfiguration IIIa



IIIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer verwendet werden

und/oder

, daß die Verbindungen der **Formel III** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer verwendet werden.

Dabei ist es besonders bevorzugt, wenn **Verbindung A** ausgewählt aus folgender Gruppe verwendet wird:

- (+)-(1R,2R)-3-(2-Dimethylaminomethyl-1-fluoro-cyclohexyl)-phenol,
- (+)-(1S,2S)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol oder
- (-)-(1R,2R)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

Für eine besonders bevorzugte Verwendung gilt, daß die **Verbindung B** ausgewählt ist aus:

Darifenacin, Duloxetin, Oxybutinin oder Tolterodin,

vorzugsweise ausgewählt ist aus

Duloxetin, Oxybutinin oder Tolterodin,

vorzugsweise ausgewählt ist aus

Oxybutinin oder Tolterodin.

Für eine andere besonders bevorzugte Verwendung gilt, daß die **Verbindung B** ausgewählt ist aus:

Venlafaxin, Fesoterodin, Solifenacin (YM905), Cizolirtine, oder Resiniferatoxin.

Auch wenn die erfindungsgemässen Verwendungen lediglich geringe Nebenwirkungen zeigen, kann es beispielsweise zur Vermeidung von bestimmten Formen der Abhängigkeit auch von Vorteil sein, neben der Kombination der **Verbindungen A** und **B** auch Morphinantagonisten, insbesondere Naloxon, Naltrexon und/oder Levallorphan, zu verwenden.

Ein weiterer Gegenstand der Erfindung ist eine Wirkstoffkombination aus wenigstens einer der **Verbindungen A** und wenigstens einer der **Verbindungen B**, mit **Verbindung A** ausgewählt aus:

Gruppe a) enthaltend:

Tramadol, O-Demethyltramadol oder O-desmethyl-N-monodesmethyl-tramadol als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe b) enthaltend:

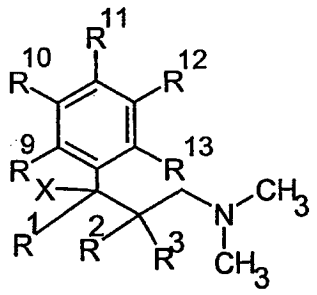
- Codein
- Dextropropxyphen

- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)
- Tilidin
- Tramadol
- Viminol
- Butorphanol
- Dextromoramid
- Dezocin
- Diacetylmorphin (Heroin)
- Hydrocodon
- Hydromorphon
- Ketobemidon
- Levomethadon
- Levomethadyl-Acetate (l-α-Acetylmethadol (LAAM))
- Levorphanol
- Morphin
- Nalorphin
- Oxycodon
- Pentazocin
- Piritramide
- Alfentanil
- Buprenorphin
- Etorphin
- Fentanyl
- Remifentanil
- Sufentanil

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe c) enthaltend:

1-Phenyl-3-dimethylamino-propanverbindungen gemäß allgemeiner **Formel I**



I

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^2 und R^3 jeweils unabhängig voneinander ausgewählt sind aus H oder C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^2 und R^3 zusammen einen gesättigten C_{4-7}-Cycloalkylrest bilden, unsubstituiert oder ein- oder mehrfach substituiert,

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die

Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

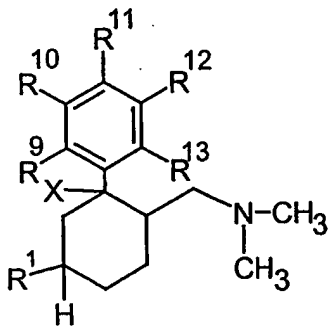
oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe d) enthaltend:

substituierte 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel II**



II

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, Benzyl, CF_3, OH, OCH_2-C_6H_5, O-C_{1-4}-Alkyl, Cl oder F und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert;

$PO(O\text{-}C_{1\text{-}4}\text{-Alkyl})_2$, $CO(OC_{1\text{-}5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1\text{-}3}\text{-Alkyl})$, $CO(C_{1\text{-}5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1\text{-}3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} $C_{1\text{-}4}$-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; $C_{1\text{-}6}$-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

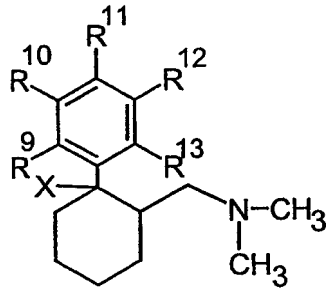
oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,
als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und/oder

Gruppe e) enthaltend:

6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel III**



III

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

mit der Maßgabe, daß, wenn R^9, R^{11} und R^{13} H entsprechen, und einer von R^{10} oder R^{12} H und der andere OCH_3 entspricht, X nicht OH sein darf,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch

verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und mit wenigstens einer der **Verbindungen B**, ausgewählt aus:

den Antimuskarinika: Atropin, Oxybutinin, Propiverin, Propanthelin, Emepronium, Trospium, Tolterodin, Darifenacin und α,α-Diphenylessigsäure-4-(N-methyl-piperidyl)-ester, sowie Duloxetin, Imipramin und Desmopressin,

sowie

Venlafaxin, Fesoterodin, Solifenacin (YM905), Cizolirtine, Resiniferatoxin, Nitro-Flurbiprofen, HCT1026, Talnetant, TAK-637, SL 251039, R 450, Rec 15/3079, (-)-DDMS, NS-8 und/oder DRP-001,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers.

Geeignete Salze im Sinne dieser Erfindung und in jedem der beschriebenen Arzneimittel sind Salze des jeweiligen Wirkstoffes mit anorganischen bzw. organischen Säuren und/oder einem Zuckeraustauschstoff wie Saccharin, Cyclamat oder Acesulfam. Besonders bevorzugt ist jedoch das Hydrochlorid.

Für die Wirkstoffkombination ist es besonders bevorzugt, wenn gilt, daß die **Verbindung A** in **Gruppe a)** ausgewählt ist aus:

Tramadol, (+)-Tramadol, (+)-O-Demethyltramadol oder (+)-O-desmethyl-N-mono-desmethyl-tramadol,
vorzugsweise Tramadol oder (+)-Tramadol,
insbesondere (+)-Tramadol.

Für die Wirkstoffkombination ist es besonders bevorzugt, wenn gilt, daß die **Verbindung A** in **Gruppe b)** ausgewählt ist aus:

- Codein
- Dextropropxyphen
- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)
- Tilidin
- Viminol
- Butorphanol
- Dezocin
- Nalorphin
- Pentazocin

- Buprenorphin

, vorzugsweise

- Codein
- Dextropropxyphen
- Dihydrocodein
- Meptazinol
- Nalbuphin
- Tilidin
- Buprenorphin

Für die Wirkstoffkombination ist es besonders bevorzugt, wenn gilt, daß die **Verbindung A** in **Gruppe c)** ausgewählt ist aus Verbindungen gemäß **Formel I** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F, $OC(O)CH_3$ oder H,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise CH_3, C_2H_5, C_4H_9 oder t-Butyl, insbesondere CH_3 oder C_2H_5,

und/oder

R^2 und R^3 unabhängig voneinander ausgewählt sind aus

H, C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise H, CH_3, C_2H_5, i-Propyl oder t-Butyl, insbesondere H oder CH_3, vorzugsweise R^3 = H,

oder

R^2 und R^3 zusammen einen C_{5-6}-Cycloalkylrest bilden, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, vorzugsweise gesättigt und unsubstituiert, insbesondere Cyclohexyl.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OCH_3 oder SCH_3

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

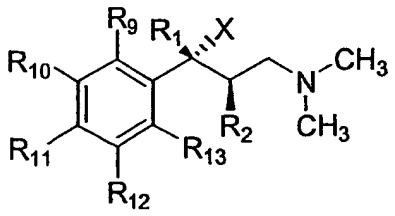
oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7.

Dabei ist es für Verbindungen der **Gruppe c)** besonders bevorzugt, wenn gilt, daß die Verbindungen der **Formel I** mit R^3 = H in Form der Diastereomeren mit der relativen Konfiguration Ia



Ia

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer

und/oder

daß die Verbindungen der **Formel I** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer vorliegen.

Dabei ist es besonders bevorzugt, wenn **Verbindung A** ausgewählt ist aus folgender Gruppe:

- (2RS,3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3,4-Dichlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Difluoromethyl-phenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-1-Dimethylamino-2-methyl-3-(3-methylsulfanyl-phenyl)-pentan-3-ol,
- (3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-4,4-dimethyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (1RS,2RS)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phe-nol,
- (+)-(1R,2R)-Essigsäure-3-dimethylamino-1-ethyl-1-(3-methoxy-phenyl)-2-methyl-propylester,
- (1RS)-1-(1-Dimethylaminomethyl-cyclohexyl)-1-(3-methoxy-

phenyl)-propan-1-ol,
- (2RS, 3RS)-3-(4-Chlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (2RS,3RS)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol und
- (+)-(2R,3R)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol,

vorzugsweise als Hydrochlorid.

Für die Wirkstoffkombination ist es besonders bevorzugt, wenn gilt, daß die **Verbindung A** in **Gruppe d)** ausgewählt ist aus Verbindungen gemäß **Formel II** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere OH,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, CF_3, OH, O-C_{1-4}-Alkyl, Cl oder F, vorzugsweise OH, CF_3 oder CH_3,

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden,

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

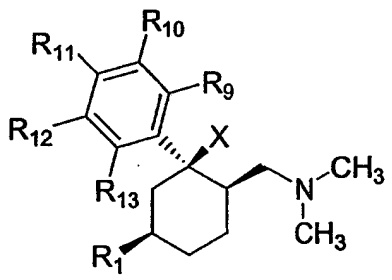
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

Dabei ist es für Verbindungen der **Gruppe d)** besonders bevorzugt, wenn gilt, daß die Verbindungen der **Formel II** in Form der Diastereomeren mit der relativen Konfiguration IIa



IIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer,

und/oder

daß die Verbindungen der **Formel I** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer vorliegen.

Dabei ist es besonders bevorzugt, wenn **Verbindung A** ausgewählt ist aus folgender Gruppe:

- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,3R,6R)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-hydroxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3SR,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,2R,5S)-3-(2-Dimethylaminomethyl-1-hydroxy-5-methyl-cyclohexyl)-phenol oder
- (1RS,2RS,5RS)-3-(2-Dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

Für die Wirkstoffkombination ist es besonders bevorzugt, wenn gilt, daß die **Verbindung A** in **Gruppe e)** ausgewählt ist aus Verbindungen gemäß **Formel III** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere F oder H.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere dadurch gekennzeichnet, daß,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

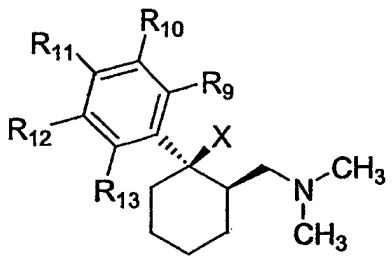
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

Dabei ist es für Verbindungen der **Gruppe e)** besonders bevorzugt, wenn gilt, daß die Verbindungen der **Formel III** in Form ihrer Diastereomeren mit der relativen Konfiguration IIIa



IIIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer

und/oder

, daß die Verbindungen der **Formel III** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer vorliegen.

Dabei ist es besonders bevorzugt, wenn **Verbindung A** ausgewählt ist aus folgender Gruppe:

- (+)-(1R,2R)-3-(2-Dimethylaminomethyl-1-fluoro-cyclohexyl)-phenol,
- (+)-(1S,2S)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol oder
- (-)-(1R,2R)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

In einer generell besonders bevorzugten Form der erfindungsgemäßen Wirkstoffkombination ist die **Verbindung B** ausgewählt aus:

Darifenacin, Duloxetin, Oxybutinin oder Tolterodin,

vorzugsweise ausgewählt ist aus

Duloxetin, Oxybutinin oder Tolterodin,

vorzugsweise ausgewählt ist aus

Oxybutinin oder Tolterodin.

Für eine besonders bevorzugte Form der erfindungsgemäßen Wirkstoffkombination gilt, daß die **Verbindung B** ausgewählt ist aus:

Venlafaxin, Fesoterodin, Solifenacin (YM905), Cizolirtine oder Resiniferatoxin.

Ein weiterer Gegenstand der Erfindung ist ein Arzneimittel, vorzugsweise zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz, enthaltend eine erfindungsgemäße Wirkstoffkombination sowie gegebenenfalls geeignete Zusatz- und/oder Hilfsstoffe.

Geeignete Zusatz- und/oder Hilfsstoffe im Sinne dieser Erfindung sind alle dem Fachmann aus dem Stand der Technik bekannten Stoffe zur Erreichung galenischer Formulierungen. Die Auswahl dieser Hilfsstoffe sowie die einzusetzenden Mengen derselben hängen davon ab, ob das Arzneimittel oral, intravenös, intraperitoneal, intradermal, intramuskulär, intranasal, buccal oder lokal appliziert werden soll. Für die orale Applikation eignen sich Zubereitungen in Form von Tabletten, Kautabletten, Dragees, Kapseln, Granulaten, Tropfen, Säften oder Sirupen, für die parenterale, topische und inhalative Applikation Lösungen, Suspensionen, leicht rekonstituierbare Trockenzubereitungen sowie Sprays. Eine weitere Möglichkeit sind Suppositorien für die Anwendung im Rektum. Die Anwendung in einem Depot in gelöster Form, einer Trägerfolie oder einem Pflaster, gegebenenfalls unter Zusatz von die Hautpenetration fördernden Mitteln, sind Beispiele für geeignete perkutane Applikationsformen. Beispiele für Hilfs- und Zusatzmitteln für die oralen Applikationsformen sind Sprengmittel, Gleitmittel, Binder, Füllmittel, Formtrennmittel, gegebenenfalls Lösungsmittel, Geschmacksstoffe, Zucker, insbesondere Trägermittel, Verdünnungsmittel, Farbstoffe, Antioxidantien etc. Für Suppositorien können u.a. Wachse bzw. Fettsäureester und für parenterale Applikationsmittel Trägerstoffe, Konservierungsmittel, Suspensionshilfsmittel etc. verwendet

werden. Die an Patienten zu verabreichenden Wirkstoffmengen variieren in Abhängigkeit vom Gewicht des Patienten, von der Applikationsart und dem Schweregrad der Erkrankung. Aus oral, rektal oder perkutan anwendbaren Zubereitungsformen können die erfindungsgemäßen Verbindungen verzögert freigesetzt werden. Bei der erfindungsgemäßen Indikation sind entsprechende Retard-Formulierungen, insbesondere in Form eines „Once-daily"-Präparats, das nur einmal am Tag eingenommen werden muß, besonders bevorzugt.

Weiter bevorzugt sind Arzneimittel, die wenigstens 0,05 bis 90,0 % des Wirkstoffes enthalten, insbesondere niedrige wirksame Dosierungen, um Neben- oder analgetische Wirkungen zu vermeiden. Üblicherweise werden 0,1 bis 5000 mg/kg, insbesondere 1 bis 500 mg/kg, vorzugsweise 2 bis 250 mg/kg Körpergewicht wenigstens einer Verbindung der Formel I appliziert. Ebenso bevorzugt und üblich ist aber auch die Applikation von 0,01 – 5 mg/kg, vorzugsweise 0,03 bis 2 mg/kg, insbesondere 0,05 bis 1 mg/kg Körpergewicht.

Hilfsstoffe können beispielsweise sein: Wasser, Ethanol, 2-Propanol, Glycerin, Ethylenglycol, Propylenglycol, Polyethylenglycol, Polypropylenglycol, Glucose, Fructose, Lactose, Saccharose, Dextrose, Melasse, Stärke, modifizierte Stärke, Gelatine, Sorbitol, Inositol, Mannitol, mikrokristalline Cellulose, Methylcellulose, Carboxymethylcellulose, Celluloseacetat, Schellack, Cetylalkohol, Polyvinylpyrrolidon, Paraffine, Wachse, natürliche und synthetische Gummis, Akaziengummi, Alginate, Dextran, gesättigte und ungesättigte Fettsäuren, Stearinsäure, Magnesiumstearat, Zinkstearat, Glycerylstearat, Natriumlaurylsulfat, genießbare Öle, Sesamöl, Kokusnußöl, Erdnußöl, Sojabohnenöl, Lecithin, Natriumlactat, Polyoxyethylen- und -propylen-fettsäureester, Sorbitanfettsäureester, Sorbinsäure, Benzoesäure, Citronensäure, Ascorbinsäure, Tanninsäure, Natriumchlorid, Kaliumchlorid, Magnesiumchlorid, Calciumchlorid, Magnesiumoxid, Zinkoxid,

Siliciumdioxid, Titanoxid, Titandioxid, Magnesiumsulfat, Zinksulfat, Calciumsulfat, Pottasche, Calciumphosphat, Dicalciumphosphat, Kaliumbromid, Kaliumiodid, Talkum, Kaolin, Pectin, Crospovidon, Agar und Bentonit.

Die Herstellung der erfindungsgemäßen Arzneimittel und pharmazeutischen Zusammensetzungen erfolgt mit Hilfe von im Stand der Technik der pharmazeutischen Formulierung wohlbekannten Mitteln, Vorrichtungen, Methoden und Verfahren, wie sie beispielsweise in "Remington`s Pharmaceutical Sciences", Hrsg. A.R. Gennaro, 17. Ed., Mack Publishing Company, Easton, Pa. (1985), insbesondere in Teil 8, Kapitel 76 bis 93, beschrieben sind.

So kann z.B. für eine feste Formulierung, wie eine Tablette, der Wirkstoff des Arzneimittels mit einem pharmazeutischen Träger, z.B. herkömmlichen Tabletteninhaltsstoffen, wie Maisstärke, Lactose, Saccharose, Sorbitol, Talkum, Magnesiumstearat, Dicalciumphosphat oder pharmazeutisch akzeptable Gummis, und pharmazeutischen Verdünnungsmitteln, wie z.B. Wasser, granuliert werden, um eine feste Zusammensetzungzu bilden, die Wirkstoff in homogener Verteilung enthält. Unter einer homogenen Verteilung wird hier verstanden, daß der Wirkstoff gleichmäßig über die gesamte Zusammensetzung verteilt ist, so daß diese ohne weiteres in gleich wirksame Einheitsdosis-Formen, wie Tabletten, Pillen oder Kapseln, unterteilt werden kann. Die feste Zusammensetzungwird anschließend in Einheitsdosis-Formen unterteilt. Die Tabletten oder Pillen des erfindungsgemäßen Arzneimittels bzw. der erfindungsgemäßen Zusammensetzungen können auch überzogen oder auf andere Weise kompoundiert werden, um eine Dosisform mit verzögerter Freisetzung bereitzustellen. Geeignete Beschichtungsmittel sind u.a. polymere Säuren und Mischungen von polymeren Säuren mit Materialien wie z.B. Schellack, Cetylalkohol und/oder Celluloseacetat.

Auch wenn die erfindungsgemässen Arzneimittel lediglich geringe Nebenwirkungen zeigen, kann es beispielsweise zur Vermeidung von bestimmten Formen der Abhängigkeit von Vorteil sein, neben der Kombination der **Verbindungen A** und **B** auch Morphinantagonisten, insbesondere Naloxon, Naltrexon und/oder Levallorphan, zu verwenden.

Weiter betrifft die Erfindung auch ein Verfahren zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz, bei dem die Wirkstoffkombination aus **Verbindung A** und **Verbindung B** verwendet wird.

Die folgenden Beispiele sollen die Erfindung erläutern, ohne daß der Gegenstand der Erfindung darauf beschränkt wäre.

Beispiele

Beispiel 1: Liste der getesteten Substanzen:

Es folgt eine Liste der auf ihre Wirksamkeit getesteten Verbindungen:

Name	Verbdg. Nr.
(2RS,3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol, Hydrochlorid	1
(+)-(2R,3R)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol, Hydrochlorid	2
(2RS,3RS)-3-(3,4-Dichlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol, Hydrochlorid	3
(2RS,3RS)-3-(3-Difluoromethyl-phenyl)-1-dimethylamino-2-methyl-pentan-3-ol, Hydrochlorid	4
(2RS,3RS)-1-Dimethylamino-2-methyl-3-(3-methylsulfanyl-phenyl)-pentan-3-ol, Hydrochlorid	5
(3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-4,4-dimethyl-pentan-3-ol, Hydrochlorid	6
(2RS,3RS)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol, Hydrochlorid	7

(1RS,2RS)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol, Hydrochlorid	8
(+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol, Hydrochlorid	9
(+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol, Hydrochlorid	10
(-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phe-nol, Hydrochlorid	11
(+)-(1R,2R)-Essigsäure-3-dimethylamino-1-ethyl-1-(3-methoxy-phenyl)-2-methyl-propylester, Hydrochlorid	12
(1RS)-1-(1-Dimethylaminomethyl-cyclohexyl)-1-(3-methoxy-phenyl)-propan-1-ol, Hydrochlorid	13
(2RS, 3RS)-3-(4-Chlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol, Hydrochlorid	14
(+)-(1R,2R)-3-(2-Dimethylaminomethyl-1-fluoro-cyclohexyl)-phenol, Hydrochlorid	18
(+)-(1S,2S)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol, Hydrochlorid	19
(-)-(1R,2R)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol, Hydrochlorid	20
rac-Tramadol	23
(-)-(2S,3S)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol, Hydrochlorid	21
(1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol, Hydrochlorid,	24
(+)-(1R,3R,6R)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol, Hydrochlorid,	25
(1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-hydroxy-phenyl)-cyclohexan-1,3-diol, Hydrochlorid,	26
(1RS,3SR,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol, Hydrochlorid,	27
(+)-(1R,2R,5S)-3-(2-Dimethylaminomethyl-1-hydroxy-5-methyl-cyclohexyl)-phenol, Hydrochlorid,	28
(1RS,2RS,5RS)-3-(2-Dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol, Hydrochlorid.	29

Beispiel 2: Testsystem Cystometrie an der wachen naiven Ratte

Es wurden cystometrische Untersuchungen an naiven, weiblichen Sprague-Dawley-Ratten nach der Methode von Ishizuka et. al. ((1997), Naunyn-Schmiedeberg's Arch. Pharmacol. 355: 787 – 793) durchgeführt. Drei Tage nach Implantation von Blasen- und venösen Kathetern wurden die Tiere im wachen Zustand, frei beweglich untersucht. Der Blasenkatheter wurde an einem Druckaufnehmer und eine Injektionspumpe ange-

schlossen. Die Tiere wurden in Stoffwechselkäfige gesetzt, die die Messung des Harnvolumens ermöglichten. Physiologische Kochsalzlösung wurde in die entleerte Blase infundiert (10 ml/Std.) und Blasendruck und Miktionsvolumen kontinuierlich aufgezeichnet. Nach einer Stabilisierungsphase wurde eine 20minütige Phase aufgezeichnet, die durch normale, reproduzierbare Miktionszyklen gekennzeichnet war. Es wurden unter anderem die folgenden Parameter bestimmt:

- Schwellendruck (threshold pressure TP, Blasendruck unmittelbar vor Miktion),
- Blasenkapazität (bladder capacity BC, Restvolumen nach vorhergehender Miktion plus Volumen der infudierten Lösung während der Füllungsphase),
- Interkontraktionsintervall (inter-contraction interval (ICI), das Zeitintervall zwischen den Miktionen).

Eine Erhöhung des Schwellendrucks (TP) zeigt eine wichtige therapeutische Wirkung bei einer der erfindungsgemässen Indikationen an. Auch das Interkontraktionsintervall (ICI) ist ein wichtiger Parameter zur Messung der physiologischen Wirksamkeit eines Stoffes in der Behandlung der Harninkontinenz, ebenso wie die Blasenkapazität (BC). Dabei ist es für eine Wirksamkeit aufgrund der sehr heterogenen Ursachen für die Symptomatik dieser Erkrankungsbilder nicht nötig, alle drei Parameter positiv zu beeinflussen. Es genügt daher völlig, wenn nur in einem dieser Parameter eine posive Wirkung festzustellen ist, um in der Harninkontinenz oder vermehrtem Harndrang einsetzbar zu sein.

Nach der Aufzeichnung von drei reproduzierbaren Miktionszyklen als Vorwert, wurden die Testsubstanzen **1** (1,0 mg/kg), **2** (0,1; 0,3 und 0,5 mg/kg), **21** (0,5 mg/kg), **7** (0,3 mg/kg), **8** (1,0 mg/kg), **9** (0,5 mg/kg) und **11** (0.5 mg/kg); im Vehikel = 0.9 % NaCl i.v. appliziert und die Wirkung auf die cystometrischen Parameter 90 bis 120 Minuten aufgezeichnet. Im

Wirkmaximum wurde der Mittelwert von 3 Miktionszyklen bestimmt und als prozentuale Veränderung gegenüber dem Vorwert dargestellt (Tabelle 1).

Verbindung: (Konzentration)	**TP** threshold pressure	**BC** bladder capacity	**ICI** inter-contraction interval
1 1,0 mg/kg iv (n=9)	+94 % **	+31 % ***	+42 %
2 0,1 mg/kg iv (n=5) 0,3 mg/kg iv (n=8) 0,5 mg/kg iv (n=9)	+28,5 % ** +122 %** +77,5 %**	+7,8 % +33 %* +20,6 %*	+15,6 % +28 %* +28,6 %**
21 0,5 mg/kg iv (n=8)	-1,1 %	+3 %	+10 %
7 0,3 mg/kg iv (n=7)	+95 %**	+32 %*	+28 %*
8 1,0 mg/kg iv (n=8)	+60 %**	+7 %	+14,4 %
9 0,5 mg/kg iv (n=7)	+56 %**	+50 %**	+21 %*
11 0,5 mg/kg iv (n=8)	+9 %	+11 %	+22,6

Tabelle 1: Beeinflussung der cystometrischen Parameter durch die Testsubstanzen (Veränderung zum Vorwert [%]); n entspricht der Anzahl der Versuchstiere. Signifikanz (Student T-Test): * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Die untersuchten Substanzen zeigen eine positive Wirkung auf die Blasenregulation und sind somit geeignet zur Behandlung der Harninkontinenz.

Unter anderem zeigt sich, daß von den Enantiomeren der racemischen Verbindung 1 nur das (+)- Enantiomere (Verbindung 2) effektiv wirksam ist (und damit eine besonders bevorzugte Verbindung dieser Erfindung ist), während das (-)-Enantiomere (Verbindung 21) nicht zur Wirkung beisteuert.

Es wurden mit anderen Verbindungfen weitere Versuche unternommen.

Nach der Aufzeichnung von drei reproduzierbaren Miktionszyklen als Vorwert, wurden die Testsubstanzen **24** (1,0; 3,0; 5,0 mg/kg), **25** (1,5 mg/kg) und **26** (3,0 mg/kg) im Vehikel = 0.9 % NaCl i.v. appliziert und die Wirkung auf die cystometrischen Parameter 90 bis 120 Minuten aufgezeichnet. Im Wirkmaximum wurde der Mittelwert von 3 Miktionszyklen bestimmt und als prozentuale Veränderung gegenüber dem Vorwert dargestellt (Tabelle 2).

Tabelle 2:

Verbindung: (Konzentration)	**TP** threshold pressure	**BC** bladder capacity	**ICI** inter-contraction interval
24			
1,0 mg/kg iv (n=7)	+44,0 %***	-8,0 %	-15 %**
3,0 mg/kg iv (n=8)	+94,0 %**	-16,0 %*	-16 %*
5,0 mg/kg iv (n=8)	+69,0 %*	-26,0 %*	-21,2 %
25			
1,5 mg/kg iv (n=8)	+62,0 %*	-14,0 %*	-9,0 %
26			
3,0 mg/kg iv (n=7)	+86,0 %***	+29,0 %*	+27,0 %*

Tabelle 2: Beeinflussung der cystometrischen Parameter durch die Testsubstanzen (Veränderung zum Vorwert [%]); n entspricht der Anzahl der Versuchstiere. Signifikanz (Student T-Test): * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Die untersuchten Substanzen zeigen eine positive Wirkung auf die Blasenregulation und sind somit geeignet zur Behandlung der Harninkontinenz.

Beispiel 3. Testsystem Cystometrie an der narkotisierten naiven Ratte

Die cystometrische Untersuchung an naiven weiblichen Ratten wurde nach der Methode von Kimura et al. (Kimura et al., 1996, Int. J. Urol. 3:218-227) durchgeführt. An narkotisierten, ventilierten Ratten wird das Abdomen eröffnet und die Harnleiter abgebunden. Der Harn wird von den Nieren abgeleitet. Ein Katheter wird in die Blase eingeführt und fixiert. Über diesen wird Saline mittels Infusionspumpe in die Blase infundiert, bis diese rhythmische Spontanaktivität in Form von Kontraktionen zeigt, welche über einen angeschlossenen Druckaufnehmer aufgenommen werden können. Die Testsubstanz wird nach Erreichen stabiler Ausgangswerte in kumulativer Weise i.v. appliziert. Eine Beeinflussung der Blasenfunktion äußert sich über die Unterdrückung der Spontankontraktionen. Dabei gilt als Parameter für die Unterdrückung das Ausbleiben der Kontraktionen über einen Zeitraum von 10 min.

Bei allen hier aufgelisteten Substanzen war eine Unterdrückung der Spontankontraktionen in den Ratten meßbar, wobei Tabelle 3 den Mittelwert der niedrigsten Dosis aus mindestens 2 Versuchen angibt, bei der erstmals Kontraktionen über einen Zeitraum von 10 min ausbleiben.

Tabelle 3:

Verbdg.-Nr.	Niedrigste Dosis (mg/kg)
3	23,3 (n=3)
4	1,7 (n=3)
5	2,3 (n=3)
6	16,7 (n=3)
10	0,2 (n = 3)
12	30,0 (n=3)
13	20,0 (n=2)
14	20,0 (n=2)

Tabelle 3; (n entspricht der Anzahl der in den Wert eingegangenen Versuche)

Die untersuchten Substanzen zeigen eine positive Wirkung auf die Blasenregulation und sind somit geeignet zur Behandlung der Harninkontinenz.

Es wurden mit anderen Verbindungen weitere Versuche unternommen.

Bei allen hier aufgelisteten Substanzen war eine Unterdrückung der Spontankontraktionen in den Ratten meßbar, wobei Tabelle 4 den Mittelwert der niedrigsten Dosis aus mindestens 2 Versuchen angibt, bei der erstmals Kontraktionen über einen Zeitraum von 10 min ausbleiben.

Tabelle 4:

Verbdg.-Nr.	Niedrigste Dosis (mg/kg)
27	115 (n=2)
28	16,7 (n=3)
29	23,3 (n=3)

Tabelle 4: (n entspricht der Anzahl der in den Wert eingegangenen Versuche)

Die untersuchten Substanzen zeigen eine positive Wirkung auf die Blasenregulation und sind somit geeignet zur Behandlung der Harninkontinenz.

Es wurden mit anderen Verbindungen weitere Versuche unternommen.

Bei allen hier aufgelisteten Substanzen war eine Unterdrückung der Spontankontraktionen in den Ratten meßbar, wobei Tabelle 5 den Mittelwert der niedrigsten Dosis aus mindestens 2 Versuchen angibt, bei der erstmals Kontraktionen über einen Zeitraum von 10 min ausbleiben.

Verbdg.-Nr.	Niedrigste Dosis (mg/kg)
18	0,2 (n=3)
19	0,1 (n=3)
20	0,5 (n=3)
23 (Tramadol)	5,3 (n=3)

Tabelle 5:(n entspricht der Anzahl der in den Wert eingegangenen Versuche)

Die untersuchten Substanzen zeigen eine positive Wirkung auf die Blasenregulation und sind somit geeignet zur Behandlung der Harninkontinenz und erscheinen darin auch gegenüber Tramadol überlegen.

Außerdem wurden die folgenden Substanzen mit dem in der Tabelle 6 dargestellten Ergebnis getestet:
Bei allen aufgelisteten Substanzen war eine Unterdrückung der Spontankontraktionen in den Ratten meßbar, wobei die Tabelle 6 den Mittelwert der niedrigsten Dosis aus 3 unabhängigen Experimenten angibt, bei der erstmals Kontraktionen über einen Zeitraum von 10 min ausbleiben.

Tabelle 6:

Verbindung	Niedrigste Dosis (mg/kg)
Tilidin	0,5 (n=3)

Meptazinol	1,0 (n=3)
Codein(Phosphat)	4,7 (n=3)

Tabelle 6; (n entspricht der Anzahl der in den Wert eingegangenen Versuche)

Die untersuchten Substanzen zeigen eine positive Wirkung auf die Blasenregulation und sind somit geeignet zur Behandlung der Harninkontinenz.

Beispiel 4: Testsystem Cystometrie an der wachen naiven Ratte

Es wurden cystometrische Untersuchungen an naiven, weiblichen Sprague-Dawley-Ratten nach der Methode von Ishizuka et. al. ((1997), Naunyn-Schmiedeberg's Arch. Pharmacol. 355: 787 – 793) durchgeführt. Drei Tage nach Implantation von Blasen- und venösen Kathetern wurden die Tiere im wachen Zustand, frei beweglich untersucht. Der Blasenkatheter wurde an einem Druckaufnehmer und eine Injektionspumpe angeschlossen. Die Tiere wurden in Stoffwechselkäfige gesetzt, die die Messung des Harnvolumens ermöglichten. Physiologische Kochsalzlösung wurde in die entleerte Blase infundiert (10 ml/Std.) und Blasendruck und Miktionsvolumen kontinuierlich aufgezeichnet. Nach einer Stabilisierungsphase wurde eine 20minütige Phase aufgezeichnet, die durch normale, reproduzierbare Miktionszyklen gekennzeichnet war. Es wurden unter anderem die folgenden Parameter bestimmt:

- Schwellendruck (threshold pressure TP, Blasendruck unmittelbar vor Miktion),
- Blasenkapazität (bladder capacity BC, Restvolumen nach vorhergehender Miktion plus Volumen der infudierten Lösung während der Füllungsphase),
- Interkontraktionsintervall (inter-contraction interval (ICI), das Zeitintervall zwischen den Miktionen).

Eine Erhöhung des Schwellendrucks (TP) zeigt eine wichtige therapeutische Wirkung bei einer der erfindungsgemässen Indikationen an. Auch das Interkontraktionsintervall (ICI) ist ein wichtiger Parameter zur Messung der physiologischen Wirksamkeit eines Stoffes in der Behandlung der Harninkontinenz, ebenso wie die Blasenkapazität (BC). Dabei ist es für eine Wirksamkeit aufgrund der sehr heterogenen Ursachen für die Symptomatik dieser Erkrankungsbilder nicht nötig, alle drei Parameter positiv zu beeinflussen. Es genügt daher völlig, wenn nur in einem dieser Parameter eine posive Wirkung festzustellen ist, um in der Harninkontinenz, erhöhter Miktionsfrequenz oder vermehrtem Harndrang einsetzbar zu sein.

Nach der Aufzeichnung von drei reproduzierbaren Miktionszyklen als Vorwert wurden 10 µg/kg Buprenorphin im Vehikel = 0,9 % NaCl i.v. appliziert und die Wirkung auf die cystometrischen Parameter 90 bis 120 Minuten aufgezeichnet. Im Wirkmaximum wurde der Mittelwert von 3 Miktionszyklen bestimmt und als prozentuale Veränderung gegenüber dem Vorwert dargestellt (Tabelle 7).

Die eingesetzte Konzentration entspricht dem ED_{50} in einem bekannten Analgesiemodell für Ratten, dem Tail Flick.

Buprenorphin	**TP** threshold pressure	**BC** bladder capacity	**ICI** inter-contraction interval
0,01 mg/kg iv (n=6)	+69,9% **	+3,6%	+10,9%

Tabelle 7: Beeinflussung der cystometrischen Parameter durch Buprenorphin (Veränderung zum Vorwert [%]); n entspricht der Anzahl der im Versuch eingesetzten Tiere. Signifikanz (Student T-Test): * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Buprenorphin zeigt gerade beim TP eine positive Wirkung auf die Blasenregulation und ist damit prinzipiell geeignet zur Behandlung der

Haminkontinenz. Allerdings war die eingesetzte Konzentration, die analgetisch wirksam ist, offenbar zu hoch, da bei 2 der 6 Tiere bereits Tropf-Inkontinenz auftrat. Bei zwei niedrigeren Konzentrationen, 0,001 mg/kg i.v. und 0,005 mg/kg i.v. trat bei n=6 eine Steigerung des TP von + 27,6 % bzw. + 37,5% auf.

Beispiel 5: Testsystem Cystometrie an der wachen geschädigten Ratte

Dieses Modell simuliert die Dranginkontinenz im Tiermodell; das eingesetzte Oxyhemoglobin (OxyHb) induziert eine Blasenüberaktivität.

Es wurden cystometrische Untersuchungen an naiven, weiblichen Sprague-Dawley-Ratten nach der Methode von Pandita et al. (J. Urol. 2000, 164:545-550) durchgeführt. Drei Tage nach Implantation von Blasen- und venösen Kathetern wurden die Tiere im wachen Zustand, frei beweglich untersucht. Der Blasenkatheter wurde an einem Druckaufnehmer und eine Injektionspumpe angeschlossen. Die Tiere wurden in Stoffwechselkäfige gesetzt, die die Messung des Harnvolumens ermöglichten. Physiologische Kochsalzlösung wurde in die entleerte Blase infundiert (10 ml/Std.) und Blasendruck und Miktionsvolumen kontinuierlich aufgezeichnet. Nach einer Stabilisierungsphase wurde eine 20minütige Phase aufgezeichnet, die durch normale, reproduzierbare Miktionszyklen gekennzeichnet war. Es wurden unter anderem die folgenden Parameter bestimmt:

- Schwellendruck (threshold pressure TP, Blasendruck unmittelbar vor Miktion),
- Blasenkapazität (bladder capacity BC, Restvolumen nach vorhergehender Miktion plus Volumen der infudierten Lösung während der Füllungsphase),

- Interkontraktionsintervall (inter-contraction interval (ICI), das Zeitintervall zwischen den Miktionen).
- Miktionsdruck (micturition pressure MP, maximaler Blasendruck während einer Miktion).

Eine Erhöhung des Schwellendrucks (TP) zeigt eine wichtige therapeutische Wirkung bei einer der erfindungsgemässen Indikationen an. Auch das Interkontraktionsintervall (ICI) ist ein wichtiger Parameter zur Messung der physiologischen Wirksamkeit eines Stoffes in der Behandlung der Harninkontinenz, ebenso wie die Blasenkapazität (BC). Dabei ist es für eine Wirksamkeit aufgrund der sehr heterogenen Ursachen für die Symptomatik dieser Erkrankungsbilder nicht nötig, alle Parameter positiv zu beeinflussen. Es genügt daher völlig, wenn nur in einem dieser Parameter eine positive Wirkung festzustellen ist, um in der Harninkontinenz, erhöhter Miktionsfrequenz oder vermehrtem Harndrang einsetzbar zu sein.

Nach der Aufzeichnung von drei reproduzierbaren Miktionszykden als Vorwert wurden $2.5x10^{-4}$M Oxyhämoglobin im Vehikel = 0,9% NaCl in die Blase infundiert. Die Wirkung auf die cystometrischen Parameter wurden etwa 20 Minuten aufgezeichnet. Im Wirkmaximum wurde der Mittelwert von 3 Miktionszyklen bestimmt und als prozentuale Veränderung gegenüber dem Vorwert dargestellt (Tabelle 8). Die Behandlung mit Oxyhämoglobin induziert eine charakteristische Veränderung der cystometrischen Parameter mit einer Erhöhung des Miktionsdrucks, einer Erniedrigung der Blasenkapazität und einer Verringerung des Interkontraktionsintervals. Diese Veränderungen bilden die Veränderungen ab, die bei Patienten mit Dranginkontinenz gefunden werden.

Die Applikation von 5 µg/kg Buprenorphin im Vehikel = 0,9 % NaCl i.v. vor der Applikation von Oxyhämoglobin ist in der Lage die Veränderungen, die durch Oxyhämoglobin induziert werden, zu unterdrücken und darüber hinaus noch einen Anstieg des Schwellendrucks zu induzieren (Tabelle 8).

Tabelle 8:

	MP Micturition pressure [cm H_2O]	TP threshold pressure [cm H_2O]	BC bladder capacity [ml]	ICI inter-contraction interval [min]
OxyHb				
2,5x10^{-4}M iv (n=5)	v: 59 ± 8 h: 97 ± 5 Dif.:+64,4% **	v: 8,72 ± 1,31 h: 9,84 ± 1,56 Diff.: +12,8%	v: 0,92 ± 0,10 h: 0,65 ± 0,06 Diff.: -29,3% **	v: 4,96 ± 0,33 h: 3,33 ± 0,18 Diff.: -32,9% **
OxyHb + Buprenorphin				
OxyHb: 2,5x10^{-4}M Buprenorphin: 0,005 mg/kg iv (n=6)	v: 54 ± 9 h: 37 ± 8 Diff.: -31,5% *	v: 9,07 ± 1,29 h: 14,28± 2,53 Diff.: +57,4 % *	v: 1,19 ± 0,12 h: 1,17 ± 0,13 Diff.: -1,7 %	v: 6,72 ± 0,73 h: 6,70 ± 0,88 Diff.: -0,3 %

Tabelle 8: Beeinflussung der cystometrischen Parameter durch Oxyhämoglobin (OxyHb) mit und ohne vorherige Gabe von Buprenorphin. Angegeben sind Durchschnittswerte mit Standardabweichungen vor (v) und nach (h) Anwendung der Substanzen sowie die Veränderung (Diff.) im Vergleich zum Vorwert [%]; n entspricht der Anzahl der im Versuch eingesetzten Tiere. Signifikanz (Student T-Test): * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Es ist zu erkennen, daß OxyHb die Blasenparameter deutlich im Sinne einer Dranginkontinenz negativ beeinflußt. Diese negative Beeinflußung wird durch Buprenorphin aufgehoben und sogar verbessert. So sinkt der Miktionsdruck im Vergleich zu der durch OxyHb ausgelösten Dranginkontinenz und auch im Vergleich zur unbehandelten Kontrolle signifikant. Weiter normalisiert Buprenorphin in diesem Dranginkontinenzmodell das Interkontraktionsintervall und die Blasenkapazität vollkommen und bewirkt weiter eine signifikante und deutliche Erhöhung des Schwellendrucks.

Damit ist der Beweis angetreten, daß Buprenorphin, insbesondere im Bereich der Dranginkontinenz, für die das OxyHb-Modell als Standardmodell steht, eine hervorragende Wirkung zeigt und zwar auch bei Schädigung, also im Krankheitsfall.

Beispiel 6: Parenterale Applikationsform

20 g Tramadol und 1 g Venlafaxin wird in 1 l Wasser für Injektionszwecke bei Raumtemperatur gelöst und anschließend durch Zugabe von NaCl auf isotone Bedingungen eingestellt.

Patentansprüche:

1. Verwendung einer Wirkstoffkombination aus wenigstens einer der **Verbindungen A** und wenigstens einer der **Verbindungen B**, mit **Verbindung A** ausgewählt aus:

Gruppe a) enthaltend:

Tramadol, O-Demethyltramadol, oder O-desmethyl-N-mono-desmethyl-tramadol als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe b) enthaltend:

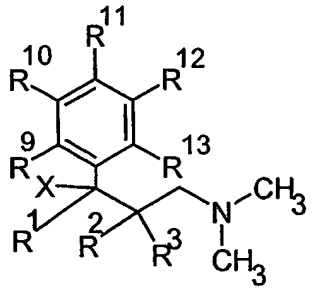
- Codein
- Dextropropxyphen
- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)
- Tilidin
- Tramadol
- Viminol
- Butorphanol

- Dextromoramid
- Dezocin
- Diacetylmorphin (Heroin)
- Hydrocodon
- Hydromorphon
- Ketobemidon
- Levomethadon
- Levomethadyl-Acetate (l-α-Acetylmethadol (LAAM))
- Levorphanol
- Morphin
- Nalorphin
- Oxycodon
- Pentazocin
- Piritramide
- Alfentanil
- Buprenorphin
- Etorphin
- Fentanyl
- Remifentanil
- Sufentanil

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe c) enthaltend:

1-Phenyl-3-dimethylamino-propanverbindungen gemäß allgemeiner **Formel I**



I

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^2 und R^3 jeweils unabhängig voneinander ausgewählt sind aus H oder C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^2 und R^3 zusammen einen gesättigten C_{4-7}-Cycloalkylrest bilden, unsubstituiert oder ein- oder mehrfach substituiert,

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

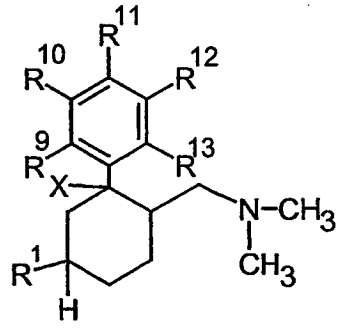
oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe d) enthaltend:

substituierte 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel II**



II

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, Benzyl, CF_3, OH, OCH_2-C_6H_5, O-C_{1-4}-Alkyl, Cl oder F und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt,

gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

oder

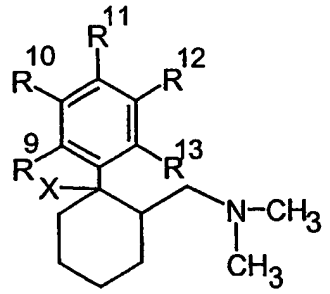
R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und/oder

Gruppe e) enthaltend:

6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel III**



III

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}$-

NHR^{18}, $CO-C_6H_4-R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

mit der Maßgabe, daß, wenn R^9, R^{11} und R^{13} H entsprechen, und einer von R^{10} oder R^{12} H und der andere OCH_3 entspricht, X nicht OH sein darf,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und mit wenigstens einer der **Verbindungen B**, ausgewählt aus:

Venlafaxin, Fesoterodin, Solifenacin (YM906), Cizolirtine, Resiniferatoxin, Nitro-Flurbiprofen, HCT1026, Talnetant, TAK-637, SL 251039, R 450, Rec 15/3079, (-)-DDMS, NS-8 und/oder DRP-001,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

zur Herstellung eines Arzneimittels zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz.

2. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe a)** ausgewählt ist aus:

Tramadol, (+)-Tramadol, (+)-O-Demethyltramadol oder (+)-O-desmethyl-N-mono-desmethyl-tramadol,
vorzugsweise Tramadol oder (+)-Tramadol,
insbesondere (+)-Tramadol.

3. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe b)** ausgewählt ist aus:

- Codein

- Dextropropxyphen
- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)
- Tilidin
- Viminol
- Butorphanol
- Dezocin
- Nalorphin
- Pentazocin
- Buprenorphin

, vorzugsweise

- Codein
- Dextropropxyphen
- Dihydrocodein
- Meptazinol
- Nalbuphin
- Tilidin
- Buprenorphin

4. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe c**) ausgewählt ist aus Verbindungen gemäß **Formel I** für die gilt:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F, $OC(O)CH_3$ oder H,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise CH_3, C_2H_5, C_4H_9 oder t-Butyl, insbesondere CH_3 oder C_2H_5,

und/oder

R^2 und R^3 unabhängig voneinander ausgewählt sind aus

H, C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise H, CH_3, C_2H_5, i-Propyl oder t-Butyl, insbesondere H oder CH_3, vorzugsweise R^3 = H,

oder

R^2 und R^3 zusammen einen C_{5-6}-Cycloalkylrest bilden, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, vorzugsweise gesättigt und unsubstituiert, insbesondere Cyclohexyl.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OCH_3 oder SCH_3

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

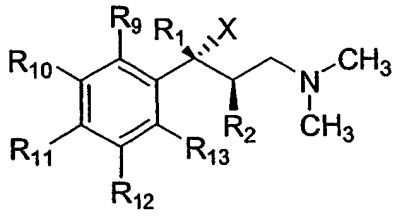
oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7.

5. Verwendung gemäß Anspruch 4, dadurch gekennzeichnet, daß Verbindungen der **Formel I** mit R^3 = H in Form der Diastereomeren mit der relativen Konfiguration Ia



Ia

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer verwendet werden

und/oder

daß die Verbindungen der **Formel I** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer verwendet werden.

6. Verwendung gemäß einem der Ansprüche 4 oder 5, dadurch gekennzeichnet, daß **Verbindung A** ausgewählt aus folgender Gruppe verwendet wird:

- (2RS,3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-me-

thyl-pentan-3-ol,
- (2RS,3RS)-3-(3,4-Dichlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Difluoromethyl-phenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-1-Dimethylamino-2-methyl-3-(3-methylsulfanyl-phenyl)-pentan-3-ol,
- (3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-4,4-dimethyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (1RS,2RS)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phe-nol,
- (+)-(1R,2R)-Essigsäure-3-dimethylamino-1-ethyl-1-(3-methoxy-phenyl)-2-methyl-propylester,
- (1RS)-1-(1-Dimethylaminomethyl-cyclohexyl)-1-(3-methoxy-phenyl)-propan-1-ol,
- (2RS, 3RS)-3-(4-Chlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (2RS,3RS)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol und
- (+)-(2R,3R)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol,

vorzugsweise als Hydrochlorid.

7. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe d)** ausgewählt ist aus Verbindungen gemäß **Formel II** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere OH,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, CF_3, OH, O-C_{1-4}-Alkyl, Cl oder F, vorzugsweise OH, CF_3 oder CH_3,

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden,

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

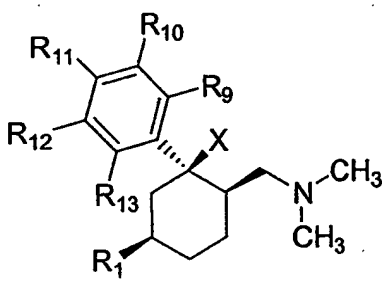
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

8. Verwendung gemäß Anspruch 7, dadurch gekennzeichnet, daß Verbindungen der **Formel II** in Form der Diastereomeren mit der relativen Konfiguration IIa



IIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer verwendet werden,

und/oder

daß die Verbindungen der **Formel II** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer verwendet werden.

9. Verwendung gemäß einem der Ansprüche 7 oder 8, dadurch gekennzeichnet, daß **Verbindung A** ausgewählt aus folgender Gruppe verwendet wird:

- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,3R,6R)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-hydroxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3SR,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,2R,5S)-3-(2-Dimethylaminomethyl-1-hydroxy-5-methyl-cyclohexyl)-phenol oder
- (1RS,2RS,5RS)-3-(2-Dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

10. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe e)** ausgewählt ist aus Verbindungen gemäß **Formel III** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere F oder H.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere dadurch gekennzeichnet, daß,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

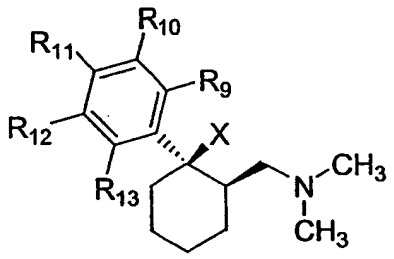
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

11. Verwendung gemäß Anspruch 10, dadurch gekennzeichnet, daß Verbindungen der **Formel III** in Form ihrer Diastereomeren mit der relativen Konfiguration IIIa



IIIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer verwendet werden

und/oder

, daß die Verbindungen der **Formel III** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer verwendet werden.

12. Verwendung gemäß einem der Ansprüche 10 oder 11, dadurch gekennzeichnet, daß **Verbindung A** ausgewählt aus folgender Gruppe verwendet wird:

- (+)-(1R,2R)-3-(2-Dimethylaminomethyl-1-fluoro-cyclohexyl)-phenol,
- (+)-(1S,2S)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol oder
- (-)-(1R,2R)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

13. Verwendung gemäß einem der Ansprüche 1 bis 12, dadurch gekennzeichnet, daß die **Verbindung B** ausgewählt ist aus:

Fesoterodin, Solifenacin (YM905), Cizolirtine, Resiniferatoxin oder Venlafaxin.

14. Wirkstoffkombination aus wenigstens einer der **Verbindungen A** und wenigstens einer der **Verbindungen B**, mit **Verbindung A** ausgewählt aus:

Gruppe a) enthaltend:

Tramadol, O-Demethyltramadol oder O-desmethyl-N-mono-desmethyl-tramadol als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe b) enthaltend:

- Codein
- Dextropropxyphen
- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)

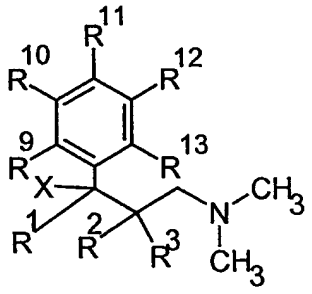
- Tilidin
- Tramadol
- Viminol
- Butorphanol
- Dextromoramid
- Dezocin
- Diacetylmorphin (Heroin)
- Hydrocodon
- Hydromorphon
- Ketobemidon
- Levomethadon
- Levomethadyl-Acetate (l-α-Acetylmethadol (LAAM))
- Levorphanol
- Morphin
- Nalorphin
- Oxycodon
- Pentazocin
- Piritramide
- Alfentanil
- Buprenorphin
- Etorphin
- Fentanyl
- Remifentanil
- Sufentanil

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder

Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe c) enthaltend:

1-Phenyl-3-dimethylamino-propanverbindungen gemäß allgemeiner **Formel I**



I

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^2 und R^3 jeweils unabhängig voneinander ausgewählt sind aus H oder C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^2 und R^3 zusammen einen gesättigten C_{4-7}-Cycloalkylrest bilden, unsubstituiert oder ein- oder mehrfach substituiert,

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder

mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

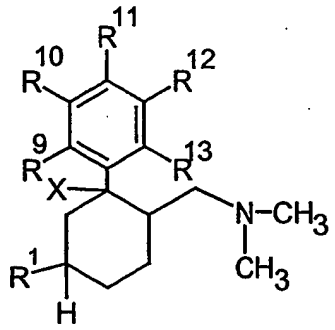
oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe d) enthaltend:

substituierte 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel II**



II

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, Benzyl, CF_3, OH, OCH_2-C_6H_5, O-C_{1-4}-Alkyl, Cl oder F und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert;

$PO(O\text{-}C_{1\text{-}4}\text{-Alkyl})_2$, $CO(OC_{1\text{-}5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1\text{-}3}\text{-Alkyl})$, $CO(C_{1\text{-}5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1\text{-}3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} $C_{1\text{-}4}$-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; $C_{1\text{-}6}$-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

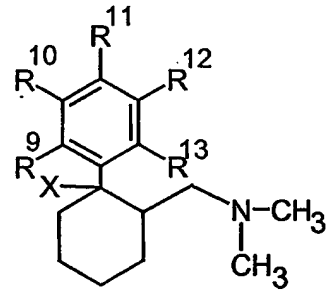
oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,
als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und/oder

Gruppe e) enthaltend:

6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel III**



III

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

mit der Maßgabe, daß, wenn R^9, R^{11} und R^{13} H entsprechen, und einer von R^{10} oder R^{12} H und der andere OCH_3 entspricht, X nicht OH sein darf,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch

verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und mit wenigstens einer der **Verbindungen B**, ausgewählt aus:

Venlafaxin, Fesoterodin, Solifenacin (YM905), Cizolirtine, Resiniferatoxin, Nitro-Flurbiprofen, HCT1026, Talnetant, TAK-637, SL 251039, R 450, Rec 15/3079, (-)-DDMS, NS-8 und/oder DRP-001,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers.

15. Wirkstoffkombination gemäß Anspruch 14, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe a**) ausgewählt ist aus:

Tramadol, (+)-Tramadol, (+)-O-Demethyltramadol oder (+)-O-desmethyl-N-mono-desmethyl-tramadol,
vorzugsweise Tramadol oder (+)-Tramadol,
insbesondere (+)-Tramadol.

16. Wirkstoffkombination gemäß Anspruch 14, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe b**) ausgewählt ist aus:

- Codein
- Dextropropxyphen
- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)
- Tilidin
- Viminol
- Butorphanol
- Dezocin
- Nalorphin
- Pentazocin
- Buprenorphin

, vorzugsweise

- Codein
- Dextropropxyphen
- Dihydrocodein
- Meptazinol
- Nalbuphin
- Tilidin
- Buprenorphin

17. Wirkstoffkombination gemäß Anspruch 14, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe c)** ausgewählt ist aus Verbindungen gemäß **Formel I** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F, $OC(O)CH_3$ oder H,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise CH_3, C_2H_5, C_4H_9 oder t-Butyl, insbesondere CH_3 oder C_2H_5,

und/oder

R^2 und R^3 unabhängig voneinander ausgewählt sind aus

H, C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise H, CH_3, C_2H_5, i-Propyl oder t-Butyl, insbesondere H oder CH_3, vorzugsweise R^3 = H,

oder

R^2 und R^3 zusammen einen C_{5-6}-Cycloalkylrest bilden, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, vorzugsweise gesättigt und unsubstituiert, insbesondere Cyclohexyl.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OCH_3 oder SCH_3

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

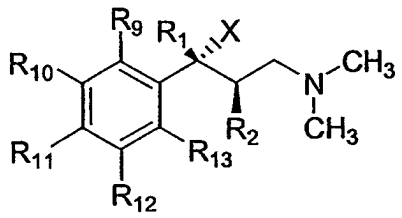
oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7.

18. Wirkstoffkombination gemäß Anspruch 17, dadurch gekennzeichnet, daß die Verbindungen der **Formel I** mit R^3 = H in Form der Diastereomeren mit der relativen Konfiguration Ia



Ia

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer

und/oder

daß die Verbindungen der **Formel I** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer vorliegen.

19. Wirkstoffkombination gemäß einem der Ansprüche 17 oder 18, dadurch gekennzeichnet, daß die **Verbindung A** ausgewählt ist aus folgender Gruppe:

- (2RS,3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3,4-Dichlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Difluoromethyl-phenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-1-Dimethylamino-2-methyl-3-(3-methylsulfanyl-phenyl)-pentan-3-ol,
- (3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-4,4-dimethyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (1RS,2RS)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phe-nol,
- (+)-(1R,2R)-Essigsäure-3-dimethylamino-1-ethyl-1-(3-methoxy-phenyl)-2-methyl-propylester,
- (1RS)-1-(1-Dimethylaminomethyl-cyclohexyl)-1-(3-methoxy-phenyl)-propan-1-ol,
- (2RS, 3RS)-3-(4-Chlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (2RS,3RS)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol und
- (+)-(2R,3R)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol,

vorzugsweise als Hydrochlorid.

20. Wirkstoffkombination gemäß Anspruch 14, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe d)** ausgewählt ist aus Verbindungen gemäß **Formel II** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere OH,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, CF_3, OH, O-C_{1-4}-Alkyl, Cl oder F, vorzugsweise OH, CF_3 oder CH_3,

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden,

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

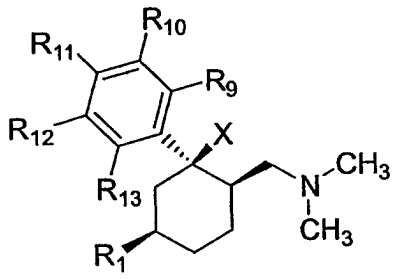
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

21. Wirkstoffkombination gemäß Anspruch 20, dadurch gekennzeichnet, daß die Verbindungen der **Formel II** in Form der Diastereomeren mit der relativen Konfiguration IIa



IIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer,

und/oder

daß die Verbindungen der **Formel II** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer vorliegen.

22. Wirkstoffkombination gemäß einem der Ansprüche 20 oder 21, dadurch gekennzeichnet, daß **Verbindung A** ausgewählt ist aus folgender Gruppe:

- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,3R,6R)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-hydroxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3SR,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,2R,5S)-3-(2-Dimethylaminomethyl-1-hydroxy-5-me-

thyl-cyclohexyl)-phenol oder
- (1RS,2RS,5RS)-3-(2-Dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

23. Wirkstoffkombination gemäß Anspruch 14, dadurch gekennzeichnet, daß die **Verbindung A** in **Gruppe e)** ausgewählt ist aus Verbindungen gemäß **Formel III** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere F oder H.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere dadurch gekennzeichnet, daß,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

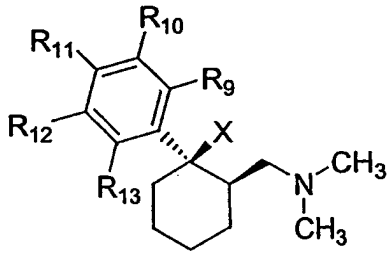
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

24. Wirkstoffkombination gemäß Anspruch 23, dadurch gekennzeichnet, daß die Verbindungen der **Formel III** in Form ihrer Diastereomeren mit der relativen Konfiguration IIIa



IIIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer

und/oder

, daß die Verbindungen der **Formel III** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer vorliegen.

25. Wirkstoffkombination gemäß einem der Ansprüche 23 oder 24, dadurch gekennzeichnet, daß die **Verbindung A** ausgewählt ist aus folgender Gruppe:

- (+)-(1R,2R)-3-(2-Dimethylaminomethyl-1-fluoro-cyclohexyl)-phenol,

- (+)-(1S,2S)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol oder
- (-)-(1R,2R)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

26. Wirkstoffkombination gemäß einem der Ansprüche 14 bis 25, dadurch gekennzeichnet, daß die **Verbindung B** ausgewählt ist aus:

Fesoterodin, Solifenacin (YM905), Resiniferatoxin, Cizolirtine oder Venlafaxin.

27. Arzneimittel, vorzugsweise zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz, enthaltend eine Wirkstoffkombination gemäß einem der Ansprüche 14 bis 26 sowie gegebenenfalls geeignete Zusatz- und/oder Hilfsstoffe.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/05529

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/135 A61K31/137 A61K31/485

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 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)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 199 47 747 A (GRUENENTHAL GMBH) 12 April 2001 (2001-04-12) claims 1,2 ---	1,2, 13-15, 26,27
Y	PANDITA R K ET AL: "Actions of tramadol on the micturition reflex in awake, freely moving rats." NEUROUROLOGY AND URODYNAMICS, vol. 20, no. 4, 2001, pages 439-440, XP008020732 31st Annual Meeting of the International Continence Society;Seoul, South Korea; September 18-21, 2001 ISSN: 0733-2467 * Seite 440, Absatz "Conclusions" * --- -/--	1,2, 13-15, 26,27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 August 2003	25/09/2003

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	Beranová, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 658 908 A (MCNUTT JR ROBERT WALTON ET AL) 19 August 1997 (1997-08-19) column 6, line 22 - line 24 column 14, line 48	1,3,13, 14,16, 26,27
Y	MALINOVSKY J-M ET AL: "THE URODYNAMIC EFFECTS OF INTRAVENOUS OPIOIDS AND KETOPROFEN IN HUMANS" ANESTHESIA AND ANALGESIA, WILLIAMS AND WILKINS, BALTIMORE, MD, US, vol. 87, no. 2, August 1998 (1998-08), pages 456-461, XP001064299 ISSN: 0003-2999 * Seite 460, linke Spalte, letzter Absatz * ---	1,3,13, 14,16, 26,27
Y	PALMER K R ET AL: "DOUBLE-BLIND CROSS-OVER STUDY COMPARING LOPERAMIDE CODEINE AND DIPHENOXYLATE IN THE TREATMENT OF CHRONIC DIARRHEA" GASTROENTEROLOGY, SAUNDERS, PHILADELPHIA, PA,, US, vol. 79, no. 6, December 1980 (1980-12), pages 1272-1275, XP001065241 ISSN: 0016-5085 * Seite 1275, linke Spalte, letzter Absatz * ---	1,3,13, 14,16, 26,27
Y	DURAND A ET AL: "Drug therapy for urinary incontinence" PRESSE MEDICALE 06 MAY 2000 FRANCE, vol. 29, no. 16, 6 May 2000 (2000-05-06), pages 917-922, XP008020716 ISSN: 0755-4982 page 920, right-hand column, paragraph 2 ---	1,3,13, 14,16, 26,27
Y	EP 1 072 260 A (NOVOSIS PHARMA AG) 31 January 2001 (2001-01-31) claims 1,18 ---	1,13,14, 26,27
Y	RIPPLE MARY G ET AL: "Lethal combination of tramadol and multiple drugs affecting serotonin." AMERICAN JOURNAL OF FORENSIC MEDICINE AND PATHOLOGY, vol. 21, no. 4, December 2000 (2000-12), pages 370-374, XP008020715 ISSN: 0195-7910 page 372, left-hand column, paragraph 2 --- -/--	1,2, 13-15, 26,27

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KRONER BEVERLY A ET AL: "Pharmacotherapy trials of urinary incontinence in the geriatric patient: A review of current literature findings." JOURNAL OF GERIATRIC DRUG THERAPY, vol. 7, no. 1, 1992, pages 23-55, XP008020717 ISSN: 8756-4629 table 2	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP03/05529

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see supplemental Sheet additionnal matter PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Box I.2

The current Claims 1, 13, 14, 26 and 27 relate to a disproportionately large number of possible compounds, of which only a small portion are supported by the description (PCT Article 6) and/or can be regarded as having been disclosed in the application (PCT Article 5). In the present case the claims lack the proper support and the application lacks the requisite disclosure to such an extent that it appears impossible to carry out a meaningful search covering the entire range of protection sought. The search was therefore directed to the parts of the claims that appear to be clear, supported and disclosed in the above sense, that is the compounds specified in the exemplary embodiments.

The applicant is advised that claims or parts of claims relating to inventions in respect of which no international search report has been established cannot normally be the subject of an international preliminary examination (PCT Rule 66.1(e)). In its capacity as International Preliminary Examining Authority the EPO generally will not carry out a preliminary examination for subjects that have not been searched. This also applies to cases where the claims were amended after receipt of the international search report (PCT Article 19) or where the applicant submits new claims in the course of the procedure under PCT Chapter II.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/05529

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19947747 A	12-04-2001	DE 19947747 A1	12-04-2001
		AU 7907600 A	10-05-2001
		CA 2386381 A1	12-04-2001
		WO 0124783 A2	12-04-2001
		EP 1217998 A2	03-07-2002
		HU 0202776 A2	28-02-2003
		JP 2003510350 T	18-03-2003
		US 2003069314 A1	10-04-2003
US 5658908 A	19-08-1997	AT 237597 T	15-05-2003
		AU 675928 B2	27-02-1997
		AU 3457393 A	01-09-1993
		CA 2129046 A1	05-08-1993
		DE 69332882 D1	22-05-2003
		DK 649414 T3	11-08-2003
		EP 0649414 A1	26-04-1995
		WO 9315062 A1	05-08-1993
		IL 104582 A	30-10-1998
		JP 3109832 B2	20-11-2000
		JP 7503247 T	06-04-1995
		NZ 246916 A	27-08-1996
		US 5681830 A	28-10-1997
		US 5574159 A	12-11-1996
		US 5854249 A	29-12-1998
		US 2002052007 A1	02-05-2002
		ZA 9300717 A	02-08-1994
EP 1072260 A	31-01-2001	DE 19934523 A1	25-01-2001
		EP 1072260 A1	31-01-2001

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 03/05529

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 7 A61K31/135 A61K31/137 A61K31/485

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 7 A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der Internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	DE 199 47 747 A (GRUENENTHAL GMBH) 12. April 2001 (2001-04-12) Ansprüche 1,2 ---	1,2, 13-15, 26,27
Y	PANDITA R K ET AL: "Actions of tramadol on the micturition reflex in awake, freely moving rats." NEUROUROLOGY AND URODYNAMICS, Bd. 20, Nr. 4, 2001, Seiten 439-440, XP008020732 31st Annual Meeting of the International Continence Society;Seoul, South Korea; September 18-21, 2001 ISSN: 0733-2467 * Seite 440, Absatz "Conclusions" * --- -/--	1,2, 13-15, 26,27

[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

* Besondere Kategorien von angegebenen Veröffentlichungen :
"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist
"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist
"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)
"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht
"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist
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"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden
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Datum des Abschlusses der Internationalen Recherche	Absendedatum des Internationalen Recherchenberichts
21. August 2003	25/09/2003

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beranová, P

Formblatt PCT/ISA/210 (Blatt 2) (Juli 1992)

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	US 5 658 908 A (MCNUTT JR ROBERT WALTON ET AL) 19. August 1997 (1997-08-19) Spalte 6, Zeile 22 - Zeile 24 Spalte 14, Zeile 48	1,3,13, 14,16, 26,27
Y	MALINOVSKY J-M ET AL: "THE URODYNAMIC EFFECTS OF INTRAVENOUS OPIOIDS AND KETOPROFEN IN HUMANS" ANESTHESIA AND ANALGESIA, WILLIAMS AND WILKINS, BALTIMORE, MD, US, Bd. 87, Nr. 2, August 1998 (1998-08), Seiten 456-461, XP001064299 ISSN: 0003-2999 * Seite 460, linke Spalte, letzter Absatz *	1,3,13, 14,16, 26,27
Y	PALMER K R ET AL: "DOUBLE-BLIND CROSS-OVER STUDY COMPARING LOPERAMIDE CODEINE AND DIPHENOXYLATE IN THE TREATMENT OF CHRONIC DIARRHEA" GASTROENTEROLOGY, SAUNDERS, PHILADELPHIA, PA,, US, Bd. 79, Nr. 6, Dezember 1980 (1980-12), Seiten 1272-1275, XP001065241 ISSN: 0016-5085 * Seite 1275, linke Spalte, letzter Absatz *	1,3,13, 14,16, 26,27
Y	DURAND A ET AL: "Drug therapy for urinary incontinence" PRESSE MEDICALE 06 MAY 2000 FRANCE, Bd. 29, Nr. 16, 6. Mai 2000 (2000-05-06), Seiten 917-922, XP008020716 ISSN: 0755-4982 Seite 920, rechte Spalte, Absatz 2	1,3,13, 14,16, 26,27
Y	EP 1 072 260 A (NOVOSIS PHARMA AG) 31. Januar 2001 (2001-01-31) Ansprüche 1,18	1,13,14, 26,27
Y	RIPPLE MARY G ET AL: "Lethal combination of tramadol and multiple drugs affecting serotonin." AMERICAN JOURNAL OF FORENSIC MEDICINE AND PATHOLOGY, Bd. 21, Nr. 4, Dezember 2000 (2000-12), Seiten 370-374, XP008020715 ISSN: 0195-7910 Seite 372, linke Spalte, Absatz 2	1,2, 13-15, 26,27

-/—

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	KRONER BEVERLY A ET AL: "Pharmacotherapy trials of urinary incontinence in the geriatric patient: A review of current literature findings." JOURNAL OF GERIATRIC DRUG THERAPY, Bd. 7, Nr. 1, 1992, Seiten 23-55, XP008020717 ISSN: 8756-4629 Tabelle 2 ----	

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 03/05529

Feld I Bemerkungen zu den Ansprüchen, die sich als nicht recherchierbar erwiesen haben (Fortsetzung von Punkt 2 auf Blatt 1)

Gemäß Artikel 17(2)a) wurde aus folgenden Gründen für bestimmte Ansprüche kein Recherchenbericht erstellt:

1. ☐ Ansprüche Nr.
weil sie sich auf Gegenstände beziehen, zu deren Recherche die Behörde nicht verpflichtet ist, nämlich

2. ☒ Ansprüche Nr. –
weil sie sich auf Teile der internationalen Anmeldung beziehen, die den vorgeschriebenen Anforderungen so wenig entsprechen, daß eine sinnvolle internationale Recherche nicht durchgeführt werden kann, nämlich

siehe Zusatzblatt WEITERE ANGABEN PCT/ISA/210

3. ☐ Ansprüche Nr.
weil es sich dabei um abhängige Ansprüche handelt, die nicht entsprechend Satz 2 und 3 der Regel 6.4 a) abgefaßt sind.

Feld II Bemerkungen bei mangelnder Einheitlichkeit der Erfindung (Fortsetzung von Punkt 3 auf Blatt 1)

Die internationale Recherchenbehörde hat festgestellt, daß diese internationale Anmeldung mehrere Erfindungen enthält:

1. ☐ Da der Anmelder alle erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht auf alle recherchierbaren Ansprüche.

2. ☐ Da für alle recherchierbaren Ansprüche die Recherche ohne einen Arbeitsaufwand durchgeführt werden konnte, der eine zusätzliche Recherchengebühr gerechtfertigt hätte, hat die Behörde nicht zur Zahlung einer solchen Gebühr aufgefordert.

3. ☐ Da der Anmelder nur einige der erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht nur auf die Ansprüche, für die Gebühren entrichtet worden sind, nämlich auf die Ansprüche Nr.

4. ☐ Der Anmelder hat die erforderlichen zusätzlichen Recherchengebühren nicht rechtzeitig entrichtet. Der internationale Recherchenbericht beschränkt sich daher auf die in den Ansprüchen zuerst erwähnte Erfindung; diese ist in folgenden Ansprüchen erfaßt:

Bemerkungen hinsichtlich eines Widerspruchs

☐ Die zusätzlichen Gebühren wurden vom Anmelder unter Widerspruch gezahlt.

☐ Die Zahlung zusätzlicher Recherchengebühren erfolgte ohne Widerspruch.

WEITERE ANGABEN PCT/ISA/ 210

Fortsetzung von Feld I.2

Die geltenden Patentansprüche 1, 13, 14, 26 und 27 beziehen sich auf eine unverhältnismäßig große Zahl möglicher Verbindungen, von denen sich nur ein kleiner Anteil im Sinne von Art. 6 PCT auf die Beschreibung stützen und als im Sinne von Art.5 PCT in der Patentanmeldung offenbart gelten kann. Im vorliegenden Fall fehlt den Patentansprüchen die entsprechende Stütze und fehlt der Patentanmeldung die nötige Offenbarung in einem solchen Maße, daß eine sinnvolle Recherche über den gesamten erstrebten Schutzbereich unmöglich erscheint. Daher wurde die Recherche auf die Teile der Patentansprüche gerichtet, welche im o.a. Sinne als gestützt und offenbart erscheinen, nämlich die Verbindungen, wie sie in den Ausführungsbeispielen angegeben sind.

Der Anmelder wird darauf hingewiesen, daß Patentansprüche, oder Teile von Patentansprüchen, auf Erfindungen, für die kein internationaler Recherchenbericht erstellt wurde, normalerweise nicht Gegenstand einer internationalen vorläufigen Prüfung sein können (Regel 66.1(e) PCT). In seiner Eigenschaft als mit der internationalen vorläufigen Prüfung beauftragte Behörde wird das EPA also in der Regel keine vorläufige Prüfung für Gegenstände durchführen, zu denen keine Recherche vorliegt. Dies gilt auch für den Fall, daß die Patentansprüche nach Erhalt des internationalen Recherchenberichtes geändert wurden (Art. 19 PCT), oder für den Fall, daß der Anmelder im Zuge des Verfahrens gemäß Kapitel II PCT neue Patentansprüche vorlegt.

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen
PCT/EP 03/05529

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
DE 19947747 A	12-04-2001	DE 19947747 A1	12-04-2001
		AU 7907600 A	10-05-2001
		CA 2386381 A1	12-04-2001
		WO 0124783 A2	12-04-2001
		EP 1217998 A2	03-07-2002
		HU 0202776 A2	28-02-2003
		JP 2003510350 T	18-03-2003
		US 2003069314 A1	10-04-2003
US 5658908 A	19-08-1997	AT 237597 T	15-05-2003
		AU 675928 B2	27-02-1997
		AU 3457393 A	01-09-1993
		CA 2129046 A1	05-08-1993
		DE 69332882 D1	22-05-2003
		DK 649414 T3	11-08-2003
		EP 0649414 A1	26-04-1995
		WO 9315062 A1	05-08-1993
		IL 104582 A	30-10-1998
		JP 3109832 B2	20-11-2000
		JP 7503247 T	06-04-1995
		NZ 246916 A	27-08-1996
		US 5681830 A	28-10-1997
		US 5574159 A	12-11-1996
		US 5854249 A	29-12-1998
		US 2002052007 A1	02-05-2002
		ZA 9300717 A	02-08-1994
EP 1072260 A	31-01-2001	DE 19934523 A1	25-01-2001
		EP 1072260 A1	31-01-2001

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(54) Title: MODIFIED RELEASE, MULTIPLE UNIT DRUG DELIVERY SYSTEMS

(57) Abstract: The invention relates to novel modified release multiple unit systems, and methods of preparing these systems, which can be easily compressed into tablets or filled into capsules or sachets without affecting the desired release characteristics of the pharmaceutical active ingredients incorporated within the systems. The multiple unit tablet includes multiple units. Each unit includes at least one core having an outer surface, a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, one or more rate controlling polymers, and one or more one active pharmaceutical ingredients. The coating layer includes one or both of the one or more active pharmaceutical ingredients and the one or more rate controlling polymers. The tablet may further include an outer layer on the outer surface of the unit which includes a material that is one or both of elastic and compressible. The material may be a wax materials, such as polyethylene glycol's (PEGS).

MODIFIED RELEASE, MULTIPLE UNIT DRUG DELIVERY SYSTEMS

FIELD OF THE INVENTION

The technical field of the invention relates to modified release multiple unit systems, and methods of preparing these systems, which can be easily compressed into tablets or filled into capsules or sachets without affecting the desired release characteristics of the pharmaceutical active ingredients incorporated within the systems.

BACKGROUND OF THE INVENTION

The need to improve the clinical results of modified release formulations is well documented in the prior art. This is particularly important for drugs that have short half-lives, have region specific absorption, produce gastric irritation, or have other side effects at high plasma concentrations. One of the most common methods of achieving modified drug release involves the use of monolithic systems designed to have modified release characteristics. These monolithic systems vary from osmotic drug delivery systems to bioerodible or non-erodible matrix based systems.

Although a major portion of the modified release formulations currently prescribed are monolithic systems, they nonetheless suffer from a few serious drawbacks. Intentional or accidental breakdown of the delivery system is one of the limitations that may cause dose dumping. Dose dumping may lead to toxic or fatal effects, depending on the pharmaceutical compound. Further, the gastric emptying of the comparatively large monolithic systems is variable and is dependent on the presence or absence of food, as well as the type of food taken by the patient.

These disadvantages have prompted a shift in modified release technology from the use of monolithic systems to multiple unit systems, wherein each individual unit is formulated with modified release characteristics. The final dosage form consists of a collection of the multiple units, compressed into a tablet, or filled into a capsule or sachet. When administered, the individual units are dispersed freely into the gastrointestinal contents, avoiding the high local concentration of drug which may lead to irritation of gastrointestinal mucosa. Also, the performance of the dosage form is independent of inter- and intra-patient variability in gastric emptying time because of the small size of the individual units that make up the system. This technology has the added advantages of (1) allowing the production of numerous doses and strengths without the need for formulation

or process changes; (2) delivery of incompatible agents together in a single dosage form; and (3) delivery of particles or individual units that have different release characteristics to achieve desired release profile.

Each individual unit of the multiple unit system is either: (a) an inert core or pellet coated with one or more layers of drug and other release controlling polymeric substances; or (b) a drug-containing core or pellet optionally coated with one or more layers of release controlling polymeric substances.

A common problem with modified release, multiple unit systems is the rupturing or cracking of the release controlling layers or membrane of the core, or the fragmentation of the core, due to the mechanical stress generated during the compression of cores or individual units into a tablet or filling into a capsule or sachet. Various approaches are described in the prior art for formulating multiple unit systems with a desired mechanical strength. For example, U.S. Patent No. 4,713,248 discloses a water-based film comprising a homogenous combination of a water dispersible film forming agent and a polymeric substance that forms a film over a controlled release multiple unit formulation containing an active substance.

U.S. Patent No. 5,783,215 describes the use of inert and non-soluble cores of glass or sand particles and soluble cores, such as sugar spheres, which are capable of withstanding mechanical stress, in combination with a plasticizing layer of a hydrophilic polymer containing the drug, optionally with additional layers of the polymer not containing the drug, layered between the core and the release controlling membrane.

SUMMARY OF THE INVENTION

In one general aspect there is provided a multiple unit dosage form that includes multiple units. Each unit includes at least one core having an outer surface; a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, the coating layer including one or both of one or more active pharmaceutical ingredients and one or more rate controlling polymers; and an outer layer. The outer layer includes a material that is one or both of elastic and compressible.

Embodiments of the multiple unit dosage form may include one or more of the following features. For example, the core may include the one or more rate controlling polymers. The core may include the one or more active pharmaceutical ingredients. The

core may include the rate controlling polymer and the active pharmaceutical ingredient. The first coating layer may include the one or more active pharmaceutical ingredients.

The core may include one or more of sugar, a non-pareil seed, microcrystalline cellulose, celphere, sand silicon dioxide, glass, plastic, polystyrene, hydroxypropyl methylcellulose. The sugar may include one or more of glucose, mannitol, lactose, xylitol, dextrose, and sucrose. The core may include one or more of an insoluble material, a soluble material, and a swellable material.

The rate controlling polymer may include one or more of cellulosic polymers, methacrylic acid polymers, and waxes. The rate controlling polymer may include one or more of ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, and hydroxyethylcellulose, hydroxypropylmethyl phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

The one or more active pharmaceutical ingredients may include one or more of antidepressants, antidiabetics, antiulcers, analgesics, antihypertensives, antibiotics, antipsychotics, antineoplastics, antimuscarinics, diuretics, antimigraine agents, antivirals, anti-inflammatory agents, sedatives, antihistaminics, antiparasitic agents, antiepileptics and lipid lowering agents. The one or more active pharmaceutical ingredients may include one or more of enalapril, captopril, benazepril, lisinopril, ranitidine, famotidine, ranitidine bismuth citrate, diltiazem, propranolol, verapamil, nifedipine, acyclovir, ciprofloxacin, simvastatin, atorvastatin, lovastatin, venlafaxine, citalopram, paroxetine, selegiline, midazolam, fluoxetine, acarbose, buspirone, nimesulide, captopril, nabumetone, glimepiride, glipizide, etodolac, nefazodone and their pharmaceutically acceptable salts. The one or more active pharmaceutical ingredients may be one or both of glipizide and venlafaxine or their salts.

The multiple unit dosage form may further include one or more additional layers. The additional layers are positioned between (a) one or more of the core and the first coating layer and (b) surrounding at least a portion of the first coating layer. The one or more additional layers include one or more of a seal coat, a film forming layer, a rate controlling polymer, and an active pharmaceutical ingredient. The seal coat may be one or more of hydroxypropyl methylcellulose, polyvinyl pyrrolidone, and methacrylic acid

copolymers. The film forming layer may be one or more of ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimelliatate, cellulose acetate phthalate, waxes, polyethylene glycol, and methacrylic acid polymers.

The multiple unit dosage form may further include an outer layer on the outer surface of the unit and the outer surface includes a material that is one or both of elastic and compressible. The material in the outer layer may be one or more wax materials. The wax material may be one or more polyethylene glycols (PEGs). The PEGs may differ by molecular weight. The polyethylene glycol (PEG) may be one or more of PEG 600, PEG 4000, PEG 6000, PEG 8000, and PEG 20000. The waxy material may be from about 1% to about 15% by weight of the total tablet weight or from about 1% to about 100% by weight of the weight of the core and first coating layer. The waxy material may be applied to each unit as a solution, suspension, dispersion, or hot melt technique. The solution, suspension, or dispersion may be made using a solvent. The solvent may be one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, and water.

The active pharmaceutical ingredient may be glipizide and may be present in one or both of the core and the first coating layer. The multiple unit dosage form may further include a buffering agent with the glipizide in one or both of the core and the first coating layer. The buffering agent may be one or more of dibasic sodium phosphate, sodium ascorbate, meglumine, sodium citrate trimethanolamine, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonia, tertiary sodium phosphate, diethanolamine, ethylenediamine, and L-lysine.

In the multiple unit dosage form, one or more of the core and the first coating layer may include one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may include surfactants, binders, diluents, disintegrants, lubricants, glidants, plasticizers, stabilizers, and coloring agents. The surfactants may include one or more of a non-ionic surfactant, an ionic surfactant, mono fatty acid esters of polyoxyethylene sorbitan, polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20), an anionic surfactant, sodium lauryl sulfate, polyoxyethylene castor oil derivative, polyoxyethyleneglycerol triiricinoleate castor oil, polyoxyl 35 castor

oil, Cremophor EL, and Vitamin E TPGS, d-alpha-tocopheryl polyethylene glycol 1000 succinate, polyethoxylated fatty acids and their derivatives, polyethylene glycol 400 distearate, polyethylene glycol - 20 dioleate, polyethylene glycol 4–150 mono dilaurate, polyethylene glycol –20 glyceryl stearate, alcohol – oil transesterification products, polyethylene glycol – 6 corn oil, polyglycerized fatty acids, polyglyceryl – 6 pentaoleate, propylene glycol fatty acid esters, propylene glycol monocaprylate, mono and diglycerides, glyceryl ricinoleate, sterol and sterol derivatives, sorbitan fatty acid esters and their derivatives, polyethylene glycol – 20 sorbitan monooleate and sorbitan monolaurate, polyethylene glycol alkyl ether or phenols, polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol, sugar esters, sucrose monopalmitate, polyoxyethylene – polyoxypropylene block copolymers, poloxamer, sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, and palmitoyl carnitine.

The binders may include one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, and propylene glycol. The diluents may include one or more of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, and sugar confectioners. The disintegrants include one or more of starch, croscarmellose, crospovidone, and sodium starch glycolate. The lubricants and glidants include one or more of colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, and white beeswax. The plasticizers include one or more of polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate, and dibutyl sebacate. The stabilizers include one or more of antioxidants, buffers, and acids.

The multiple unit dosage form may further include one or more pharmaceutically acceptable excipients around the individual units. The dosage form may be a tablet and the tablet may be formed by application of a compressive force. The dosage form may be a capsule.

The active pharmaceutical ingredients of the multiple unit dosage form may be one or more of atorvastatin and amlodipine, metformin and glipizide, simvastatin and ramipril, simvastatin and amlodipine, metformin XL and glipizide XL, ramipril and atorvastatin, ramipril and amlodipine, metformin XL and glimiperide, fosinopril and amlodipine.

In another general aspect, there is provided a process for the preparation of a multiple unit dosage form. The process includes providing at least one core having an outer surface, forming a coated core by applying one or more coating layers to the core such that the one or more coating layers surround at least a portion of the outer surface of the core or the coating layers, forming an individual unit by applying a waxy material to the coated core to form a wax layer, and combining one or more units to form a multiple unit dosage form. One or both of the core and the coating layers includes one or more rate controlling polymers and active pharmaceutical ingredients.

Embodiments of the process may include one or more of the following features. For example, the process may further include applying one or both of a seal layer or a film forming layer between the core and the coating layer, between the one or more coating layers, and between the one or more coating layers and the wax layer. The waxy material may be one or more polyethylene glycols (PEGs) of one or more molecular weights. The polyethylene glycols (PEG) may be one or more of PEG 600, PEG 4000, PEG 6000, PEG 8000, and PEG 20000. The waxy material may be from about 1% to about 15% by weight of the total tablet weight. The waxy material may be from about 1% to about 100% by weight of the weight of the core and the one or more coating layers.

Applying the waxy material may include applying a coating of a solid waxy material by using a hot melt technique. Applying the waxy material may include applying a coating of waxy material by using as one or more of a solution, a suspension, and a dispersion. The solution or the suspension may be prepared in a solvent. The solvent may be selected from one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, and water.

The core may be an inert core. The core may include one or more pharmaceutically acceptable excipients. The core may include one or more active pharmaceutical ingredients. The one or more active pharmaceutical ingredients may be one or more of antidepressants, antidiabetics, antiulcers, analgesics, antihypertensives,

antibiotics, antipsychotics, antineoplastics, antimuscarinics, diuretics, antimigraine agents, antivirals, anti-inflammatory agents, sedatives, antihistaminics, antiparasitic agents, antiepileptics and lipid lowering agents. The one or more active pharmaceutical ingredients may be one or more of enalapril, captopril, benazepril, lisinopril, ranitidine, famotidine, ranitidine bismuth citrate, diltiazem, propranolol, verapamil, nifedipine, acyclovir, ciprofloxacin, simvastatin, atorvastatin, lovastatin, venlafaxine, citalopram, paroxetine, selegiline, midazolam, fluoxetine, acarbose, buspirone, nimesulide, captopril, nabumetone, glimepiride, glipizide, etodolac, nefazodone and their pharmaceutically acceptable salts. In particular, the active pharmaceutical ingredient may be venlafaxine or glipizide.

The core may be prepared by extrusion-spheronization. The extrusion-spheronization process may include granulating an inert core material with or without other pharmaceutical excipients with a binder solution to form a wet mass, passing the wet mass through an extruder to form extrudates, and spheronizing the extrudates. The core may be prepared by granulation. The granulation process may include wetting a dry mix of core material with or without other pharmaceutical excipients with a binder solution.

The units may be prepared by coating the cores with active pharmaceutical ingredients and rate controlling polymers. The units may be prepared by coating cores with a first layer comprising an active pharmaceutical ingredient and a second outer layer comprising a rate controlling polymer.

The process may further include applying a seal coat or a film forming layer between the core and the subsequent layers. The process may further include applying a seal coat or a film forming layer between a layer comprising an active pharmaceutical ingredient and a layer comprising a release rate controlling polymer

The rate controlling polymer may include one or more of cellulosic polymers, methacrylic acid polymers, and waxes. The rate controlling polymer may be one or more of ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethyl phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

In another general aspect, a method for preparing a modified release multiple unit dosage form includes providing a core having a coating, forming individual units by coating the coated core with a coating material that is one or both of compressible and elastic, and forming the dosage form by combining one or more individual units. One or both of the core and the coating may be one or more rate controlling polymers and one or more active pharmaceutical ingredients.

Embodiments of the method of preparing a modified release multiple unit dosage form may include one or more of the following features, including any one or more of the features described above. For example, the coating material may be a waxy material. The coating material may be a polyethylene glycol. Combining one or more individual units may include filling the individual units into a capsule or sachet or compressing the individual units into a tablet.

In another general aspect, a method of treating a medical condition includes administering a multiple unit tablet for oral ingestion. Each unit includes a core, one or more layers surrounding the core, and an outer layer. The core includes one or more of a pharmaceutically acceptable excipient, an active pharmaceutical ingredient, and a rate controlling polymer. The one or more layers includes one or more of a pharmaceutically acceptable excipient, an active pharmaceutical ingredient, a rate controlling polymer, a sealing layer, and a film forming layer. The outer layer includes a material that is one or both of compressible or elastic to partially or completely absorb a compressive force exerted in combining the units.

Embodiments of the method of treating a medical condition may include one or more of the following features, including any one or more of the features described above. For example, the material of the outer layer may be a waxy material. The waxy material may be one or more polyethylene glycols of different molecular weights.

In another general aspect, a combination drug, multiple unit dosage form includes first units and second units. Each first unit includes at least one core having an outer surface, a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, and an outer layer surrounding at least a portion of an outer surface of the first coating layer, the first coating layer including a first active pharmaceutical ingredient. Each second unit includes at least one core having an outer

surface, a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, and an outer layer surrounding at least a portion of an outer surface of the first coating layer, the first coating layer including a second active pharmaceutical ingredient. One or both of the cores and the coating layers may include the rate controlling polymer. One or both of the outer layers may include a waxy material.

Embodiments of the combination drug, multiple unit dosage form may include one or more of the following features, including any one or more of the features described above. For example, waxy material may include one or more polyethylene glycols.

In another general aspect, a multiple unit dosage form includes multiple units. Each unit includes at least one core having an outer surface and comprising one or more one active pharmaceutical ingredients; and a coating layer surrounding at least a portion of the outer surface of the core, having an outer surface and comprising a waxy material.

Embodiments of the dosage form may include one or more of the following features. For example, the waxy material may be one or more polyethylene glycols of different molecular weights. The dosage form may be a tablet or a capsule.

In another general aspect, a multiple unit dosage form includes multiple units. Each unit includes at least one core having an outer surface and a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface. The coating layer includes glipizide or its pharmaceutically acceptable salt and optionally one or more rate controlling polymers.

In one embodiment, the pharmaceutically acceptable salt comprises one or more of mineral acid salts, organic acid salts, and organosulphonic acid salts.

In another general aspect, a modified release multiple unit system includes units of glipizide. The units include an inert core; a drug layer surrounding the inert core, the drug layer including glipizide; and a rate controlling polymer layer surrounding the drug layer.

Embodiments of the modified release multiple unit system may include one or more of the following features. For example, the system may be a tablet or a capsule.

In another general aspect, a modified release multiple unit system includes units of glipizide. The units include an inert core; a drug layer surrounding the inert core; a rate

controlling polymer layer surrounding the drug layer; and a waxy layer surrounding the drug layer.

Embodiments of the modified release multiple unit system may include one or more of the following features. For example, the system may be a tablet or a capsule. The units can be compressed into tablet, or filled into a capsule or a sachet; without affecting the desired release characteristics of drug.

In another general aspect, a modified release multiple unit system includes units of venlafaxine. The units include an inert core; a drug layer surrounding the inert core; and a rate controlling polymer layer surrounding the drug layer.

Embodiments of the modified release multiple unit system may include one or moreof the following features. For example, the system may be a tablet. The units can be compressed into tablet without affecting the desired release characteristics of drug.

In another general aspect, a modified release multiple unit system includes units of venlafaxine. The units include an inert core; a drug layer surrounding the inert core; a rate controlling polymer layer surrounding the drug layer; and a waxy layer surrounding the rate controlling polymer layer.

Embodiments of the modified release multiple unit system may include one or more of the following features. For example, the system may be a tablet. The units can be compressed into tablet without affecting the desired release characteristics of the venlafaxine.

In another general aspect, a modified release multiple unit system comprises units of a drug. The units include an inert core; a drug layer surrounding the inert core; a rate controlling polymer layer surrounding the drug layer; and a waxy layer surrounding the rate controlling polymer layer.

Embodiments of the modified release multiple unit system may include one or more of the following features. For example, the system may be compressed into tablet, or filled in capsule or sachet without affecting the desired release characteristics of drug.

In another general aspect, a process for the preparation of a modified release multiple unit system of a drug includes the steps of coating inert pellets with a drug and

rate controlling polymer layer; coating with a waxy layer; optionally blending with pharmaceutically acceptable excipients; compressing into a tablet, or filling into a capsule or a sachet of suitable size.

In another general aspect, a process for the preparation of a modified release multiple unit system of drug includes the steps of coating inert pellets with a drug and rate controlling polymer layer; coating with a waxy layer; optionally blending with pharmaceutically acceptable excipients; and compressing into tablet of suitable size.

Embodiments of the modified release multiple unit system may include one or more of the following features. For example, the drug may be venlafaxine or a pharmaceutically acceptable salt.

In another general aspect, a process for the preparation of modified release multiple unit system of drug includes the steps of coating drug containing cores with a rate controlling polymer layer; coating the rate controlling polymer layer with a waxy layer; optionally blending with pharmaceutically acceptable excipients; and compressing into a tablet, or filling into a capsule or a sachet of suitable size.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and claims.

DETAILED DESCRIPTION OF THE INVENTION

As described above with respect to the difficulties associated with prior art compositions, there exists a need for universally applicable, multiple unit dosage form or systems of desired mechanical strength. The difficulties in the prior art are believed to be addressed by the techniques, compositions, and concepts described herein for a modified release, multiple unit system that can be easily compressed into a tablet or filled into a capsule or sachet without affecting the desired release characteristics of the drug. To address the above described problems of the prior art associated with mechanical stress due to compression or filling, the inventors have found that there are benefits to providing an outermost coating of a waxy material to each unit of the multiple unit systems. The inventors have found that the application of a coating of waxy material to each unit provides favorable mechanical properties that withstand cracking. Specifically, the coating of waxy material withstands cracking of the release controlling membrane when

exposed to mechanical stress, for example, during compression into a tablet or filling into a capsule or sachet.

The inventors have applied the multiple unit dosage form or system techniques, compositions, and concepts to active pharmaceutical ingredients, including venlafaxine and glipizide. In so doing, the inventors have developed separate multiple unit dosage form or systems of venlafaxine and glipizide that are in the form of controlled release tablets in which the waxy layer is an optional component. These venlafaxine and glipizide controlled release, multiple unit tablets that include coated pellets of venlafaxine or glipizide, respectively, overcome the known problem of limited dosing associated with capsules. The term "controlled release" as used herein includes any type of modified release such as prolonged release, delayed release, sustained release, extended release and the like.

The waxy coating imparts a certain degree of elasticity or compressibility to the units and makes possible the compression of the multiple units into tablets or filling into capsules or sachets without altering the dissolution profile and hence the bioavailability and desired clinical effects. Further, this approach can be used over any types of pre-functional layers and irrespective of drug characteristics. Hence, the waxy coating provides a method for the preparation of modified or controlled release, multiple unit dosage forms or systems that include a final or outer coating of a waxy material and these units can be easily compressed into tablets, or filled into capsules or sachets without affecting the desired release characteristics of drug (e.g., dissolution profile, bioavailability, and clinical effects). In particular, the waxy layer can protect the release control polymer layer from cracking during compression, for example, during the production of tablets.

In general, the multiple units can be for use in any dosage forms, such as a tablet, capsule or sachet, and include a core or pellet, one or more layers around the pellet, and an outer waxy layer. The core or pellet can be entirely or partially an active pharmaceutical ingredient or an inert material, or a combination of both. The layers around the core may include one or more release or rate controlling polymers and/or active pharmaceutical ingredients. The layers also may be in the form of sealing or film forming layers around or between the polymer and active pharmaceutical ingredients. The various layers and

core may optionally contain pharmaceutically acceptable excipients. The outer waxy layer may consist entirely of a waxy material or may be a mixture of a waxy material and one or more pharmaceutically acceptable functional excipients.

The multiple units of the improved multiple unit systems may contain (1) inert pellets or cores or (2) drug containing pellets or cores in which the drug is incorporated within the pellets or cores. Cores and pellets generally are used interchangeably herein. The inert core of the improved multiple unit systems is either a commercially available product or prepared in the laboratory. The inert core may be of any geometric shape, although spherical beads have the advantage of providing ease of uniform coating. The bead diameter may vary from about 50 μm to 700 μm. The pellet weight may vary from about 3% to about 40% by weight of the total tablet weight.

The commercially available inert cores include sugar spheres, non pariel seeds, celpheres and the like. The laboratory or otherwise manufactured cores may be prepared according to any suitable method including:

a. Extrusion-Spheronization: The inert core material with or without drug and other pharmaceutical excipients is granulated by addition of a binder solution. The wet mass is passed through an extruder equipped with a screen. The extrudates are spheronized in a marumerizer. The resulting spheroids or pellets are dried and sieved for further applications.

b. Granulation: The inert core material with or without drug and other pharmaceutical excipients is dry-mixed and then the mixture is wetted by addition of a binder solution in a high shear-granulator/mixer. The granules are kneaded after wetting by the combined actions of mixing and milling. The resulting granules or pellets are dried and sieved for further applications.

The material from which the inert pellet or core is prepared may be selected from one or more of pharmaceutically inert insoluble, soluble, and/or swellable materials, with or without pharmaceutically acceptable excipients. The insoluble inert core material may be, for example, one or more of sand (silicon dioxide), glass, microcrystalline cellulose (e.g., celpheres) or plastic (e.g., polystyrene) material. The soluble inert core material may be, for example, one or more sugar such as glucose, mannitol, lactose, xylitol, dextrose,

sucrose, and the like. The swellable inert core material may be, for example, hydroxypropyl methylcellulose or a similar material. The core also can be a combination of two or more of these three general types of core materials.

Alternatively, drug-containing cores can also be prepared by completely or partially replacing the inert core material with one or more active pharmaceutical ingredients in the above two methods of preparing inert cores.

The improved, modified release multiple units may be prepared from inert cores by (a) coating the inert core with one or more drug and rate controlling polymer layers; or (b) coating the inert core with one or more drug layers and rate controlling polymer layers separately. Both of these options may contain a seal or film coat between the inert core and the drug layer and/or between the drug layer and the rate controlling polymer layer.

The improved, modified release multiple units also may be prepared from drug containing cores by (a) coating drug containing cores with rate controlling polymer; or (b) coating drug containing cores with drug and rate controlling polymer. Both of these options may contain a seal or film coat between the drug containing core and the polymer layer and/or over the polymer layer. The seal or film coat layer also can be formed between the drug containing core and the drug/polymer layer and/or over the drug/polymer layer.

The improved, modified release units are further processed by applying a final layer of a waxy material over each unit prepared by the above processes. Although the application of this waxy layer is the general rule, the inventors nonetheless have successfully formed tables from multiple units without the waxy layer. This may be dependent on, for example, the active pharmaceutical ingredient of the tablet.

The modified release units prepared by any of the above methods can be mixed with other pharmaceutically acceptable excipients, to the extent required or desired, and compressed into tablets or filled into capsules and sachets using techniques known in the art for these purposes. The final tablets or capsules may optionally be coated, if desired.

The drug layer of the improved multiple unit tablet includes one or more active pharmaceutical ingredients, and optionally includes other pharmaceutically acceptable excipients. The drug layer may be applied as an aqueous or non-aqueous solution or

dispersion of drug in water or organic solvent, or mixtures thereof. The one or more drugs may be selected from, for example, one or more of antidepressants, antidiabetics, antiulcers, analgesics, antihypertensives, antibiotics, antipsychotics, antineoplastics, antimuscarinics, diuretics, antimigraine agents, antivirals, anti-inflammatory agents, sedatives, antihistaminics, antiparasitic agents, antiepileptics and lipid lowering agents.

Illustrative examples of drugs of the above classes include enalapril, captopril, benazepril, lisinopril, ranitidine, famotidine, ranitidine bismuth citrate, diltiazem, propranolol, verapamil, nifedipine, acyclovir, ciprofloxacin, simvastatin, atorvastatin, lovastatin, venlafaxine, citalopram, paroxetine, selegiline, midazolam, fluoxetine, acarbose, buspirone, nimesulide, captopril, nabumetone, glimepiride, glipizide, etodolac, nefazodone and their pharmaceutically acceptable salts.

The rate controlling polymer layer includes one or more polymers with or without other pharmaceutically acceptable excipients. This layer may be applied as an aqueous or non-aqueous solution or dispersion of polymers in a water or organic solvent. Suitable rate controlling polymers include one or more of cellulosic polymers such as ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, and hydroxyethylcellulose; waxes; hydroxypropylmethyl phthalate; cellulose acetate phthalate; cellulose acetate trimellitate; and methacrylic acid polymers such as Eudragit ® RL and RS. The single drug and rate controlling layer may contain the above described drug and polymers in the same layer. Based on the desired release profile, the controlled release polymer layer weight may constitute from about 5% to about 75% of the total tablet weight.

The waxy material may be selected from, for example, a range of polyethylene glycols (PEGs) of various molecular weights, such as PEG 600, PEG 4000, PEG 6000, PEG 8000, PEG 20000 and the like. In general, the waxy material should be at least of approximately as compressible or elastic as PEG. The waxy material layer may constitute, for example, from about 1% to about 15% by weight of the total tablet weight, although the amount may be varied up or down if necessary. The amount of the waxy material may vary from about 1% to about 100% by weight of the weight of the core and coating layer or one or more coating layers. The waxy layer is applied as a solution or suspension using any conventional coating technique known in the art, including spray

coating in a conventional coating pan or fluidized bed processor, dip coating of each unit of a multiple unit system, or using a hot melt technique.

The solvents used for making a solution, dispersion, or suspension of the waxy material may be selected from, for example, one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, and water. In general, the solvent should adequately dissolve, disperse, or suspend whichever waxy material or materials is selected.

The seal coat may include suitable polymers, such as hydroxypropyl methylcellulose, polyvinyl pyrrolidone, methacrylic acid copolymers and the like. The film forming coat or agents may include one or more of ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimelliatate, cellulose acetate phthalate, waxes such as polyethylene glycol, and methacrylic acid polymers such as Eudragit® RL and RS. Alternatively, the film forming layer or agents may be commercially available coating compositions including film-forming polymers marketed under various trade names, such as Opadry®. Film forming layers generally are provided for achieving a smooth surface and better appearance. Seal layer generally are applied to separate two incompatible layers, provide protection from moisture, etc. In general, the film forming layers and the seal layers may be the same or similar polymers used in different combinations or concentrations.

The other pharmaceutically acceptable excipients as used herein include surfactants, binders, diluents, disintegrants, lubricants, glidants, plasticizers, stabilizers and coloring agents.

Suitable surfactants include one or more of non-ionic and ionic (i.e., cationic, anionic and Zwitterionic) surfactants suitable for use in pharmaceutical compositions. For example, suitable surfactants include non-ionic surfactants such as mono fatty acid esters of polyoxyethylene sorbitan (e.g., polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20)); anionic surfactants (e.g., sodium lauryl sulfate); polyoxyethylene castor oil derivatives (e.g., polyoxyethyleneglycerol triiricinoleate or polyoxyl 35 castor oil (Cremophor EL)); and Vitamin E TPGS (d-alpha-tocopheryl

polyethylene glycol 1000 succinate). Other suitable surfactants include polyethoxylated fatty acids and their derivatives (e.g., polyethylene glycol 400 distearate, polyethylene glycol - 20 dioleate, polyethylene glycol 4–150 mono dilaurate, and polyethylene glycol – 20 glyceryl stearate); alcohol – oil transesterification products (e.g., polyethylene glycol – 6 corn oil); polyglycerized fatty acids (e.g., polyglyceryl – 6 pentaoleate); propylene glycol fatty acid esters (e.g., propylene glycol monocaprylate); mono and diglycerides (e.g., glyceryl ricinoleate); sterol and sterol derivatives; sorbitan fatty acid esters and their derivatives (e.g., polyethylene glycol – 20 sorbitan monooleate and sorbitan monolaurate); polyethylene glycol alkyl ether or phenols (e.g., polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol); sugar esters (e.g., sucrose monopalmitate; polyoxyethylene – polyoxypropylene block copolymers known as "poloxamer"); and ionic surfactants (e.g., sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, and palmitoyl carnitine).

Suitable binders include one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Suitable diluents include one or more of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners and mixtures thereof.

Suitable disintegrants include one or more of starch, croscarmellose, crospovidone, sodium starch glycolate and the like. Suitable lubricants and glidants include one or more of colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax and the like. Suitable plasticizers include one or more of polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate, dibutyl sebacate and the like. Suitable stabilizers include one or more of antioxidants, buffers, acids and the like. Suitable coloring agents include any FDA approved colors for oral use.

The improved multiple unit systems described herein can be applied to most classes of drugs and most individual drugs. For example, two particular drugs that would benefit from an improved modified release multiple unit system are venlafaxine and glipizide. Venlafaxine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and is a weak inhibitor of dopamine reuptake. It is widely indicated for the treatment of depression and generalized anxiety disorder. The term "venlafaxine" as used herein includes venlafaxine base as well as any pharmaceutically acceptable salt thereof. Examples of pharmaceutically acceptable venlafaxine salts include venlafaxine hydrochloride. The venlafaxine layer weight may constitute from about 15% to about 75% of the total tablet weight.

Venlafaxine has been administered in the form of immediate release compressed tablets in doses ranging from 75 to 350 mg/day, in divided doses, two to three times a day. Such therapeutic dosing leads to wide fluctuations in the blood plasma levels of venlafaxine, with high concentrations at one extreme leading to severe side effects, such as nausea and/or vomiting shortly after administration, and less than therapeutic levels at the other extreme. Moreover, requiring frequent administration of the drug (e.g., two to three doses per day) is associated with patient non-compliance. Most of these problems associated with frequent dosing can be overcome by formulating controlled or extended release dosage forms of venlafaxine.

Venlafaxine hydrochloride is available as an extended release, once per day capsule which is marketed by Wyeth under the trade name Effexor® XR. This capsule appears to be described in U.S. Patent No. 6,274,171, which discloses an extended release formulation of venlafaxine hydrochloride that includes spheroids of venlafaxine hydrochloride, microcrystalline cellulose, and optional hydroxypropyl methylcellulose coated with a mixture of ethylcellulose and hydroxypropyl methylcellulose. These film-coated spheroids are filled into capsules. However, these capsules suffer from a limitation that only a small number of coated beads or pellets can be put into a capsule of appropriate size that is convenient to swallow. Hence, there still exists a need for better controlled-release dosage forms of venlafaxine hydrochloride.

Glipizide is an oral blood glucose-lowering drug and is indicated as an adjunct to diet for the control of hyperglycemia and its associated symptoms in patients with non-

insulin dependent diabetes mellitus. Glipizide stimulates secretion of insulin from the beta cells of pancreatic islet tissue and also exhibits extra-pancreatic action, including the ability to increase the number of insulin receptors. Chemically, glipizide is N-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl] ethyl]-5-methylpyrazine carboxamide. Glipizide is a white, odorless powder with a pKa of 5.9, and is insoluble in both water and alcohol. These physicochemical properties of glipizide demand special techniques to formulate a dosage form that can be used to administer the drug at a controlled and predetermined rate.

Glipizide is available in the form of extended release oral tablets from Pfizer and is marketed under the trade name Glucotrol® XL. The extended release tablets are an osmotic drug delivery device that is based on push-pull technology. The delivery device includes a bi-layered core tablet that is coated with a semipermeable membrane having an orifice drilled on the coat for release of glipizide. The bilayered core tablet consists of a glipizide layer and a push layer of swellable polymers. When placed in dissolution media or gastrointestinal fluid, the device absorbs water through the semipermeable membrane, which leads to a swelling of the polymers in the push layer. This exerts a physical force on the drug layer forcing it out of the device through the orifice.

The glipizide layer of the pellets includes glipizide with or without other one or more of the pharmaceutically inert excipients described above. Optionally, this layer also may contain buffering agents. Buffers are used to maintain the pH of the glipizide layer and/or local environment surrounding the controlled release particles above to thereby aid in dissolution of glipizide in the dissolution media or gastrointestinal fluids. The buffering agents may be applied as an aqueous or non-aqueous solution or dispersion of drug in water/organic solvent, or mixtures thereof. Suitable buffering agents include one or more of dibasic sodium phosphate, sodium ascorbate, meglumine, sodium citrate trimethanolamine, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonia, tertiary sodium phosphate, diethanolamine, ethylenediamine, and L-lysine.

The inventors have developed improved multiple unit, controlled release tablets of venlafaxine that advantageously (1) can be administered in one half tablet or one half dosage and (2) can be prepared with a large amount of drug by compressing into a tablet

of acceptable size that is easy to swallow. When administered, the controlled release tablet disintegrates rapidly into individual coated pellets of venlafaxine, which are dispersed into gastric fluid. Venlafaxine then is released in a controlled manner over a prolonged period of time from the individual coated pellets. Use of small controlled release coated pellets (i.e., units) decreases the chances of dose dumping and the performance of the units is also largely independent of gastric emptying time.

The improved multiple unit, controlled release tablet of venlafaxine can be prepared by processes known in the relevant art, e.g., comminuting, mixing, granulating, sizing, filling, molding, spraying, immersing, coating, compressing, etc.

In one of the embodiments, improved, multiple unit, controlled release tablets of venlafaxine can be prepared by coating inert pellets or cores with one or more venlafaxine layers which are further coated with a controlled release polymer layer. Optionally, the controlled release layer and/or venlafaxine layer may also be coated with a waxy layer to form the individual units. Further, these coated pellets or cores, or the units, may be blended with pharmaceutically acceptable excipients and compressed into suitably sized, multiple unit tablets.

Alternatively, the improved, multiple unit, controlled release tablets of venlafaxine can be prepared by coating inert pellets or cores with a single layer of venlafaxine and controlled release polymer. Optionally, the single layer of venlafaxine and polymer may be coated with a waxy layer to form the individual units. Further, these coated pellets or cores, or the units, may be blended with pharmaceutically acceptable excipients and compressed into suitably sized, multiple unit tablets.

The coating layers over the inert pellets or cores, or over the tablet, may be applied as a solution or dispersion of coating ingredients using any conventional technique known in the prior art, such as spray coating in a conventional coating pan or fluidized bed processor, dip coating, and the like. Alternatively, the layers over the inert pellet or core may be applied using a hot melt technique.

Optionally, the pellets or cores may be coated with one or more additional layers comprising film forming or sealing agents and/or pharmaceutically acceptable excipients between the above layers, over any of the layers, or over the inert pellet or core. The

multiple unit tablets also may be further coated, if desired. Optionally, these additional coating layers over the tablet may comprise the active pharmaceutical ingredient (e.g., venlafaxine, glipizide) for immediate release. These layers may comprise film forming or sealing agents with or without other pharmaceutically acceptable excipients.

The improved, multiple unit systems described above are further illustrated by the following examples. Although these examples are illustrative of the techniques, compositions, and concepts described herein, they are not intended to be limiting.

EXAMPLE 1

(A) Modified release multiple units:

	Example 1 (wt/tablet) mg
Inert Core	
Non pariel seeds	65
Drug Layer	
Venlafaxine hydrochloride	171 (equivalent to 150 mg of venlafaxine)
Magnesium stearate	15
Colloidal silica	25
Hydroxypropyl methylcellulose	15
Water	q.s
Rate controlling layer	
Ethyl cellulose	93.12
Hydroxypropyl methylcellulose	23.28
Triacetin	1% of total polymers
Wax layer	
Polyethylene glycol 6000	30.55

Procedure:

1. Venlafaxine was dissolved in water and colloidal silica and then magnesium stearate and hydroxypropyl methylcellulose were added under stirring.
2. Non-pareil seeds were loaded in a Glatt Wurster column and coated with the drug dispersion of Step 1.
3. The drug coated pellets of Step 2 were coated with a mixture of ethyl cellulose and hydroxypropyl methylcellulose dissolved in a mixture of isopropyl alcohol and methylene chloride.

4. The coated pellets of Step 3 then were coated with a solution of PEG 6000 in methylene chloride.

(B) Compressed tablet:

Ingredient	Example 1 (wt/tablet) mg
Modified release multiple units of (A)	438
Silicified microcrystalline cellulose	217
PEG 4000	80
Crospovidone	90
Magnesium Stearate	5

Procedure: The modified release multiple units of (A) were mixed with other excipients and compressed to form tablets.

The compressed tablets prepared according to Example 1 had an acceptable hardness of about 7-13 Kp and disintegration times of about five minutes. Table 1 illustrates the comparative release patterns *in vitro* for modified release multiple units and tablets prepared according to Example 1.

Table 1. Comparative *in vitro* release patterns of modified release multiple units and tablets using USP apparatus – II, at 50 rpm and pH 6.8.

Time (Hours)	Cumulative percentage release of venlafaxine	
	Modified release multiple units	Tablets
1	14	17
2	32	33
4	59	57
6	72	69
8	82	79
12	94	91
16	100	97
20	100	100

As shown in Table 1, the compression of modified release multiple units into tablets did not alter the sustained release pattern of venlafaxine.

EXAMPLE 2

(A) Modified release multiple units:

	Example 2 (wt/tablet) mg
Inert Core	
Non pariel seeds	65
Drug Layer	
Venlafaxine hydrochloride	171 (equivalent to 150 mg of venlafaxine)
Magnesium stearate	13.5
Colloidal silica	19.7
Hydroxypropyl methylcellulose	13.5
Water	q.s
Rate controlling layer	
Ethyl cellulose	93
Hydroxypropyl methylcellulose	24
Triacetin	1% of total polymers
Wax layer	
Polyethylene glycol 6000	30

Procedure:

1. Venlafaxine was dissolved in water and colloidal silica and then magnesium stearate and hydroxypropyl methylcellulose were added under stirring.
2. Non-pareil seeds were loaded in a Glatt Wurster column and coated with the drug dispersion of Step 1.
3. The drug coated pellets of Step 2 were coated with a mixture of ethyl cellulose and hydroxypropyl methylcellulose that was dissolved in a mixture of isopropyl alcohol and methylene chloride.

4. The coated pellets of Step 3 then were coated with a solution of PEG 6000 in methylene chloride.

(B) Compressed tablet:

Ingredient	Example 2 (wt/tablet) mg
Modified release multiple units of (A)	473
Silicified microcrystalline cellulose	288
PEG 6000	71
Crospovidone	102
Magnesium Stearate	6

Procedure: The modified release multiple units of A were mixed with other excipients and compressed to form tablets.

The compressed tablets prepared according to Example 2 had an acceptable hardness of about 7-13 Kp and disintegration times of about five minutes. Table 2 illustrates the comparative release patterns *in vitro* for modified release multiple units and tablets prepared according to Example 2.

Table 2. Comparative *in vitro* release patterns of modified release multiple units and tablets using USP apparatus – II, at 50 rpm and pH 6.8.

Time (Hours)	Cumulative percentage release of venlafaxine	
	Modified release multiple units	Tablets
1	7	7
2	18	20
4	43	44
8	65	71
12	75	80

As shown in Table 2, the compression of modified release multiple units into tablets did

not alter the sustained release pattern of venlafaxine.

EXAMPLE 3

(A) Modified release multiple units:

	Example 3 (wt/tablet) mg
Inert Core	
Celpheres	148
Drug Layer	
Glipizide	10
Polyethylene glycol	4.7
Hydroxypropyl methylcellulose	1.7
Polyvinyl pyrrolidone	3.0
Tween 80	0.5
Lactose	3.0
Rate controlling layer	
Ethyl cellulose	8
Hydroxypropyl methylcellulose	4
Triacetin	1.3
Talc	0.4
Wax layer	
Polyethylene glycol 6000	13.9

Procedure:

1. Polyethylene glycol, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, Tween and lactose were dissolved in water and glipizide then was dispersed in the solution.
2. Celpheres were loaded in a Glatt Wurster column and coated with the drug dispersion

of Step 1.

3. A solution of ethyl cellulose, hydroxypropyl methylcellulose and triacetin was prepared in a mixture of methylene chloride and isopropyl alcohol into which talc was dispersed.
4. The drug loaded pellets of Step 2 then were coated with the dispersion of Step 3 using a Glatt Wurster column.
5. The coated pellets of Step 4 then were coated with a solution of PEG 6000 in mixture of isopropyl alcohol and methylene chloride.

(B) Compressed tablet:

Ingredient	**Example 3 (wt/tablet) mg**
Modified release multiple units of (A)	197.4
Silicified microcrystalline cellulose	122.4
PEG 6000	29.6
Crospovidone	43.4
Magnesium Stearate	2.0

Procedure: The modified release multiple units of (A) were mixed with other excipients and compressed to form tablet

The compressed tablets prepared according to Example 3 had an acceptable hardness of about 8-10 Kp and disintegration time of about three minutes. Tables 3a and 3b illustrate the comparative release patterns *in vitro* for modified release multiple units and tablets, respectively, prepared according to Example 3.

Table 3a. *In vitro* release pattern of modified release multiple units using USP apparatus – II, at 50 rpm and pH 7.5

Time (Hours)	Cumulative percentage release of glipizide from modified release multiple units
1	6
2	13
4	23
8	45
12	62
16	78
20	94
24	102

Table 3b. *In vitro* release pattern of tablets using USP apparatus – II, at 50 rpm and pH 7.5

Time (Hours)	Cumulative percentage release of glipizide from tablets
0.3	3
2.3	18
6.3	44
10.3	65
14.3	83
18.3	100
22.3	107

As shown in Tables 3a and 3b above, the compression of modified release multiple units into tablets did not alter the sustained release pattern of glipizide.

The above examples illustrate that the techniques, compositions, and concepts described herein can provide modified release multiple unit systems that can withstand the mechanical stresses of tablet formation without affecting the desired release characteristics.

EXAMPLES 4-7

Additional formulations of controlled release tablets of venlafaxine prepared according to the compositions of Examples 4-7 are provided in Tables 4 and 5

Table 4. Composition of coated pellets

	Example 4 (wt/tablet) mg	Example 5 (wt/tablet) mg	Example 6 (wt/tablet) mg	Example 7 (wt/tablet) mg
Inert pellets				
Non pariel seeds	65	65	65	65
Venlafaxine layer				
Venlafaxine hydrochloride	171	171	171	171
Magnesium stearate	13.5	13.5	13.55	13.55
Colloidal silica	19.7	19.7	19.70	19.70
Hydroxypropyl methyl cellulose	13.5	13.5	13.55	13.55
Water	q.s	q.s	q.s	q.s
Controlled release polymer layer				
Ethyl cellulose	81.42	91.61	101.77	110.84
Hydroxypropyl methylcellulose	20.35	22.89	25.44	27.68
Triacetin	1.01	1.14	1.27	1.38
Waxy layer				
Polyethylene glycol 6000	28.8	30	30.72	33.27

Procedure:

1. A solution of venlafaxine hydrochloride was prepared in water. Colloidal silica, magnesium stearate and hydroxypropyl methylcellulose were added to the solution under stirring to form a uniform dispersion.
2. Non pareil seeds were loaded in a Glatt Wurster column and coated with the drug

dispersion of Step 1.

3. The venlafaxine coated pellets of Step 2 then were coated with a solution of ethyl cellulose and hydroxypropyl methylcellulose that was dissolved in a mixture of isopropyl alcohol and methylene chloride.
4. The coated pellets of Step 3 then were coated with a solution of Polyethylene glycol 6000 in isopropyl alcohol and methylene chloride.

Table 5. Composition of controlled release venlafaxine tablets

Ingredient	Example 4 (wt/tablet) mg	Example 5 (wt/tablet) mg	Example 6 (wt/tablet) mg	Example 7 (wt/tablet) mg
Coated Pellets	459	473	450	465
Silicified microcrystalline cellulose	288	288	276	285
Polyethylene glycol 6000	70	71	85	89
Crospovidone	102	102	98	100
Magnesium Stearate	6	6	6	6

Procedure:

The coated pellets were blended with silicified microcrystalline cellulose, polyethylene glycol 6000, and crospovidone; lubricated with magnesium stearate; and compressed into suitably sized tablets.

***In vitro* dissolution study**

The *in vitro* release of venlafaxine hydrochloride from controlled release tablets made according to the compositions of Examples 4-7 was studied in 900 ml of phosphate buffer (pH–6.8) using USP apparatus – II, at 50 rpm. The results of this testing are listed in Table 6.

Table 6: *In vitro* release of venlafaxine hydrochloride from controlled release tablets

Time (Hours)	Cumulative percentage (%) release of venlafaxine from tablets			
	Example 4	Example 5	Example 6	Example 7
1	7	7	4	3
2	24	20	12	11
4	51	44	34	30
8	79	71	57	53
12	91	80	68	64
14	95	84	72	68
16	98	88	75	71
18	101	90	76	74
20	102	91	79	76
24	102	95	82	80

***In Vivo* Bioavailability Study**

The *in vivo* performance of venlafaxine hydrochloride tablets prepared as per the composition of Examples 4 and 5 were evaluated with respect to the Effexor® XR 150mg capsules in 11 healthy male volunteers under fasting condition. The study protocol followed was open randomized 3 treatment, 3 period, 6 sequence cross over study with a wash out period of at least 5 days. Blood samples were collected at appropriate time intervals over a period of 48 hours and venlafaxine content analyzed using a validated inhouse LCMS - MS method. Pharmacokinetic parameters C_{max} (Maximum plasma concentration), T_{max} (Time to attain maximum plasma concentration), AUC_{0-t} (Area under the plasma concentration *vs* time curve from 0 hours to the time of last sample collected) and $AUC_{0-\alpha}$ (Area under the plasma concentration *vs.* time curve from 0 hours to infinity) were calculated from the data obtained. The results of the study are given in Table 7.

Table 7. Comparative pharmacokinetic data

Pharmacokinetic parameter	T_{max} (h)	C_{max} μg/ml	AUC_{0-t} (μg/ml) (h)	$AUC_{0-\infty}$ (μg/ml) (h)
Tablets of Example 4	4.85	114.31	1633.51	1795.72
Tablets of Example 5	5.091	130.56	1813.84	2006.79
Effexor® XR capsules	6.45	99.92	1719.49	2406.27

The controlled release tablets produced demonstrated comparable extent of absorption when compared to the reference Effexor® XR. It is within the skill of one ordinary skill in the art to develop a product with matching C_{max} and AUC_{0-t} with respect to the reference product. The controlled release tablets can provide therapeutic blood concentrations of venlafaxine over a period of at least twenty four hours.

Examples 8 and 9, described below, provide additional examples of controlled release, multiple unit formulations of glipizide that deliver glipizide over twenty four hours. In contrast to Example 3 of a glipizide formulation having a waxy layer, these glipizide examples have the rate controlling polymer layer but not the waxy layer.

EXAMPLE 8

Controlled release multiple units:

	Example 8 (wt/tablet) mg
Inert Core	
Celpheres	148
Drug Layer	
Glipizide	10
Polyethylene glycol	4.7
Hydroxypropyl methylcellulose	1.7
Polyvinyl pyrrolidone	3.0
Tween 80	0.5
Lactose	3.0
Rate controlling layer	
Ethyl cellulose	10
Hydroxypropyl methylcellulose	5
Triacetin	1.7
Talc	0.5

Procedure:

1. Polyethylene glycol, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, Tween and lactose were dissolved in water and glipizide then was dispersed in the solution.
2. Celpheres were loaded in a Glatt Wurster column and coated with the drug dispersion of Step 1.
3. A solution of ethyl cellulose, hydroxypropyl methylcellulose and triacetin was prepared in a mixture of methylene chloride and isopropyl alcohol into which talc was dispersed.

4. The drug loaded pellets of Step 2 then were coated with the dispersion of Step 3 using a Glatt Wurster column to prepare controlled release multiple units.

Table 8 illustrates the comparative release patterns *in vitro* for the controlled release multiple units prepared according to example 8.

Table 8. *In vitro* release pattern of controlled release multiple units using USP apparatus – II, at 50 rpm and pH 7.5

Time (Hours)	Cumulative percentage release of glipizide from controlled release multiple units
1	10
2	18
4	29
8	46
12	62
16	74
20	89
24	98

EXAMPLE 9

Controlled release multiple units:

	Example 9 (wt/tablet) mg
Inert Core	
Celpheres	148
Drug Layer	
Glipizide	10.0
Polyethylene glycol	4.7
Hydroxypropyl methylcellulose	1.7
Polyvinyl pyrrolidone	3.0
Tween 80	0.5
Lactose	3.0
Rate controlling layer	
Ethyl cellulose	4.6
Hydroxypropyl methylcellulose	2.9
Triacetin	0.8
Talc	0.3

Procedure:

1. Polyethylene glycol, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, lactose and Tween were dissolved in water and glipizide then was dispersed in the solution.
2. Celpheres were loaded in a Glatt Wurster column and coated with the drug dispersion of Step 1.
3. A solution of ethyl cellulose, hydroxypropyl methylcellulose and triacetin was prepared in a mixture of methylene chloride and isopropyl alcohol into which talc was dispersed.

4. The drug loaded pellets of Step 2 then were coated with the dispersion of Step 3 using a Glatt Wurster column to prepare controlled release multiple units.

Table 9 illustrates the comparative release patterns *in vitro* for controlled release multiple units prepared according to Example 9.

Table 9. *In vitro* release pattern for controlled release multiple units using USP apparatus – II, at 50 rpm and pH 7.5

Time (Hours)	Cumulative percentage release of glipizide from controlled release multiple units
1	26
2	37
4	55
8	74
12	86
16	93
20	97
24	98

Tables 8 and 9 indicate that controlled release, multiple unit systems of glipizide can be prepared that can provide therapeutic blood concentrations of glipizide over a period of at least twenty four hours.

While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. For example, the waxy layer can, for example, affect the release of the units, or a mixture of a waxy material and a functional material, such as an active pharmaceutical ingredient or a functional pharmaceutical excipient. The mixture of waxy material and active pharmaceutical ingredients may provide an immediate release of the active pharmaceutical ingredient in the mixture. The waxy layer can be designed based on, for example, thickness or material to impart rate controlling properties to the units or pellets. The improved multiple unit systems also generally are intended for application to any active pharmaceutical ingredient and provide advantages to those that are primarily formulated as a capsule and/or are problematic to prepare as a tablet. Moreover, the multiple unit

systems can be prepared as a tablet, capsule, or sachet that includes a core and a coating of a waxy material. The core can consist of one or more active pharmaceutical ingredients and those pharmaceutically acceptable excipients necessary to form the core. The coating of waxy material allows the coated cores (i.e., units) to be compress as a tablet or filled into a capsule or sachet. In this manner, the dosage form can be immediate release. By adding a rate controlling polymer to the core, the dosage form can be an extended release. The dosage form also can be made from a mixture of immediate release and extended release units to provide immediate and extended release of the one or more active pharmaceutical ingredients.

Pharmaceutically acceptable salts of venlafaxine and glipizide may be used in the dosage forms, tablets, and capsules described herein. Pharmaceutically acceptable salts of venlafaxine and glipizide include mineral acid salts such as hydrochloride, hydroiodide, hydroflouride, sulphate, etc.; organic acid salts such as citrate, maleate, tartarate, etc.; and organosulphonic acid salts such as mesylate, besylate, tosylate, etc.

The improved multiple unit systems can be used to deliver combination drug products, such as combinations of atorvastatin and amlodipine, metformin and glipizide, simvastatin and ramipril, simvastatin and amlodipine, metformin XL and glipizide XL, ramipril and atorvastatin, ramipril and amlodipine, metformin XL and glimiperide, fosinopril and amlodipine. These combination drug products can be produced by separately forming individual units of each active pharmaceutical ingredient and then combining them into tablets, capsules, or sachets in a subsequent production step. In this manner, each of the active pharmaceutical ingredients can be fabricated to separately optimize the release of that active ingredient and then the final dosage form can be produced that has the desired ratio of each of the active ingredients. One or both of each of the active ingredients can be formed as units of one or more of an immediate release, a controlled release, a modified release, a delayed release, or an extended release form.

Further, it is contemplated that any single feature or any combination of optional features of the inventive variations described herein may be specifically excluded from the claimed inventions and be so described as a negative limitation. Accordingly, it is not intended that the inventions be limited, except as by the appended claims.

WE CLAIM:

1. A multiple unit dosage form comprising multiple units, each unit comprising: at least one core having an outer surface;

a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, the coating layer including one or both of one or more active pharmaceutical ingredients and one or more rate controlling polymers; and

an outer layer, the outer layer comprising a material that is one or both of elastic and compressible.

2. The multiple unit dosage form of claim 1, wherein the core includes the one or more rate controlling polymers.

3. The multiple unit dosage form of claim 1, wherein the core includes the one or more active pharmaceutical ingredients.

4. The multiple unit dosage form of claim 1, wherein the core includes one or more of sugar, a non-pareil seed, microcrystalline cellulose, celphere, sand silicon dioxide, glass, plastic, polystyrene, hydroxypropyl methylcellulose.

5. The multiple unit dosage form of claim 4, wherein the sugar comprises one or more of glucose, mannitol, lactose, xylitol, dextrose, and sucrose.

6. The multiple unit dosage form of claim 1, wherein the core comprises one or more of an insoluble material, a soluble material, and a swellable material.

7. The multiple unit dosage form of claim 1, wherein the rate controlling polymer comprises one or more of cellulosic polymers, methacrylic acid polymers, and waxes.

8. The multiple unit dosage form of claim 1, wherein the rate controlling polymer comprises one or more of ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, and hydroxyethylcellulose, hydroxypropylmethyl phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

9. The multiple unit dosage form of claim 1, wherein the one or more active pharmaceutical ingredients comprises one or more of antidepressants, antidiabetics,

antiulcers, analgesics, antihypertensives, antibiotics, antipsychotics, antineoplastics, antimuscarinics, diuretics, antimigraine agents, antivirals, anti-inflammatory agents, sedatives, antihistaminics, antiparasitic agents, antiepileptics and lipid lowering agents.

10. The multiple unit dosage form of claim 1, wherein the one or more active pharmaceutical ingredients comprise one or more of enalapril, captopril, benazepril, lisinopril, ranitidine, famotidine, ranitidine bismuth citrate, diltiazem, propranolol, verapamil, nifedipine, acyclovir, ciprofloxacin, simvastatin, atorvastatin, lovastatin, venlafaxine, citalopram, paroxetine, selegiline, midazolam, fluoxetine, acarbose, buspirone, nimesulide, captopril, nabumetone, glimepiride, glipizide, etodolac, nefazodone and their pharmaceutically acceptable salts.

11. The multiple unit dosage form of claim 1, wherein the one or more active pharmaceutical ingredients comprises one or both of glipizide and venlafaxine or their salts.

12. The multiple unit dosage form of claim 1, wherein the core includes the rate controlling polymer and the active pharmaceutical ingredient.

13. The multiple unit dosage form of claim 1, wherein the first coating layer further includes the active pharmaceutical ingredient.

14. The multiple unit dosage form of claim 1, wherein the first coating layer includes the one or more active pharmaceutical ingredients.

15. The multiple unit dosage form of claim 1, further comprising one or more additional layers, wherein the additional layers are positioned between (a) one or more of the core and the first coating layer and (b) surrounding at least a portion of the first coating layer,

wherein the one or more additional layers comprise one or more of a seal coat, a film forming layer, a rate controlling polymer, and an active pharmaceutical ingredient.

16. The multiple unit dosage form of claim 15, wherein the seal coat comprises one or more of hydroxypropyl methylcellulose, polyvinyl pyrrolidone, and methacrylic acid copolymers.

17. The multiple unit dosage form of claim 15, wherein the film forming layer includes one or more of ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimelliatate, cellulose acetate phthalate, waxes, polyethylene glycol, and methacrylic acid polymers.

18. The multiple unit dosage form of claim 1, wherein the material in the outer layer comprises one or more wax materials.

19. The multiple unit dosage form of claim 18, wherein the wax material comprises one or more polyethylene glycols (PEGs).

20. The multiple unit dosage form of claim 19, wherein the one or more polyethylene glycols (PEGs) differ by molecular weight.

21. The multiple unit dosage form of claim 20, wherein the polyethylene glycol (PEG) comprises one or more of PEG 600, PEG 4000, PEG 6000, PEG 8000, and PEG 20000.

22. The multiple unit dosage form of claim 19, wherein the waxy material comprises from about 1% to about 15% by weight of the total dosage form weight.

23. The multiple unit dosage form of claim 19, wherein the waxy material comprises from about 1% to about 100% by weight of the weight of the core and the first coating layer.

24. The multiple unit dosage form of claim 19, wherein the waxy material is applied to each unit as a solution, suspension, dispersion, or hot melt technique.

25. The multiple unit dosage form of claim 24, wherein the solution, suspension, or dispersion is made using a solvent,

wherein the solvent comprises one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, and water.

26. The multiple unit dosage form of claim 1, wherein the active pharmaceutical ingredient comprises glipizide and is in one or both of the core and the first coating layer.

27. The multiple unit dosage form of claim 26, further comprising a buffering agent with the glipizide in one or both of the core and the first coating layer.

28. The multiple unit dosage form of claim 27, wherein the buffering agent comprises one or more of dibasic sodium phosphate, sodium ascorbate, meglumine, sodium citrate trimethanolamine, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonia, tertiary sodium phosphate, diethanolamine, ethylenediamine, and L-lysine.

29. The multiple unit dosage form of claim 1, wherein one or more of the core and the first coating layer includes one or more pharmaceutically acceptable excipients.

30. The multiple unit dosage form of claim 29, wherein the pharmaceutically acceptable excipients includes surfactants, binders, diluents, disintegrants, lubricants, glidants, plasticizers, stabilizers, and coloring agents.

31. The multiple unit dosage form of claim 30, wherein the surfactants include one or more of a non-ionic surfactant, an ionic surfactant, mono fatty acid esters of polyoxyethylene sorbitan, polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20), an anionic surfactant, sodium lauryl sulfate, polyoxyethylene castor oil derivative, polyoxyethyleneglycerol triiricinoleate castor oil, polyoxyl 35 castor oil, Cremophor EL, and Vitamin E TPGS, d-alpha-tocopheryl polyethylene glycol 1000 succinate, polyethoxylated fatty acids and their derivatives, polyethylene glycol 400 distearate, polyethylene glycol - 20 dioleate, polyethylene glycol 4–150 mono dilaurate, polyethylene glycol –20 glyceryl stearate, alcohol – oil transesterification products, polyethylene glycol – 6 corn oil, polyglycerized fatty acids, polyglyceryl – 6 pentaoleate, propylene glycol fatty acid esters, propylene glycol monocaprylate, mono and diglycerides, glyceryl ricinoleate, sterol and sterol derivatives, sorbitan fatty acid esters and their derivatives, polyethylene glycol – 20 sorbitan monooleate and sorbitan monolaurate, polyethylene glycol alkyl ether or phenols, polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol, sugar esters, sucrose monopalmitate,

polyoxyethylene – polyoxypropylene block copolymers, poloxamer, sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, and palmitoyl carnitine.

32. The multiple unit dosage form of claim 30, wherein the binders includes one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, and propylene glycol.

33. The multiple unit dosage form of claim 30, wherein the diluents include one or more of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, and sugar confectioners.

34. The multiple unit dosage form of claim 30, wherein the disintegrants include one or more of starch, croscarmellose, crospovidone, and sodium starch glycolate.

35. The multiple unit dosage form of claim 30, wherein the lubricants and glidants include one or more of colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, and white beeswax.

36. The multiple unit dosage form of claim 30, wherein the plasticizers include one or more of polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate, and dibutyl sebacate and the stabilizers include one or more of antioxidants, buffers, and acids.

37. The multiple unit dosage form of claim 1, wherein the dosage form comprises a tablet.

38. The multiple unit dosage form of claim 37, wherein the tablet further includes one or more pharmaceutically acceptable excipients around the individual units.

39. The multiple unit dosage form of claim 1, wherein the dosage form comprises a capsule.

40. The multiple unit dosage form of claim 1, wherein the active pharmaceutical ingredients comprise one or more of atorvastatin and amlodipine, metformin and glipizide, simvastatin and ramipril, simvastatin and amlodipine, metformin XL and glipizide XL, ramipril and atorvastatin, ramipril and amlodipine, metformin XL and glimiperide, fosinopril and amlodipine.

41. A process for the preparation of a multiple unit dosage form, the process comprising:

providing at least one core having an outer surface;

forming a coated core by applying one or more coating layers to the core such that the one or more coating layers surround at least a portion of the outer surface of the core or the coating layers;

forming an individual unit by applying a waxy material to the coated core to form a wax layer;

combining one or more units to form a multiple unit dosage form,

wherein one or both of the core and the coating layers includes one or more rate controlling polymers and active pharmaceutical ingredients.

42. The process of claim 41, further comprising applying one or both of a seal layer or a film forming layer between the core and the coating layer, between the one or more coating layers, and between the one or more coating layers and the wax layer.

43. The process of claim 41, wherein the waxy material comprises one or more polyethylene glycols (PEGs) of one or more molecular weights.

44. The process of claim 43, wherein the polyethylene glycols (PEG) comprise one or more of PEG 600, PEG 4000, PEG 6000, PEG 8000, and PEG 20000.

45. The process of claim 41, wherein the waxy material comprises from about 1% to about 15% by weight of the total dosage form weight.

46. The process of claim 41, wherein the waxy material comprises from about 1% to about 100% by weight of the weight of the core and the one or more coating layers.

47. The process of claim 41, wherein applying the waxy material comprises applying a coating of a solid waxy material by using a hot melt technique.

48. The process of claim 41, wherein applying the waxy material comprises applying a coating of waxy material by using as one or more of a solution, a suspension, and a dispersion.

49. The process of claim 48, wherein the solution or the suspension is prepared in a solvent.

50. The process of claim 49, wherein the solvent is selected from one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, and water.

51. The process of claim 41, wherein the core comprises an inert core.

52. The process of claim 41, wherein the core comprises one or more pharmaceutically acceptable excipients.

53. The process of claim 41, wherein the core comprises one or more active pharmaceutical ingredients.

54. The process of claim 41, wherein the one or more active pharmaceutical ingredients comprises one or more of antidepressants, antidiabetics, antiulcers, analgesics, antihypertensives, antibiotics, antipsychotics, antineoplastics, antimuscarinics, diuretics, antimigraine agents, antivirals, anti-inflammatory agents, sedatives, antihistaminics, antiparasitic agents, antiepileptics and lipid lowering agents.

55. The process of claim 41, wherein the one or more active pharmaceutical ingredients comprise one or more of enalapril, captopril, benazepril, lisinopril, ranitidine, famotidine, ranitidine bismuth citrate, diltiazem, propranolol, verapamil, nifedipine, acyclovir, ciprofloxacin, simvastatin, atorvastatin, lovastatin, venlafaxine, citalopram, paroxetine, selegiline, midazolam, fluoxetine, acarbose, buspirone, nimesulide, captopril, nabumetone, glimepiride, glipizide, etodolac, nefazodone and their pharmaceutically acceptable salts.

56. The process of claim 41, wherein the core is prepared by extrusion-spheronization.

57. The process of claim 56, wherein the extrusion-spheronization process comprises:

granulating an inert core material with or without other pharmaceutical excipients with a binder solution to form a wet mass;

passing the wet mass through an extruder to form extrudates; and

spheronizing the extrudates.

58. The process of claim 41, wherein the core is prepared by granulation.

59. The process of claim 58, wherein the granulation process comprises wetting a dry mix of core material with or without other pharmaceutical excipients with a binder solution.

60. The process of claim 41, wherein the units are prepared by coating the cores with active pharmaceutical ingredients and rate controlling polymers.

61. The process of claim 41, wherein the units are prepared by coating cores with a first layer comprising an active pharmaceutical ingredient and a second outer layer comprising a rate controlling polymer.

62. The process of claim 41, further comprising applying a seal coat or a film forming layer between the core and the subsequent layers or between a layer comprising an active pharmaceutical ingredient and a layer comprising a release rate controlling polymer

63. The process of claim 41, wherein the rate controlling polymer comprises one or more of cellulosic polymers, methacrylic acid polymers, waxes, ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, and hydroxyethylcellulose, hydroxypropylmethyl phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

64. The process of claim 41, wherein the active pharmaceutical ingredient comprises venlafaxine.

65. The process of claim 41, wherein the active pharmaceutical ingredient comprises glipizide.

66. The process of claim 41, wherein the dosage form comprises a tablet.

67. The process of claim 41, wherein the dosage form comprises a capsule.

68. A method for preparing a modified release multiple unit dosage form, the method comprising:

providing a core having a coating, wherein one or both of the core and the coating include one or more of rate controlling polymers and active pharmaceutical ingredients;

forming individual units by coating the coated core with a coating material that is one or both of compressible and elastic; and

forming the dosage form by combining one or more individual units.

69. The method of claim 68, wherein combining one or more individual units comprises compressing the individual units into a tablet

70. The method of claim 68, wherein combining one or more individual units comprises filling the individual units into a capsule or sachet.

71. The method of claim 68, wherein the coating material comprises a waxy material.

72. The method of claim 68, wherein the coating material comprises a polyethylene glycol.

73. A method of treating a medical condition, the method comprising administering a multiple unit dosage form for oral ingestion, each unit comprising a core, one or more layers surrounding the core, and an outer layer, wherein

the core comprises one or more of a pharmaceutically acceptable excipients, an active pharmaceutical ingredient, and a rate controlling polymer,

the one or more layers comprises one or more of a pharmaceutically acceptable excipient, an active pharmaceutical ingredient, a rate controlling polymer, a sealing layer, and a film forming layer, and

the outer layer comprises a material that is one or both of compressible and elastic to partially or completely absorb a force exerted in forming the multiple unit dosage form by combining the units.

74. The method of claim 73, wherein the material of the outer layer comprises a waxy material.

75. The method of claim 74, wherein the waxy material comprises one or more polyethylene glycols of different molecular weights.

76. The method of claim 73, wherein the dosage form comprises a tablet.

77. The method of claim 73, wherein the dosage form comprises a capsule.

78. A multiple unit dosage form comprising multiple units, each unit comprising:

at least one core having an outer surface and comprising one or more one active pharmaceutical ingredients; and

a coating layer surrounding at least a portion of the outer surface of the core, having an outer surface and comprising a waxy material.

79. The multiple unit dosage form of claim 78, wherein the waxy material comprises one or more polyethylene glycols of different molecular weights.

80. The multiple unit dosage form of claim 78, wherein the dosage form comprises a tablet.

81. The multiple unit dosage form of claim 78, wherein the dosage form comprises a capsule.

82. A combination drug, multiple unit dosage form comprising:

first units; and

second units,

each first unit comprising at least one core having an outer surface, a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, and an outer layer surrounding at least a portion of an outer surface of the first coating layer, the first coating layer including a first active pharmaceutical ingredient,

each second unit comprising at least one core having an outer surface, a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, and an outer layer surrounding at least a portion of an outer surface of the first coating layer, the first coating layer including a second active pharmaceutical ingredient,

wherein one or both of the cores and the coating layers comprise a rate controlling polymer, and

one or both of the outer layers comprise a waxy material,.

83. The combination drug, multiple unit dosage form of claim 82, wherein the waxy material comprises one or more polyethylene glycols.

84. The combination drug, multiple unit dosage form of claim 82, wherein the dosage form comprises a tablet.

84. The combination drug, multiple unit dosage form of claim 82, wherein the dosage form comprises a capsule.

85. A multiple unit dosage form comprising multiple units, each unit comprising:

at least one core having an outer surface;

a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, the coating layer including glipizide or its pharmaceutically acceptable salt and optionally one or more rate controlling polymers.

86. The multiple unit dosage form of claim 85, wherein the pharmaceutically acceptable salt comprises one or more of mineral acid salts, organic acid salts, and organosulphonic acid salts.

87. The multiple unit dosage form of claim 85, wherein the core includes one or more of sugar, a non-pareil seed, microcrystalline cellulose, celphere, sand silicon dioxide, glass, plastic, polystyrene, hydroxypropyl methylcellulose.

88. The multiple unit dosage form of claim 87, wherein the sugar comprises one or more of glucose, mannitol, lactose, xylitol, dextrose, and sucrose.

89. The multiple unit dosage form of claim 85, wherein the core comprises one or more of an insoluble material, a soluble material, and a swellable material.

90. The multiple unit dosage form of claim 85, wherein the rate controlling polymer comprises one or more of cellulosic polymers, methacrylic acid polymers, waxes, ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose,

carboxymethylcellulose, hydroxymethylcellulose, and hydroxyethylcellulose, hydroxypropylmethyl phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

91. The multiple unit dosage form of claim 85, wherein the core includes rate controlling polymer and glipizide.

92. The multiple unit dosage form of claim 85, further comprising one or more additional layers, wherein the additional layers are positioned between (a) one or more of the core and the first coating layer and (b) surrounding at least a portion of the first coating layer,

wherein the one or more additional layers comprise one or more of a seal coat, a film forming layer, a rate controlling polymer, and an active pharmaceutical ingredient.

93. The multiple unit dosage form of claim 92, wherein the seal coat comprises one or more of hydroxypropyl methylcellulose, polyvinyl pyrrolidone, and methacrylic acid copolymers and the film forming layer comprises one or more of ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimelliatate, cellulose acetate phthalate, waxes, polyethylene glycol, and methacrylic acid polymers.

94. The multiple unit dosage form of claim 85, further comprising an outer layer, the outer layer comprising a material that is one or both of elastic and compressible.

95. The multiple unit dosage form of claim 94, wherein the material in the outer layer comprises one or more wax materials.

96. The multiple unit dosage form of claim 95, wherein the wax material comprises one or more polyethylene glycols (PEGs).

97. The multiple unit dosage form of claim 85, further comprising a buffering agent with the glipizide in the first coating layer.

98. The multiple unit dosage form 97, wherein the buffering agent comprises one or more of dibasic sodium phosphate, sodium ascorbate, meglumine, sodium citrate trimethanolamine, sodium hydroxide, potassium hydroxide, calcium hydroxide,

magnesium hydroxide, ammonia, tertiary sodium phosphate, diethanolamine, ethylenediamine, and L-lysine.

99. The multiple unit dosage form of claim 85, wherein the dosage form comprises a tablet.

100. The multiple unit dosage form of claim 85, wherein the dosage form comprises a capsule.

101. A modified release multiple unit system comprising units of glipizide, wherein the units comprise:

an inert core;

a drug layer surrounding the inert core, the drug layer comprising glipizide; and

a rate controlling polymer layer surrounding the drug layer.

102. The modified release multiple unit system of claim 101, wherein the system comprises a tablet.

103. The modified release multiple unit system of claim 101, wherein the system comprises a capsule.

104. A modified release multiple unit system comprising units of glipizide wherein the units comprise:

an inert core;

a drug layer surrounding the inert core;

a rate controlling polymer layer surrounding the drug layer; and

a waxy layer surrounding the drug layer.

105. The modified release multiple unit system of claim 104, wherein the units can be compressed into tablet, or filled into a capsule or a sachet; without affecting the desired release characteristics of drug.

106. The modified release multiple unit system of claim 104, wherein the system comprises a tablet.

107. The modified release multiple unit system of claim 104, wherein the system comprises a capsule.

108. A modified release multiple unit system comprising units of venlafaxine, wherein the units comprise:

an inert core;

a drug layer surrounding the inert core; and

a rate controlling polymer layer surrounding the drug layer.

109. The modified release multiple unit system of claim 108, wherein the system comprises a tablet.

110. A modified release multiple unit system comprising units of venlafaxine wherein the units comprise:

an inert core;

a drug layer surrounding the inert core;

a rate controlling polymer layer surrounding the drug layer; and

a waxy layer surrounding the rate controlling polymer layer.

111. The modified release multiple unit system of claim 110, wherein the units can be compressed into tablet without affecting the desired release characteristics of drug.

112. A modified release multiple unit system comprising units of a drug wherein the units comprise:

an inert core;

a drug layer surrounding the inert core;

a rate controlling polymer layer surrounding the drug layer; and

a waxy layer surrounding the rate controlling polymer layer.

113. The modified release multiple unit system of claim 112, wherein the units can be compressed into tablet, or filled in capsule or sachet; without affecting the desired release characteristics of drug.

114. A process for the preparation of a modified release multiple unit system of a drug, the process comprising the steps of:

coating inert pellets with a drug and rate controlling polymer layer;

coating with a waxy layer;

optionally blending with pharmaceutically acceptable excipients;

compressing into a tablet, or filling into a capsule or a sachet of suitable size.

115. A process for the preparation of a modified release multiple unit system of drug, the process comprising the steps of:

coating inert pellets with a drug and rate controlling polymer layer;

coating with a waxy layer;

optionally blending with pharmaceutically acceptable excipients;

compressing into tablet of suitable size.

116. The process of claim 115, wherein the drug comprises venlafaxine or a pharmaceutically acceptable salt.

117. A process for the preparation of modified release multiple unit system of drug comprising the steps of:

coating drug containing cores with a rate controlling polymer layer;

coating the rate controlling polymer layer with a waxy layer;

optionally blending with pharmaceutically acceptable excipients; and

compressing into tablet, or filling into capsule or sachet of suitable size.

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234/DEL/2003	6 March 2003 (06.03.2003)	IN

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(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, EC, 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, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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— *with international search report*

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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.

(54) Title: MODIFIED RELEASE, MULTIPLE UNIT DRUG DELIVERY SYSTEMS

(57) Abstract: The invention relates to novel modified release multiple unit systems, and methods of preparing these systems, which can be easily compressed into tablets or filled into capsules or sachets without affecting the desired release characteristics of the pharmaceutical active ingredients incorporated within the systems. The multiple unit tablet includes multiple units. Each unit includes at least one core having an outer surface, a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, one or more rate controlling polymers, and one or more one active pharmaceutical ingredients. The coating layer includes one or both of the one or more active pharmaceutical ingredients and the one or more rate controlling polymers. The tablet may further include an outer layer on the outer surface of the unit which includes a material that is one or both of elastic and compressible. The material may be a wax materials, such as polyethylene glycol's (PEGS).

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/24 A61K9/26 A61K9/28 A61K9/52 A61K31/4965 A61K31/137

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 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)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/12524 A (NYCOMED DANMARK A S ;BERTELSEN POUL (DK); SKINHOEJ ANNETTE (DK)) 18 March 1999 (1999-03-18) example 1 claim 51 page 33, line 31 - line 35	1-9,12, 29-35, 37-39, 68-70, 73,76,77
X	US 4 713 248 A (KJORNAES KIM ET AL) 15 December 1987 (1987-12-15) cited in the application examples 2,7 abstract	1-4,6-9, 12,37, 38,68, 69,73,76

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 September 2003	22 01. 2004

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	Sindel, U

INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 783 215 A (ARWIDSSON HANS ET AL) 21 July 1998 (1998-07-21) cited in the application claim 1 examples 1,5	1,4-6,9, 13,14, 29,30, 32,33, 37,38, 68,69, 73,76
X,P	WO 03/041692 A (KARMA PHARM LTD ;SELA YORAM (IL)) 22 May 2003 (2003-05-22) examples 1-4 claims 1,6	1,4-11, 13,14, 29,30, 32,73, 108

INTERNATIONAL SEARCH REPORT

PCT/IB 03/02186

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 73-77 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [X] Claims Nos.: 1, 41 (part.), 68, 73 (part.), 82
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-14, 18-40, 41-67 (part), 68-72, 73-77 (part), 101-103, 108-109, 114-117

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 41 (part.), 68, 73 (part.), 82

Present claims 1, 41 (part.), 68, 73 (part.) and 82 relate to an extremely large number of possible compounds and products. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds and products claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the formulations mentioned in the examples.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14, 18-40, 41-67 (part.), 68-72, 73-77 (part.), 101-103, 108-109, 114-117

   Multiple unit dosage form, each unit comprising at least one core, a first coating layer and an outer layer

   ---

2. claims: 15-17, 41-67 (part.), 73-77 (part.), 104-107, 110-113

   Multiple unit dosage form, each unit comprising at least one core, a first coating layer, one or more additional layers and an outer layer

   ---

3. claims: 78-81, 85-100

   Multiple unit dosage form, each unit comprising at least one core and a coating layer

   ---

4. claims: 82-84

   Combination drug comprising two different multiple unit dosage forms

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INTERNATIONAL SEARCH REPORT

PCT/IB 03/02186

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9912524 A	18-03-1999	AT 252892 T	15-11-2003
		AU 9062998 A	29-03-1999
		CA 2301883 A1	18-03-1999
		CN 1277550 T	20-12-2000
		DE 69819351 D1	04-12-2003
		WO 9912524 A1	18-03-1999
		EA 2806 B1	31-10-2002
		EP 1017370 A1	12-07-2000
		JP 2001515854 T	25-09-2001
		NO 20001290 A	28-04-2000
		US 6599529 B1	29-07-2003
US 4713248 A	15-12-1987	AU 570540 B2	17-03-1988
		AU 3935885 A	27-08-1985
		AU 571312 B2	14-04-1988
		AU 3935985 A	27-08-1985
		CA 1248023 A1	03-01-1989
		CA 1247009 A1	20-12-1988
		DE 3586600 D1	15-10-1992
		DE 3586600 T2	18-02-1993
		DE 3587274 D1	27-05-1993
		DE 3587274 T2	09-09-1993
		DK 462585 A ,B,	09-10-1985
		DK 462685 A ,B,	09-10-1985
		WO 8503436 A1	15-08-1985
		WO 8503437 A1	15-08-1985
		EP 0153104 A2	28-08-1985
		EP 0153105 A2	28-08-1985
		FI 853934 A ,B,	09-10-1985
		HK 1000201 A1	06-02-1998
		HK 1001554 A1	26-06-1998
		IE 59287 B1	09-02-1994
		IE 59797 B1	06-04-1994
		JP 7059499 B	28-06-1995
		JP 7059500 B	28-06-1995
		JP 61501151 T	12-06-1986
		NO 853955 A ,B,	14-11-1985
		US 4716041 A	29-12-1987
US 5783215 A	21-07-1998	AU 700949 B2	14-01-1999
		AU 2993695 A	09-02-1996
		BR 9506026 A	14-10-1997
		CA 2170526 A1	25-01-1996
		CN 1134108 A	23-10-1996
		CZ 9600731 A3	14-08-1996
		EE 3280 B1	15-08-2000
		EP 0723434 A1	31-07-1996
		FI 961056 A	06-05-1996
		HU 75772 A2	28-05-1997
		IL 114448 A	22-09-1999
		JP 9502738 T	18-03-1997
		NO 960837 A	29-02-1996
		NZ 289947 A	28-07-1998
		PL 313386 A1	24-06-1996
		RU 2141822 C1	27-11-1999
		WO 9601621 A1	25-01-1996
		SK 30396 A3	10-09-1997
		TR 960034 A2	21-06-1996

INTERNATIONAL SEARCH REPORT

PCT/IB 03/02186

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5783215 A		TW 460300 B	21-10-2001
		ZA 9505545 A	08-01-1996
WO 03041692 A	22-05-2003	WO 03041692 A1	22-05-2003

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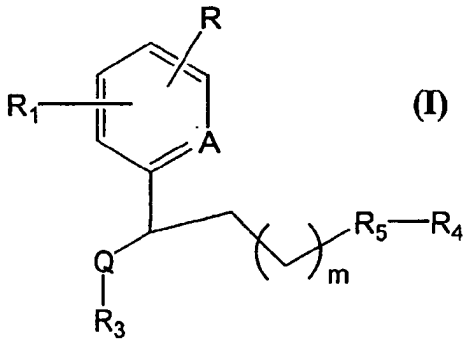
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

[Continued on next page]

(54) Title: PHENYLALKYLAMINES AND PYRIDYLALKYLAMINES



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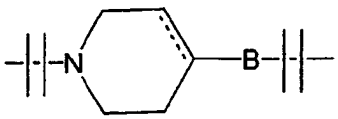

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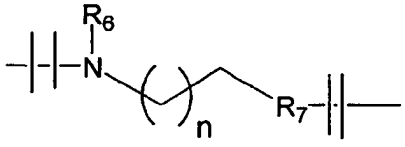


(III)

(57) Abstract: Compounds of formula (I): (A is CH or N, R and R_1 are a wide range of substituents, Q is CO, CHOH or $CHOR_2$, R_2 is alkyl, alkenyl, alkynyl or cycloalkyl group, each of which is optionally substituted, or is alkanoyl, alkanoyoxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminothiocarbonyl, alkylaminothiocarbonyl or dialkylaminothiocarbonyl, R_3 is H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclic group, each of which is optionally substituted, m is 1 or 2, R_4 is an aryl or heteroaryl group, either of which is optionally substituted, R_5 is either (II) or (III), wherein m is 1 or 2, R_6 is H or alkyl, R_7 is O, S, NR_6 or CH_2, B is a bond, O, S, NR_6 or CH_2 and ------- represents a single or double bond) have affinity for serotoninergic receptors. These compounds and their enantiomers, diastereoisomers, N-piperazine oxides, polymorphs, solvates and pharmaceutically acceptable salts are useful in the treatment of patients with neuromuscular dysfunction of the lower urinary tract and diseases related to 5-HT_{1A} receptor activity.

WO 03/106421 A2

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.

TITLE

Phenylalkylamines and Pyridylalkylamines

DESCRIPTION

The invention relates to phenylalkylamines and pyridylalkylamines having affinity for serotoninergic receptors, pharmaceutical compositions thereof and uses for such compounds and compositions.

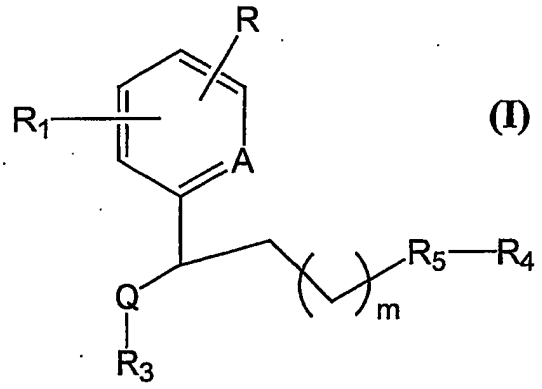
In mammals, micturition (urination) is a complex process that requires the integrated action of the bladder, its internal and external sphincters, the musculature of the pelvic floor and neurological control over these muscles at three levels (in the bladder wall or sphincter itself, in the autonomic centres of the spinal cord and in the central nervous system at the level of the pontine micturition centre (PMC) in the brainstem (pons) under the control of the cerebral cortex) (De Groat, *Neurobiology of Incontinence*, Ciba Foundation Symposium 151:27, 1990). Micturition results from contraction of the detrusor muscle, which consists of interlacing smooth-muscle fibres, under the control of the parasympathetic autonomic system originating from the sacral spinal cord. A simple voiding reflex is triggered by sensory nerves for pain, temperature and distension that run from the bladder to the sacral spinal cord. However, sensory tracts from the bladder reach the PMC too, generating nerve impulses that normally suppress the sacral spinal suppression of cortical inhibition of the reflex arc, and relaxing the muscles of the pelvic floor and external sphincter. Finally, the detrusor muscle contracts and voiding occurs. Abnormalities of lower-urinary tract function, e.g. dysuria, incontinence and enuresis, are common in the general population. Dysuria includes urinary frequency, nocturia and urgency, and may be caused by cystitis (including interstitial cystitis), prostatitis or benign prostatic hyperplasia (BPH) (which affects about 70% of elderly males), or by neurological disorders. Incontinence syndromes include stress incontinence, urgency incontinence, overflow incontinence and mixed incontinence. Enuresis refers to the involuntary passage of urine at night or during sleep.

Previously, treatment of neuromuscular dysfunction of the lower urinary tract involved administration of compounds that act directly on the bladder muscles, such as flavoxate, a spasmolytic drug (Ruffman, *J. Int. Med. Res.* 16:317, 1988) which is also active on the PMC (Guarneri *et al.*, *Drugs of Today*, 30:91, 1994), or anticholinergic compounds such as oxybutynin (Andersson, *Drugs* 36:477, 1988) and tolterodine

(Nilvebrant, *Life Sci.* 68(22-23): 2549, 2001). The use of α1-adrenergic receptor antagonists for the treatment of BPH is common too, but is based on a different mechanism of action (Lepor, *Urology*, 42:483, 1993). However, treatments that involve direct inhibition of the pelvic musculature (including the detrusor muscle) may have unwanted side effects, such as incomplete voiding or accommodation paralysis, tachycardia and dry mouth (Andersson, *Drugs* 35:477, 1988). Thus, it would be preferable to utilize compounds that act via the central nervous system to, for example, affect the sacral spinal reflex and/or the PMC inhibition pathways in a manner that restores normal functioning of the micturition mechanism.

EP 0982304 discloses 5-HT_{1A} binding agents which may be used in the treatment of CNS disorders, such as depression.

The invention provides compounds of formula I



(I)

wherein

R represents a hydrogen atom or one or more substituents selected from the group consisting of (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylthio, hydroxy, halo, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_1-C_6)-haloalkyl, (C_1-C_6)-haloalkoxy, (C_1-C_6)-hydroxyalkyl, alkoxy-(C_1-C_6)-alkyl, nitro, amino, (C_1-C_6)-aminoalkyl, N-(C_1-C_6)-alkylamino, N-(C_1-C_6)-alkylamino-(C_1-C_6)-alkyl, N, N-di-(C_1-C_6)-alkylamino, acylamino, (C_1-C_6)-alkylsulphonylamino, aminosulphonyl, (C_1-C_6)-alkylaminosulphonyl, cyano, aminocarbonyl, N-(C_1-C_6)-alkylaminocarbonyl, N, N-di-(C_1-C_6)-alkylaminocarbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylcarbonyl, alkylcarbonyl-(C_1-C_6)-alkyl, formyl, alkanoyloxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkylaminocarbonylamino, (C_1-C_6)-alkylsulphinyl, (C_1-C_6)-alkylsulphonyl, and N, N-di-(C_1-C_6)-alkylaminosulphonyl groups;

R_1 is selected from the group consisting of hydrogen, cycloalkyl, aryl, aryloxy,

aralkyl, aralalkoxy, heterocyclic, heterocycloxy, heterocycloalkyl and heterocycloalkoxy groups, each group being optionally substituted with one or more substituent R, defined as above;

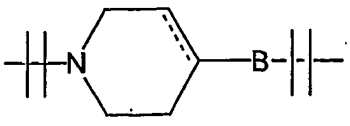
Q represents -C(O)- or -CH(OR_2)- where R_2 represents a member selected from the group consisting of hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl and cycloalkyl groups, wherein each group is optionally substituted with one or more groups selected from R_8 or R_9, where R_8 is selected from the group consisting of halo, (C_1-C_6)-alkoxy, (C_1-C_6)-haloalkoxy, cyano, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylcarbonyl, alkoxyalkyl, aminocarbonyl, N-(C_1-C_6)-alkylaminocarbonyl, N, N-di-(C_1-C_6)-alkylaminocarbonyl groups and R_9 is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, and heteroarylalkoxy groups, each optionally substituted with R, or R_2 represents -C(O)-(C_1-C_6)-alkyl, -C(O)O-(C_1-C_6)-alkyl, -C(O)$NR_{10}R_{11}$ or -C(S)$NR_{10}R_{11}$ wherein R_{10} and R_{11} are independently hydrogen or (C_1-C_6)-alkyl;

R_3 represents (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, cycloalkyl, aryl or heterocycle, each being optionally substituted with one or more substituent R or R_1, defined as above;

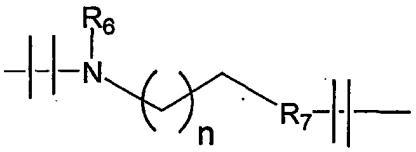
R_4 represents aryl or heterocyclic, each being optionally substituted with one or more substituents R, defined as above;

A represents CH or N,

R_5 represents group (i) or group (ii)



(i)



(ii)

(where R_4 is bound to the right of each group)

m and n are independently 1 or 2,

R_6 represents H or alkyl,

R_7 represents O, S, NR_6 or CH_2;

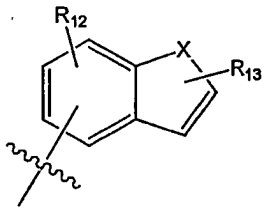
B represents a bond, O, S, NR_6 or CH_2; and

------- represents a single or double bond,

or an enantiomer, optical isomer, diastereomer, N-oxide (e.g., N-piperidine oxide), crystalline form, hydrate, solvate or pharmaceutically acceptable salt thereof.

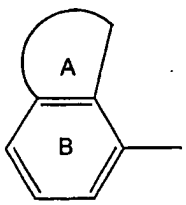
In certain embodiments, the invention provides compounds of formula I with the

proviso that the substituents of formula I are not such that simultaneously Q represents -C(O)- or -CH(OR_2)- where R_2 represents hydrogen; R represents a hydrogen atom or one or more substituents selected from the group consisting of (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylthio, hydroxy, halo, (C_1-C_6)-haloalkyl, nitro, amino and cyano groups; R_1 is selected from the group consisting of hydrogen, unsubstituted phenyl, and alkylphenyl groups; R_3 represents cycloalkyl, aryl or heterocycle, each being optionally substituted with one or more substituent selected from the group consisting of (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylthio, hydroxy, halo, (C_1-C_6)-haloalkyl, nitro, amino, cyano, unsubstituted phenyl, and alkylphenyl groups; R_5 represents group (i) wherein B represents a bond or CH_2; and R_4 represents the group



wherein X represents O, S, NH, N(C_1-C_6-alkyl), S(=O) or S(=O)$_2$, and R_{12} and R_{13} each represent one or more member selected independently from the group consisting of halo, hydroxy, alkyl, alkoxy, haloalkyl, alkylthio, nitro, amino, cyano, N-(C_1-C_6)-alkylamino, N, N-di-(C_1-C_6)-alkylamino, aminocarbonyl, N-(C_1-C_6)-alkylaminocarbonyl, N, N-di-(C_1-C_6)-alkylaminocarbonyl and acylamino groups.

In certain embodiments, the invention provides compounds of formula I with the proviso that the substituents of formula I are not such that simultaneously Q represents -C(O)-; R represents a hydrogen atom or one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, nitro, amino, alkylamino, N, N-di-alkylamino, aminocarbonyl and alkoxycarbonyl groups; R_1 represents hydrogen; R_5 represents group (i) wherein B represents a bond or CH_2; R_4 represents an aryl or fully aromatic heteroaryl, each optionally substituted with one or more substituent selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, nitro, amino, alkylamino, N, N-di-alkylamino, aminocarbonyl and alkoxycarbonyl groups, or R_4 represents a bicyclic heteroaryl radical of formula



wherein A is a saturated or unsaturated ring having one or more heteroatoms, where rings A and B are each independently substituted with one or more substituent selected from the group consisting of alkyl, halo, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl, alkanoyloxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, , amino, N-alkylamino and N,N,- di-alkylamino; and R_3 represents a saturated heterocyclic ring comprising a nitrogen atom, through which said saturated heterocyclic ring is bonded to the adjacent carbonyl group at Q, and which may optionally include a further hetero atom, and which may also be optionally substituted with one or more substituent selected from the group consisting of alkyl, alkoxy, halo and haloalkyl groups.

Preferred compounds of the invention include those whose preparation is described in the Examples below.

Compounds of formula I can exist as four stereoisomers, which may be present in racemic mixtures or in any other combination. Racemic mixtures can be resolved, i.e., subjected to enantiomeric enrichment, to yield compositions enriched with a particular enantiomer. Enantiomeric enrichment can be expressed as ee (enantiomeric excess) as defined below.

The invention also includes metabolites of the foregoing compounds having the same type of activity, hereinafter referred to as active metabolites.

The invention also contemplates prodrugs which are metabolized in the body to generate any of the foregoing compounds.

In another embodiment, the invention provides pharmaceutical compositions comprising compounds of formula I, enantiomers, diastereomers, N-oxides, crystalline forms, hydrates, solvates or pharmaceutically acceptable salts of such compounds of formula I, in admixture with pharmaceutically acceptable diluents or carriers such as those disclosed.

Yet another embodiment is a method for reducing the frequency of bladder contractions due to bladder distension in a mammal (such as a human) in need thereof by administering an effective amount of at least one compound of the present invention to reduce the frequency of bladder contractions due to bladder distension to the mammal.

Yet another embodiment is a method for increasing urinary bladder capacity in a mammal (such as a human) in need thereof by administering an effective amount of at least one compound of the present invention to increase urinary bladder capacity to the mammal.

Yet another embodiment is a method for treating disorders of the urinary tract in a mammal (such as a human) in need thereof by administering an effective amount of at least one compound of the present invention to ameliorate at least one condition among urinary urgency, overactive bladder, increased urinary frequency, decreased urinary compliance (decreased bladder storage capacity), cystitis (including interstitial cystitis), incontinence, urine leakage, enuresis, dysuria, urinary hesitancy and difficulty in emptying the bladder.

In yet other embodiments, the invention provides for methods of treating the above disorders, by administering a compound of formula I in combination with other agents such as, for example, one or more additional $5HT_{1A}$ antagonist, antimuscarinic drugs, α1-adrenergic antagonists, inhibitors of the cyclooxygenase enzyme, which may inhibit both COX1 and COX2 isozymes or which may, alternatively, be selective for COX2 isozyme, and NO donor derivatives thereof.

In yet another embodiment, the present invention provides a method for treating a mammal suffering from a central nervous system (CNS) disorder manifest in a serotoninergic dysfunction by administering an effective amount of at least one compound of the present invention to treat the CNS disorder. Such dysfunctions include, but are not limited to, anxiety, depression, hypertension, sleep/wake cycle disorders, feeding disorders, behaviour disorders, sexual dysfunction and cognition disorders in mammals (particularly in humans) associated with stroke, injury, dementia, and originated by neurological development, attention-deficit hyperactivity disorders (ADHD), drug addiction, drug withdrawal, irritable-bowel syndrome. Treatment may be effected by delivering a compound of the invention to the environment of a $5\text{-}HT_{1A}$ serotoninergic receptor, for example, to the extracellular medium (or by systemically or locally administering the compound to a mammal possessing such receptor) an amount of a compound of the invention effective to increase the duration of bladder quiescence with no contractions.

COMPOUNDS

The invention relates to compounds of formula I as disclosed above. The invention includes the enantiomers, diastereoisomers, N-oxides, crystalline forms, hydrates, solvates or pharmaceutically acceptable salts of these compounds, as well as active metabolites of these compounds having the same type of activity.

The term "haloalkyl" includes alkyl groups substituted by a single halogen atom (monohaloalkyl) and those substituted by more than one halogen atom (polyhaloalkyl). Examples of the latter are trifluoromethyl and 2,2,2-trifluoroethyl groups. The term haloalkoxy is to be interreted correspondingly. Preferred haloalkoxy groups include trifluoromethoxy and 2,2,2-trifluoroethoxy groups.

The term "aryl", alone or in combination, refers to a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" includes aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl.

The terms "heterocyclic" and "heterocyclo" refer to saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulphur and oxygen. Examples of saturated heterocyclic radicals include saturated heteromonocylic groups containing 1 to 4 nitrogen atoms (e.g., pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl); saturated heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., morpholinyl); saturated heteromonocyclic groups containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl). Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

The terms "heterocyclo" and "heterocyclic" encompass the term "heteroaryl," which refers to unsaturated heterocyclic radicals. Examples of "heteroaryl" radicals include unsaturated 5 to 6 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl) tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl); unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl); unsaturated 3 to 6-membered heteromonocyclic groups containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl; unsaturated 5 to 6-membered heteromonocyclic groups containing a sulphur atom, for example, 2-thienyl, 3-thienyl; unsaturated 5- to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl); unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., benzoxazolyl, benzoxadiazolyl); unsaturated 5 to 6-membered

heteromonocyclic groups containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl); unsaturated condensed heterocyclic groups containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl) and the like. The term "heteroaryl" also refers to radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclic group" may have 1 to 3 substituents such as, for example and without limitation, lower alkyl, hydroxy, oxo, amino and lower alkylamino. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. Examples of heteroaryl radicals include benzofuryl, 2,3-dihydrobenzofuryl, benzothienyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, and pyrazinyl.

The term "cycloalkyl" refers to saturated carbocyclic radicals having three to ten carbon atoms. Preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A most preferred cycloalkyl group is cyclohexyl.

The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from a carboxylic acid. Preferred acyl groups are alkanoyl groups, such as acetyl.

A "metabolite" of a compound disclosed herein is a derivative of a compound which is formed when the compound is metabolized. The term "active metabolite" refers to a biologically active derivative of a compound that is formed when the compound is metabolised. The term "metabolized" refers to the sum of the processes by which a particular substance is changed in the living body.All compounds present in the body are manipulated by enzymes within the body in order to derive energy and/or to remove them from the body. Specific enzymes produce specific structural alterations to the compound. Cytochrome P450, for example, catalyses a variety of oxidative and reductive reactions. Uridine diphosphate glucuronyltransferases , for example, catalyse the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphhydryl groups. Further information on metabolism may be obtained from *The Pharmacological Basis of Therapeutics*, 9th Edition, McGraw-Hill (1996), pages 11-17.

The metabolites of the compounds disclosed herein can be identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells or other *in vitro* systems such as cytochromes or microsomes, and analysis of the resulting compounds. Both methods are well known in the art.

As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. As used herein, the term "optical isomer" is equivalent to the term "enantiomer". Compounds that are stereoisomers of one another, but are not enantiomers of one another, are called diastereoisomers. The terms "racemate" or "racemic mixture" refer to a mixture of equal parts of enantiomers. The term "chiral center" refers to a carbon atom to which four different groups are attached. The term "enantiomeric enrichment" as used herein refers to the increase in the amount of one enantiomer as compared to the other. A convenient method of expressing the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee", which is found using the following equation:

$$ee = \frac{E1 - E2}{E1+E2} * 100$$

wherein E1 is the amount of the first enantiomer and E2 is the amount of the second enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of 50:30 is achieved, the ee with respect to the first enantiomer is 25%. However, if the final ratio is 90:10, the ee with respect to the first enantiomer is 80%. According to one embodiment of the invention, an ee of greater than 90% is preferred, an ee of greater than 95% is most preferred and an ee of greater than 99% is most especially preferred. Enantiomeric enrichment is determined by one of ordinary skill in the art using standard techniques and procedures, such as high performance liquid chromatography with a chiral column. Choice of the appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is within the knowledge of one of ordinary skill in the art. In addition, the enantiomers of compounds of formula I can be resolved by one of ordinary skill in the art using standard techniques well known in the art, such as

those described by J. Jacques, et al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981. Examples of resolutions include recrystallization techniques or chiral chromatography.

Diastereoisomers differ in both physical properties and chemical reactivity. A mixture of diastereomers can be separated into enantiomeric pairs based on solubility, fractional crystallization or chromatographic properties, e.g., thin layer chromatography, column chromatography or HPLC.

Purification of complex mixtures of diastereomers into enantiomers typically requires two steps. In a first step, the mixture of diastereomers is resolved into enantiomeric pairs, as described above. In a second step, enantiomeric pairs are further purified into compositions enriched for one or the other enantiomer or, more preferably resolved into composition comprising pure enantiomers. Resolution of enantiomers typically requires reaction or molecular interaction with a chiral agent, e.g., a solvent or column matrix. Resolution of enantiomers may be achieved, for example, by converting the mixture of enantiomers, e.g., a racemic mixture, into a mixture of diastereomers by reaction with a pure enantiomer of a second agent, i.e., a resolving agent. The two resulting diastereomeric products can then be separated. The separated diastereomers are then reconverted to the pure enantiomers by reversing the initial chemical transformation.

Resolution of enantiomers can also be accomplished by differences in their non-covalent binding to a chiral substance, e.g., by chromatography on homochiral absorbants. The noncovalent binding between enantiomers and the chromatographic adsorbant establishes diastereomeric complexes, leading to differential partitioning in the mobile and bound states in the chromatographic system. The two enantiomers therefore move through the chromatographic system, e.g, column, at different rates, allowing for their separation.

Chiral resolving columns are well known in the art and are commercially available (e.g., from MetaChem Technologies Inc., a division of ANSYS Technologies, Inc., Lake Forest, CA). Enantiomers can be analyzed and purified, for example,using chiral stationary phases (CSPs) for HPLC. Chiral HPLC columns tipically contain one form of an enantiomeric compound immobilized to the surface of a silica packing material. For chiral resolution to occur, there must be at least three points of simultaneous interaction between the CSP and one analyte enantiomer, with one or more of these interactions being stereochemically dependent.

D-phenylglycine and L-leucine are Type I CSPs and use combinations of p-p