US007357891B2

(12) **United States Patent**
Yang et al.

(10) **Patent No.: US 7,357,891 B2**
(45) **Date of Patent: Apr. 15, 2008**

(54) **PROCESS FOR MAKING AN INGESTIBLE FILM**

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(73) Assignee: **MonoSol Rx, LLC**, Portage, IN (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 616 days.

(21) Appl. No.: **10/768,809**

(22) Filed: **Jan. 30, 2004**

(65) **Prior Publication Data**

US 2004/0258896 A1 Dec. 23, 2004

Related U.S. Application Data

(63) Continuation-in-part of application No. PCT/US02/32575, filed on Oct. 11, 2002, which is a continuation-in-part of application No. PCT/US02/32594, filed on Oct. 11, 2002, which is a continuation-in-part of application No. PCT/US02/32542, filed on Oct. 11, 2002.

(60) Provisional application No. 60/328,868, filed on Oct. 12, 2001, provisional application No. 60/386,937, filed on Jun. 7, 2002, provisional application No. 60/414,276, filed on Sep. 27, 2002, provisional application No. 60/328,868, filed on Oct. 12, 2001, provisional application No. 60/386,937, filed on Jun. 7, 2002, provisional application No. 60/371,940, filed on Apr. 11, 2002, provisional application No. 60/443,741, filed on Jan. 30, 2003.

(51) **Int. Cl.**
B29C 47/88 (2006.01)

(52) **U.S. Cl.** **264/211.12**; 264/260; 264/234

(58) **Field of Classification Search** .... None
See application file for complete search history.

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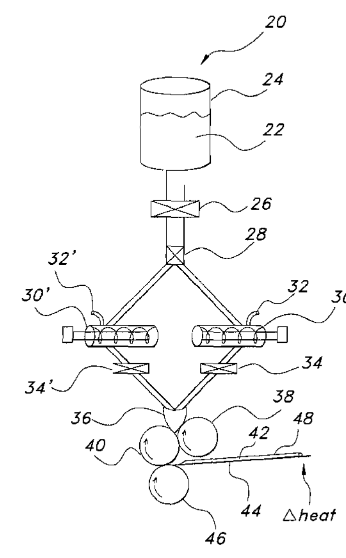
Primary Examiner—Edmund H. Lee
(74) *Attorney, Agent, or Firm*—Hoffman & Baron, LLP

(57) **ABSTRACT**

The invention relates to film products containing desired levels of active components and methods of their preparation. Desirably, the films disintegrate in water and may be formed by a controlled drying process, or other process that maintains the required uniformity of the film. Desirably, the films may be exposed to temperatures above that at which the active components typically degrade without concern for loss of the desired activity.

9 Claims, 33 Drawing Sheets



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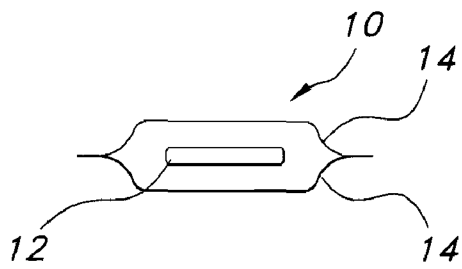


FIG. 1

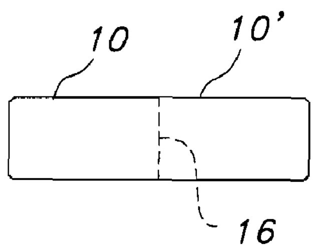
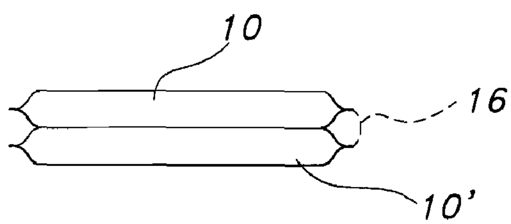


FIG. 2



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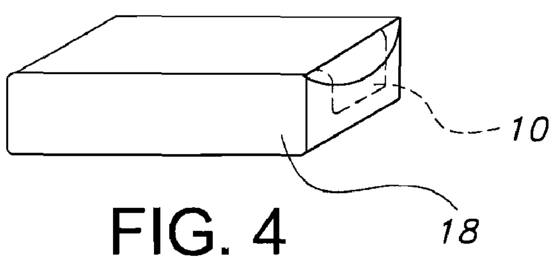

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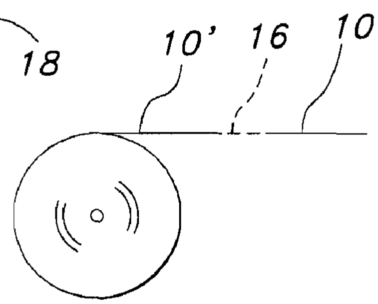

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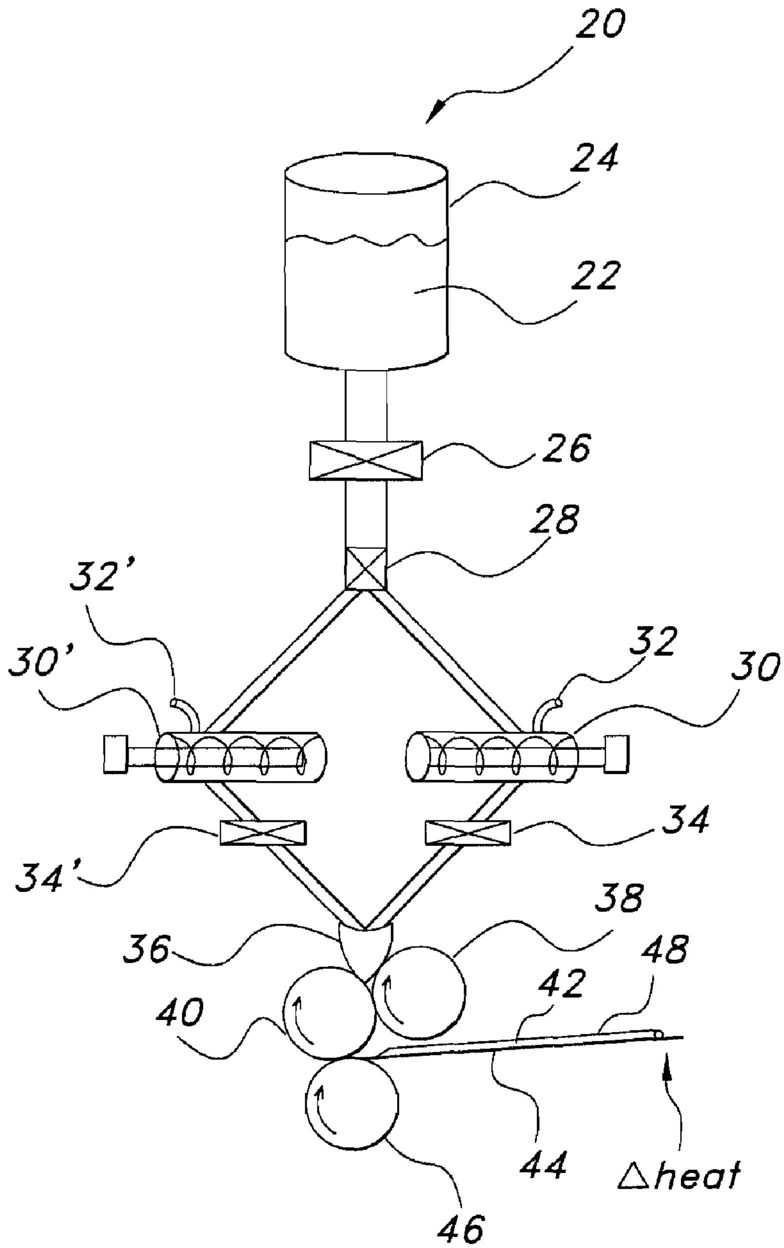

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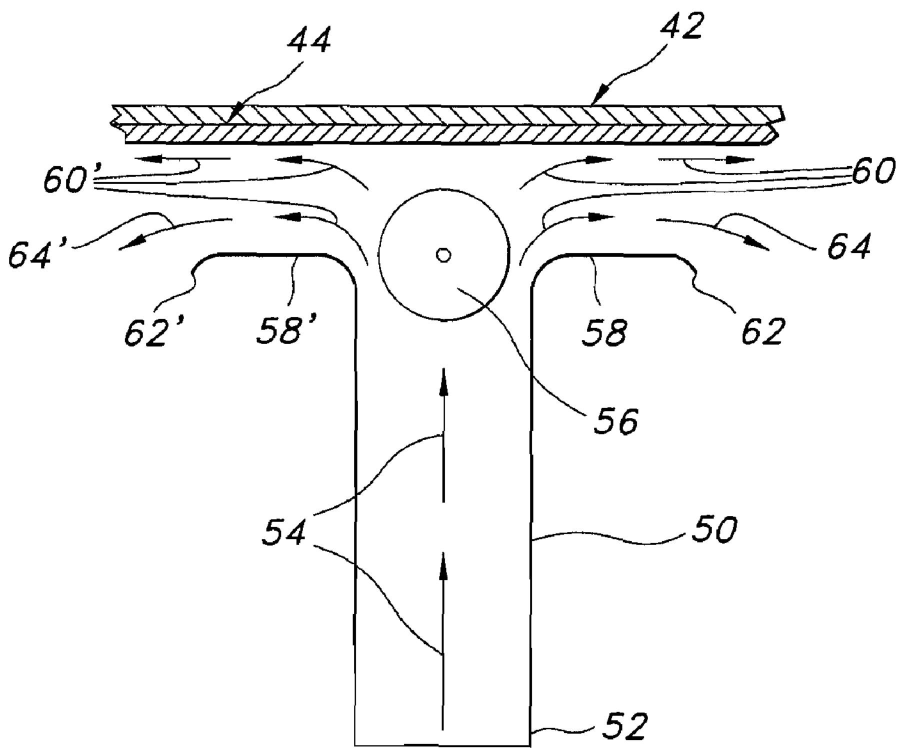

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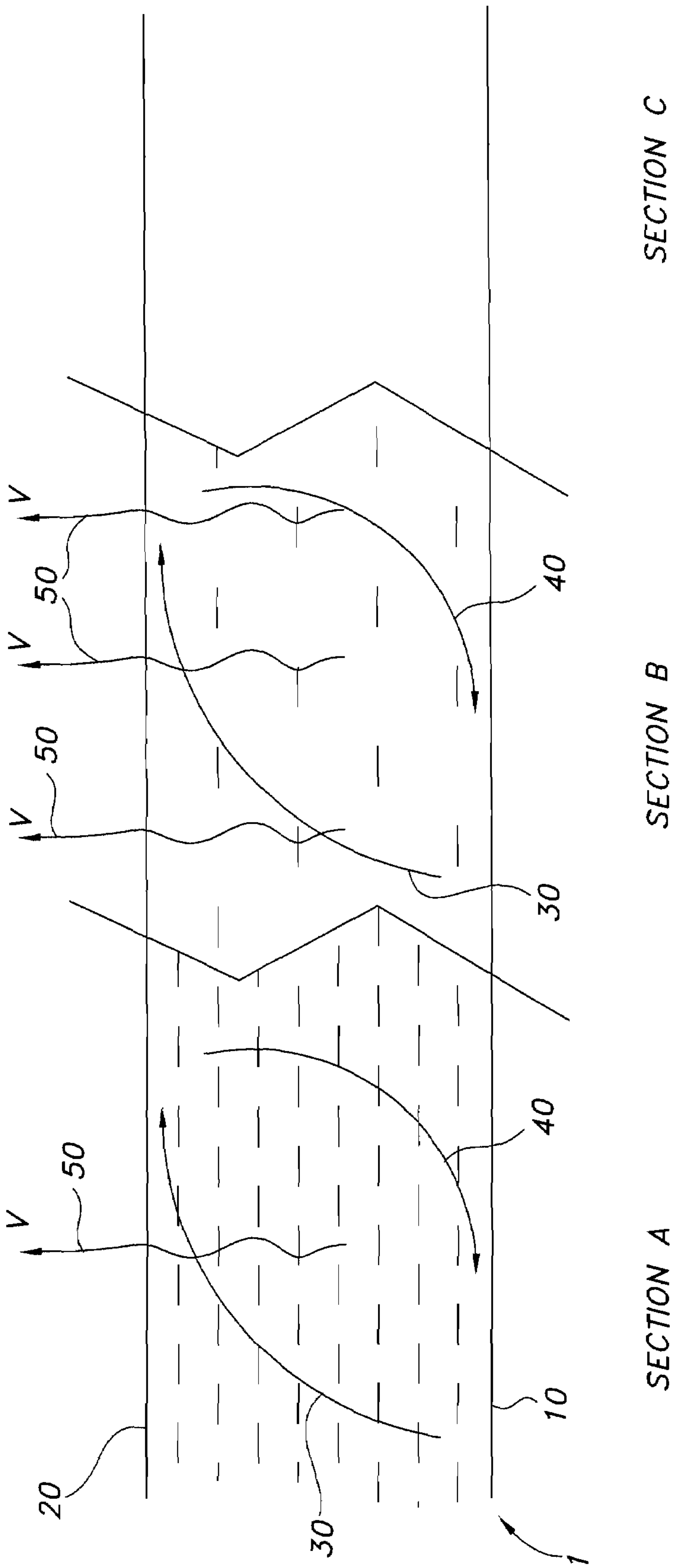

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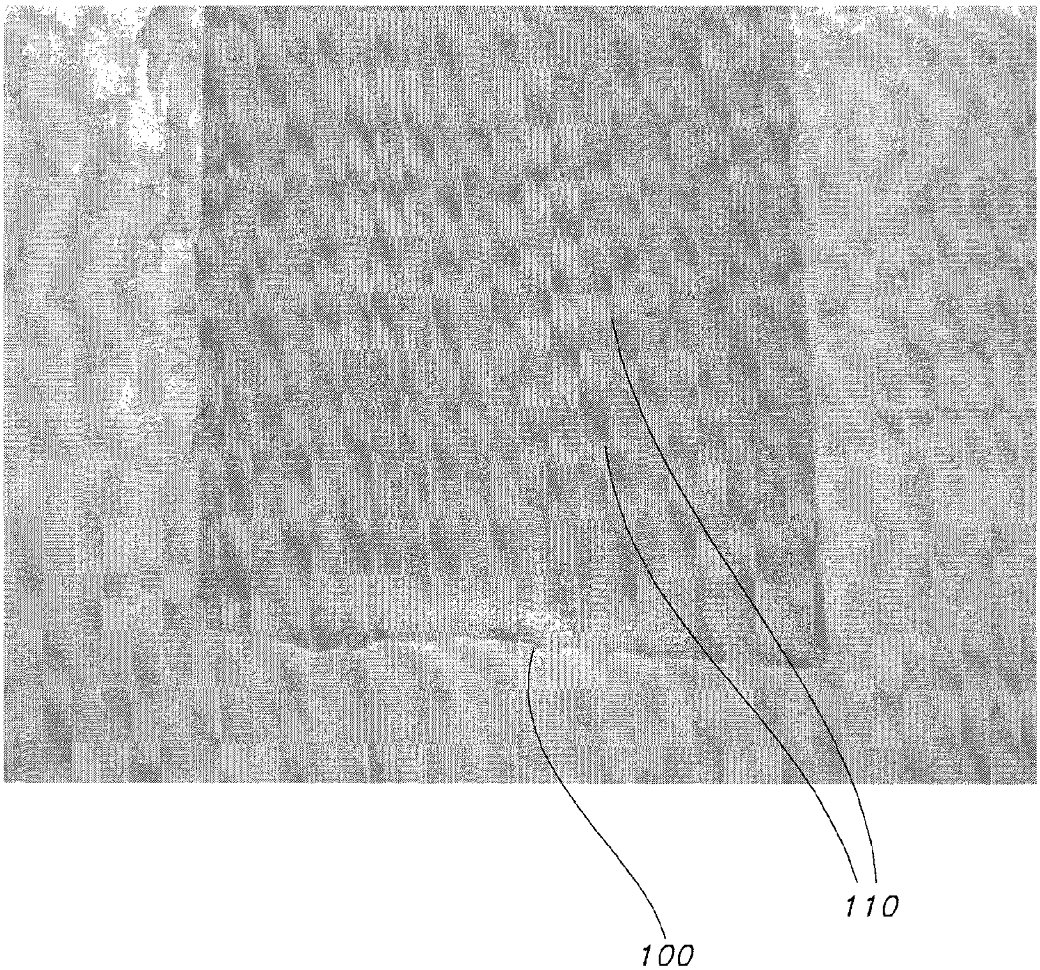

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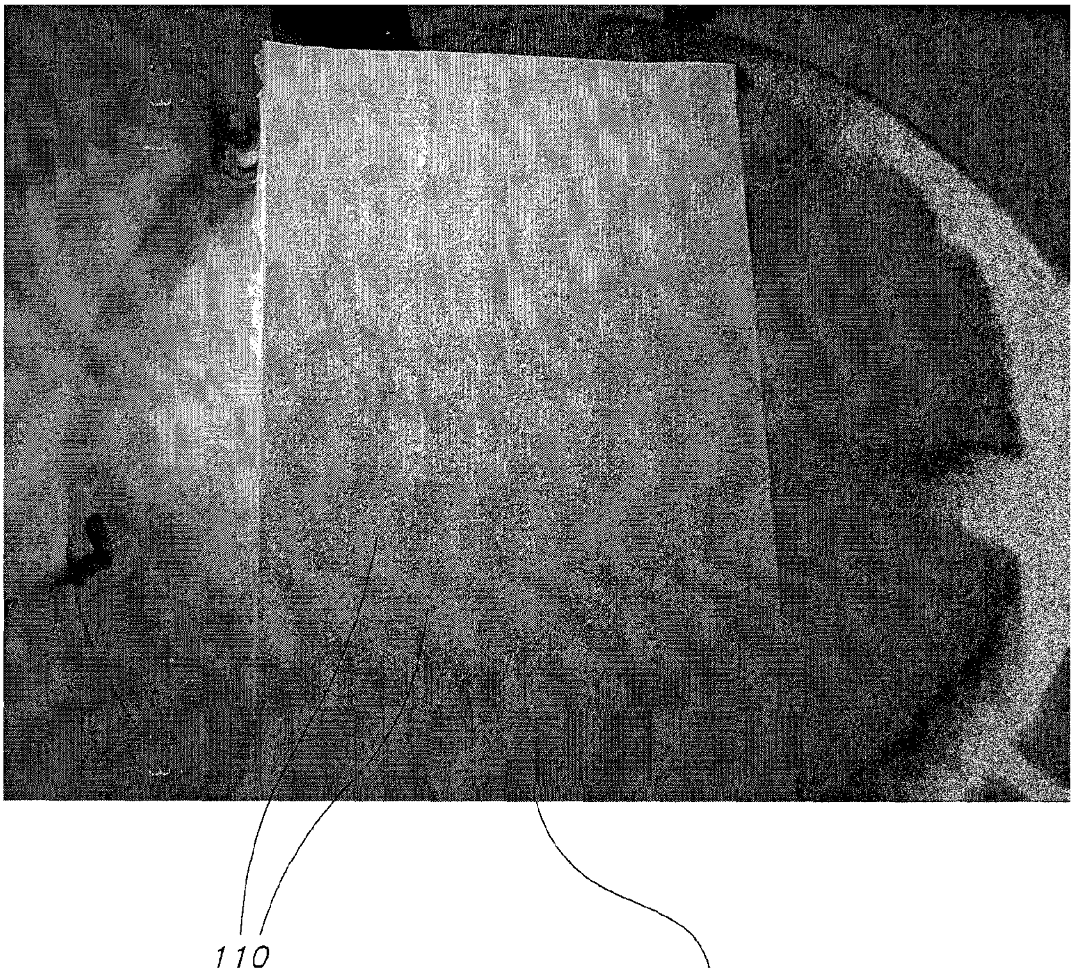

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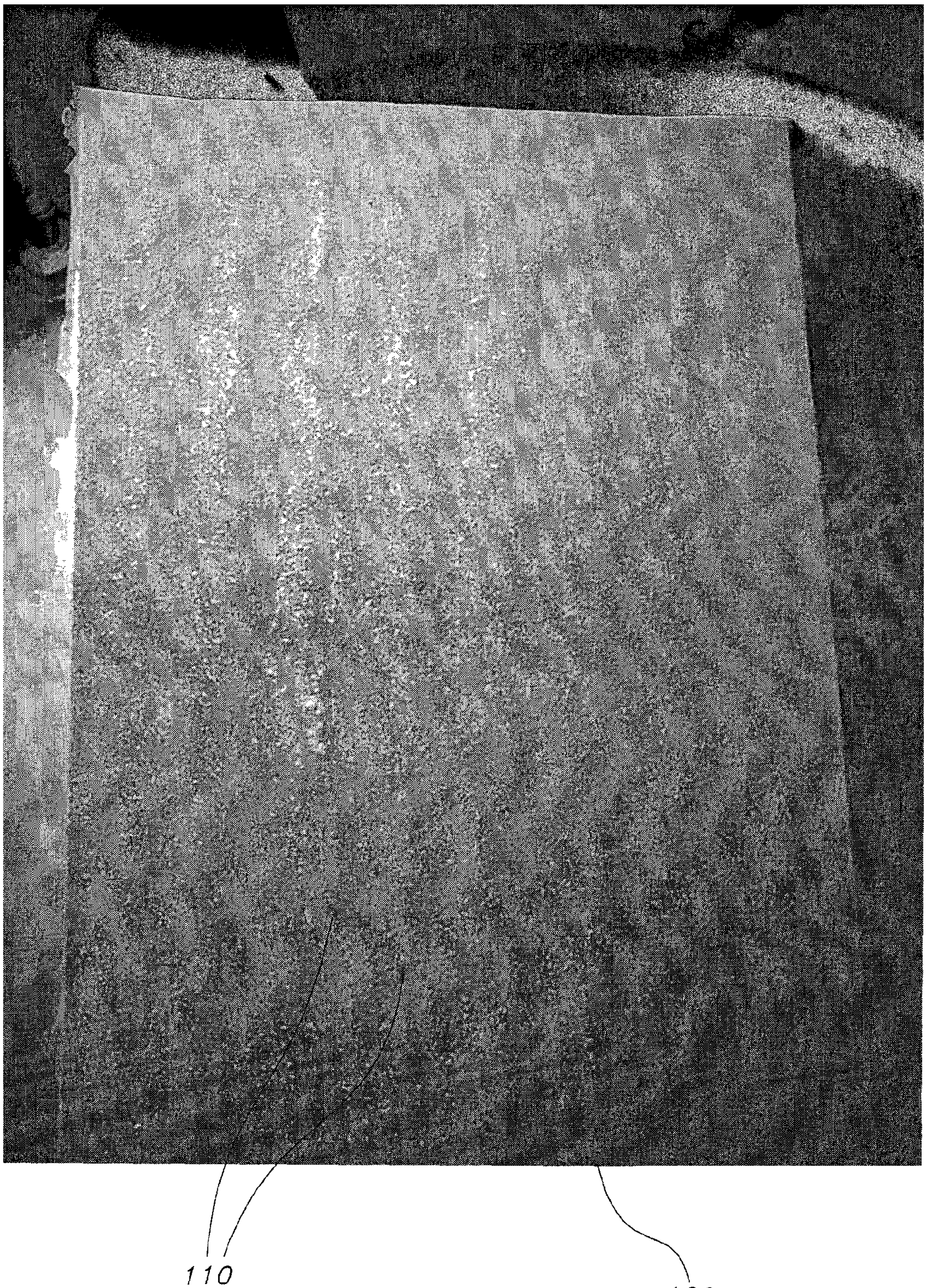

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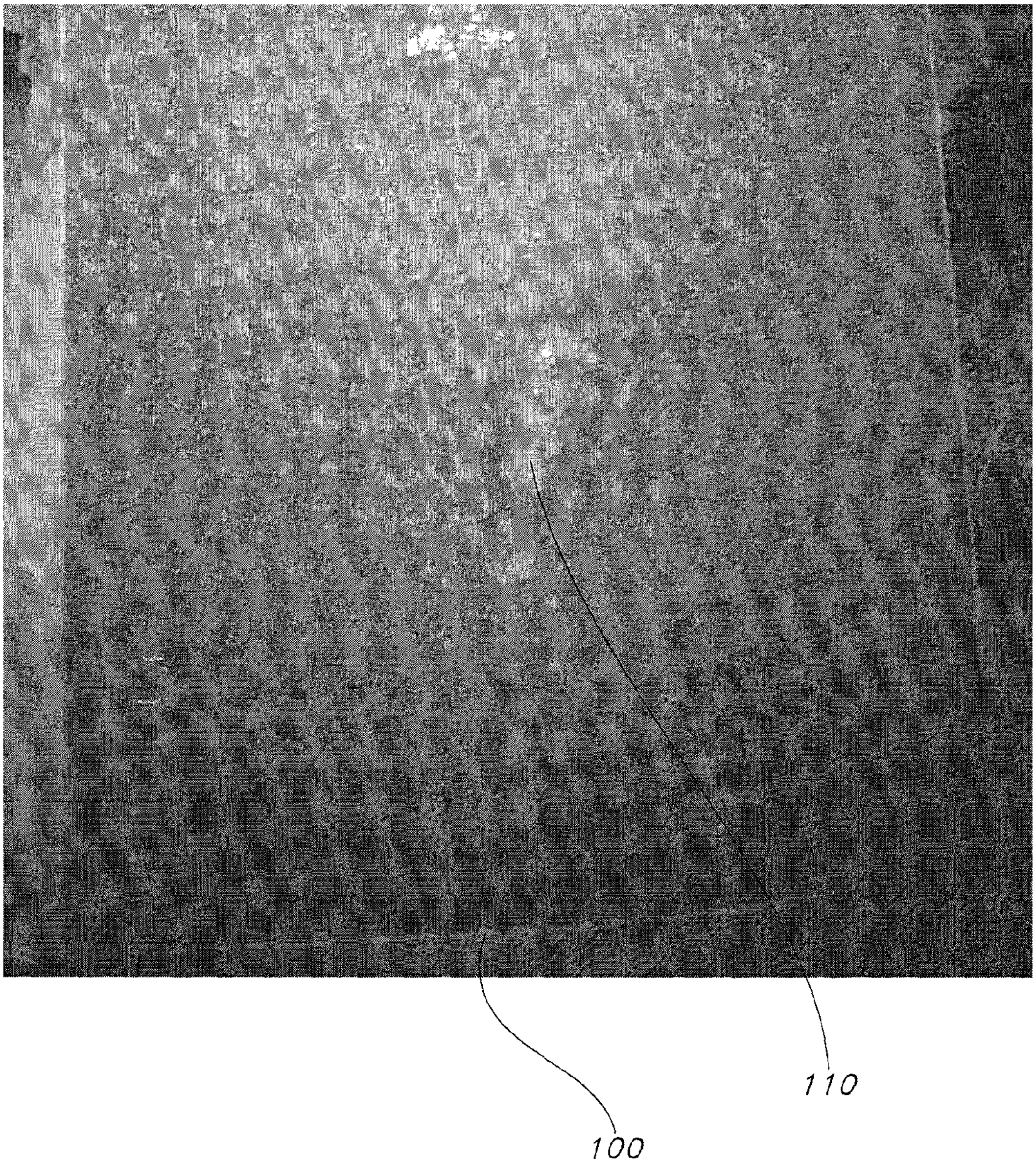

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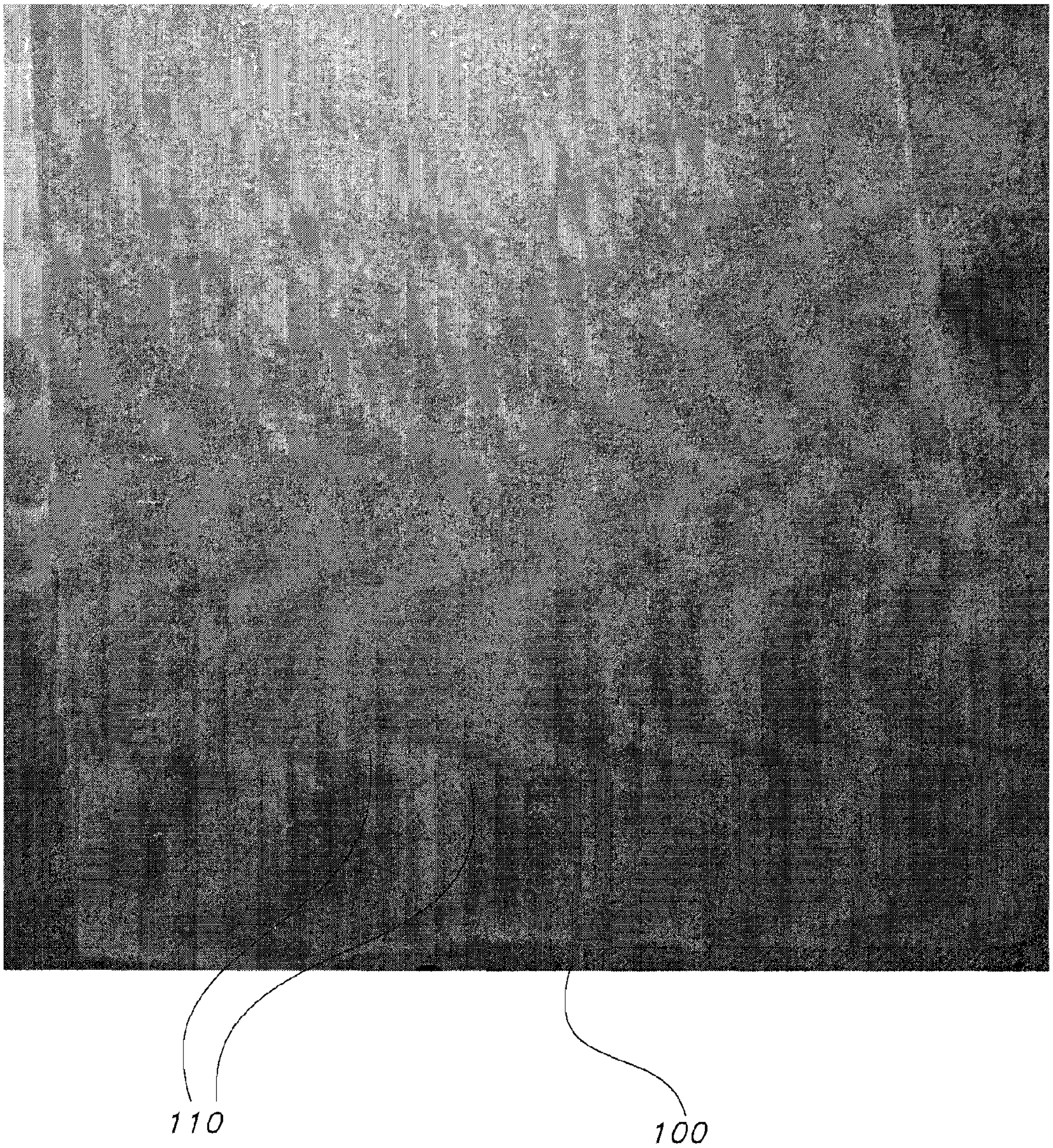

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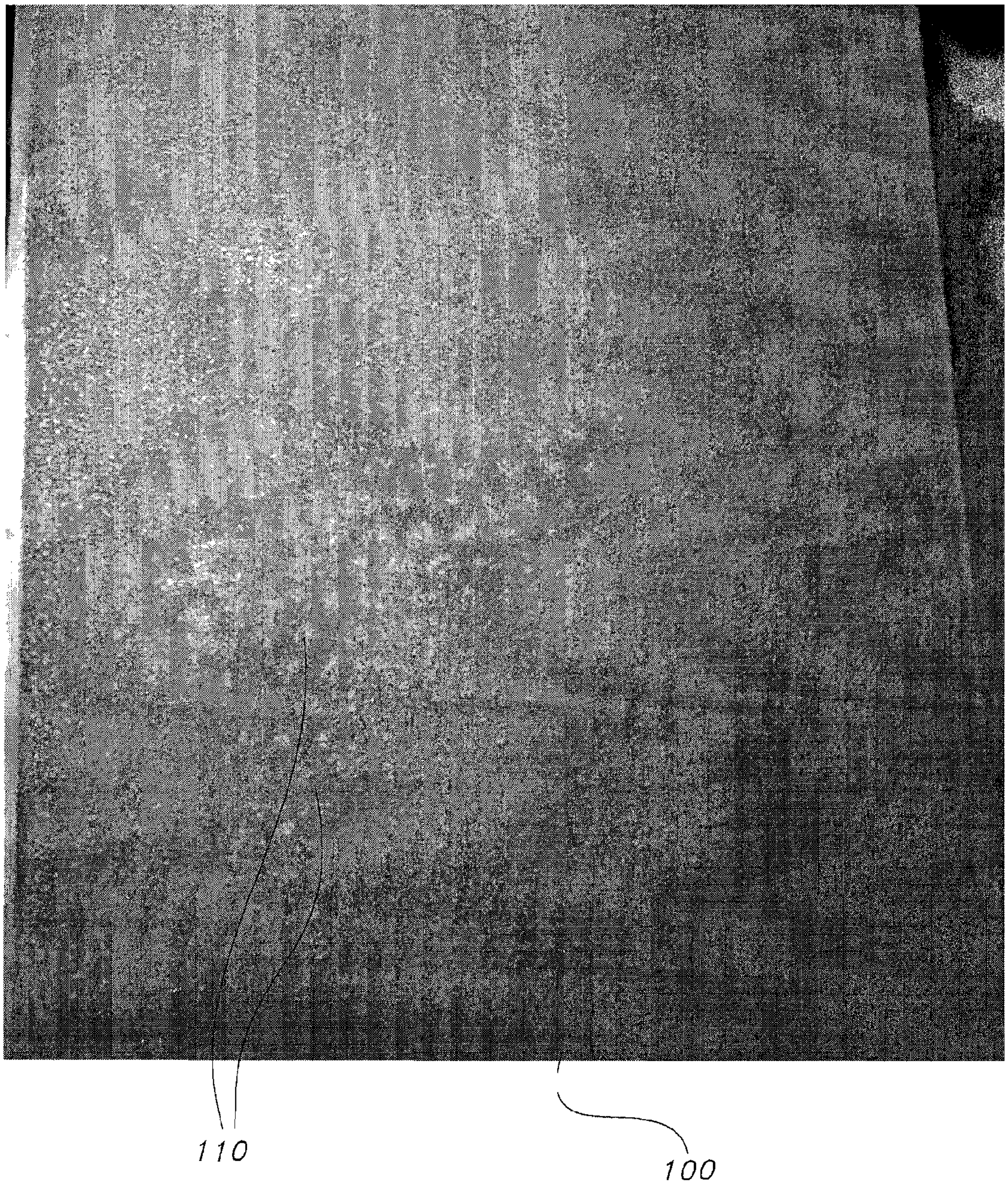

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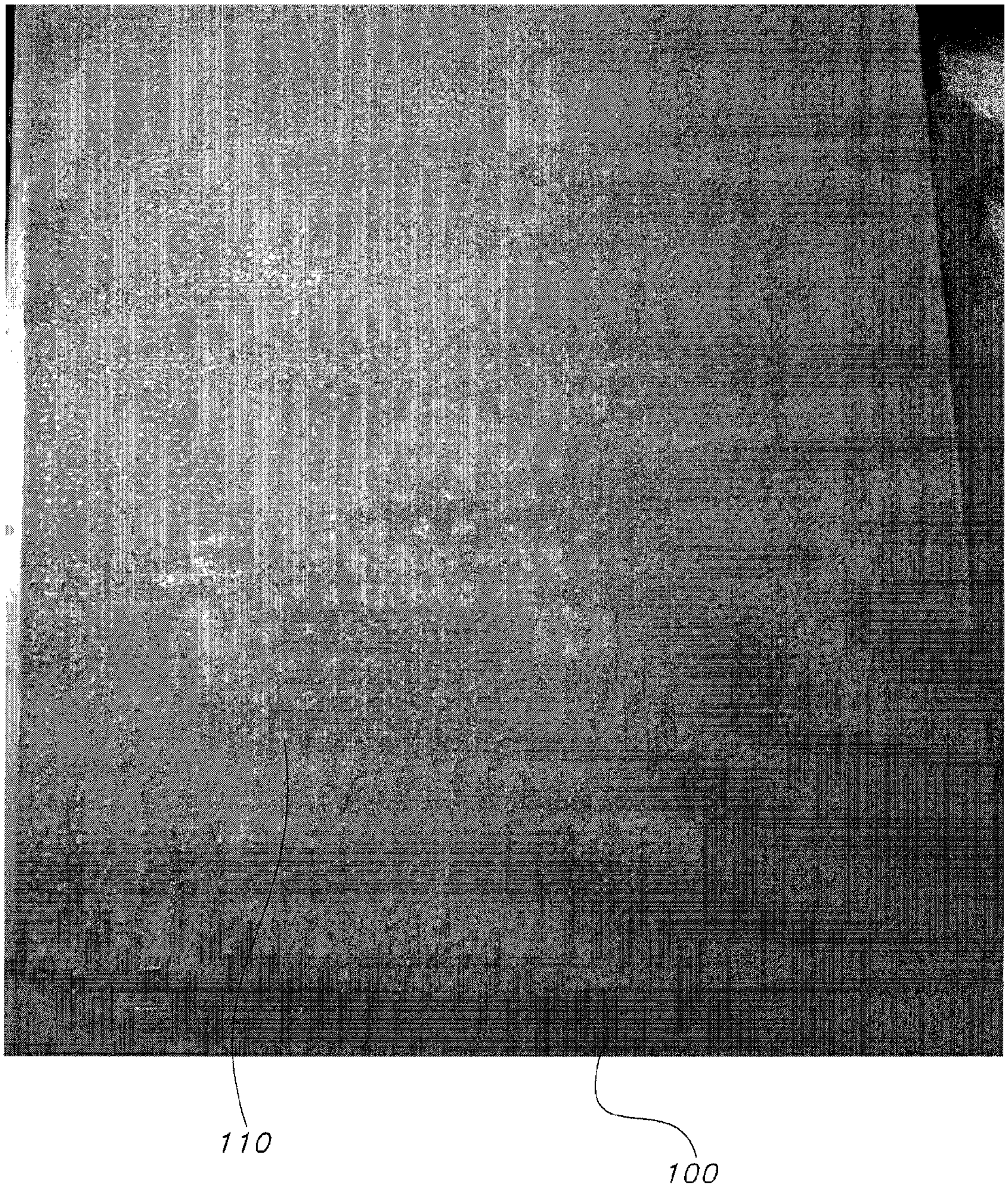

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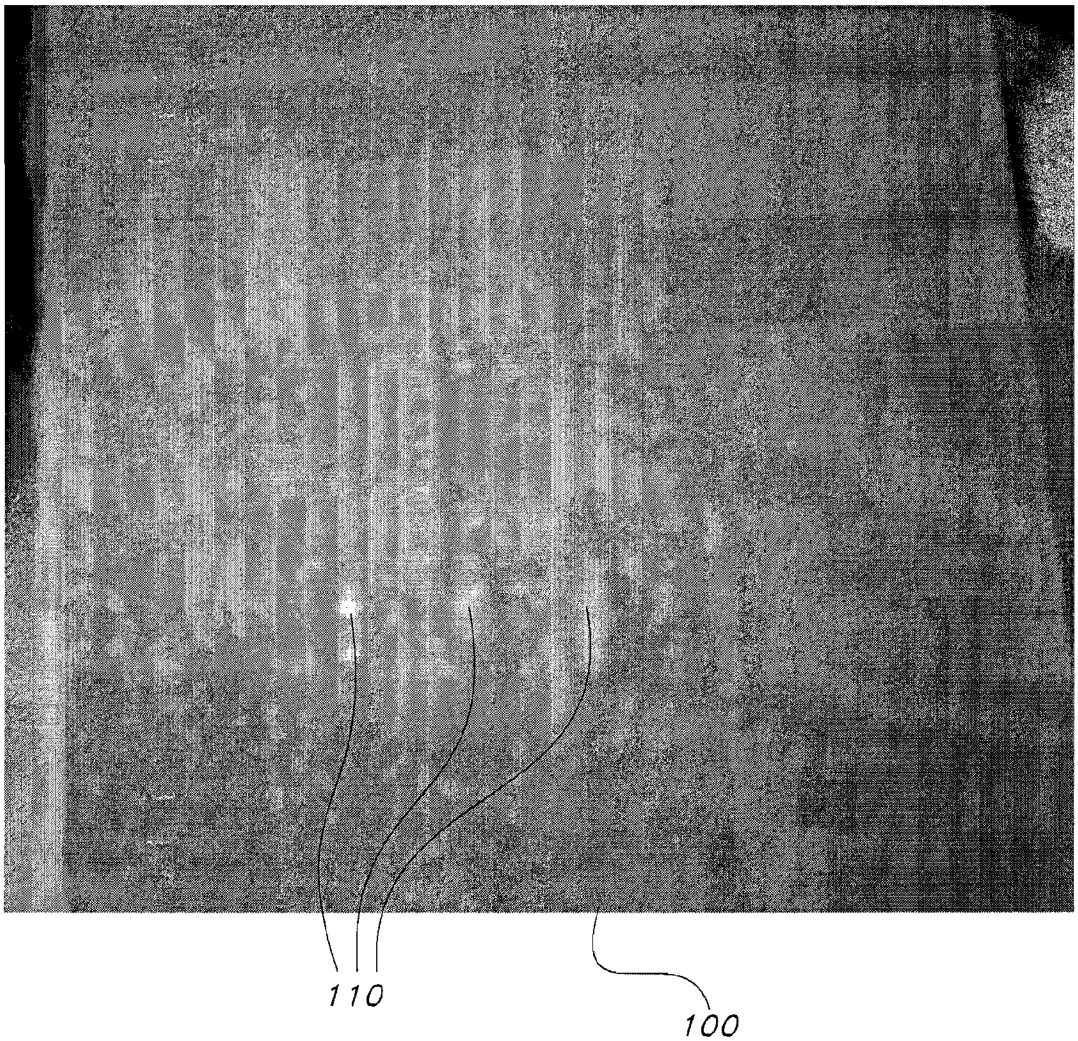

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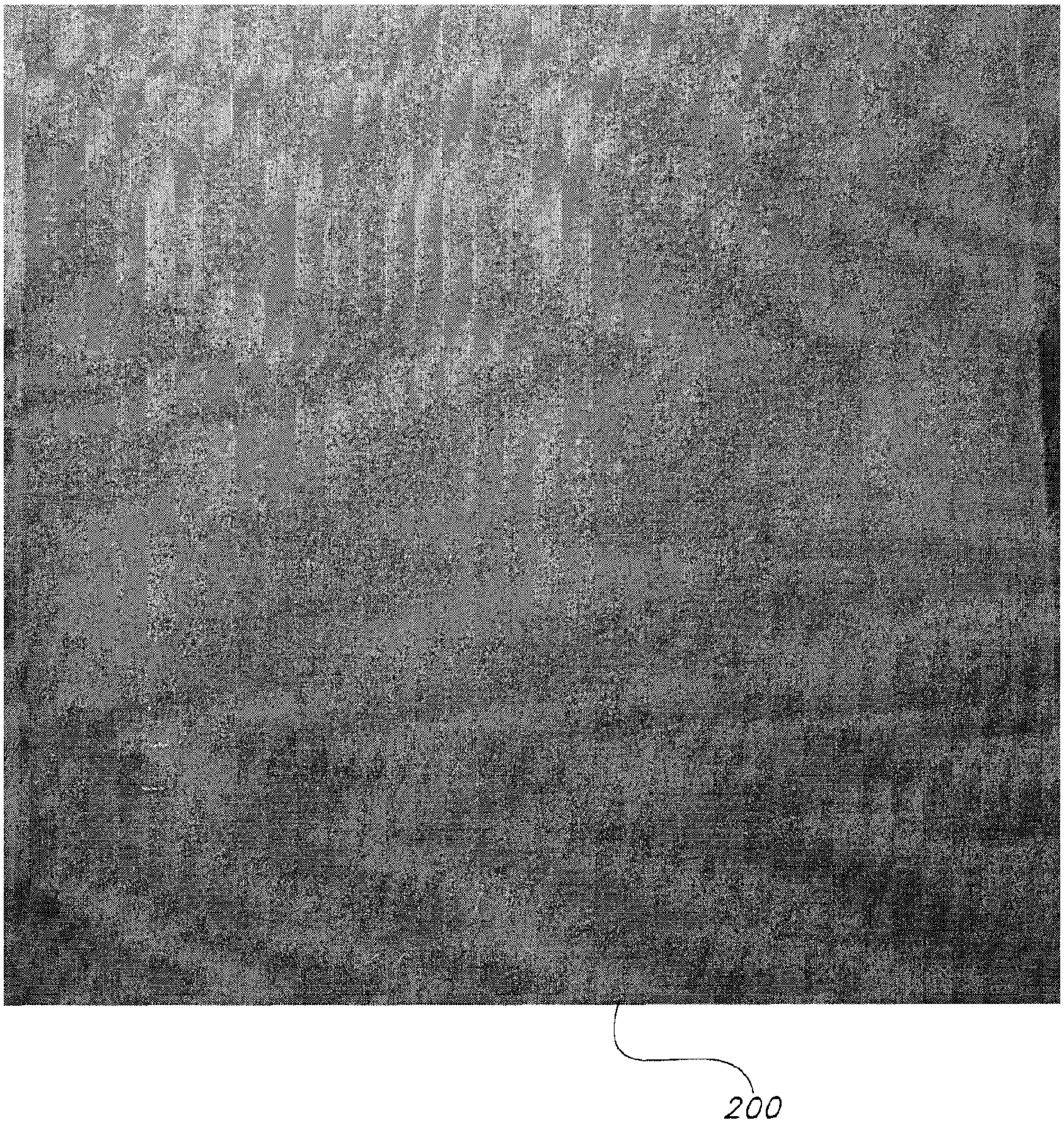

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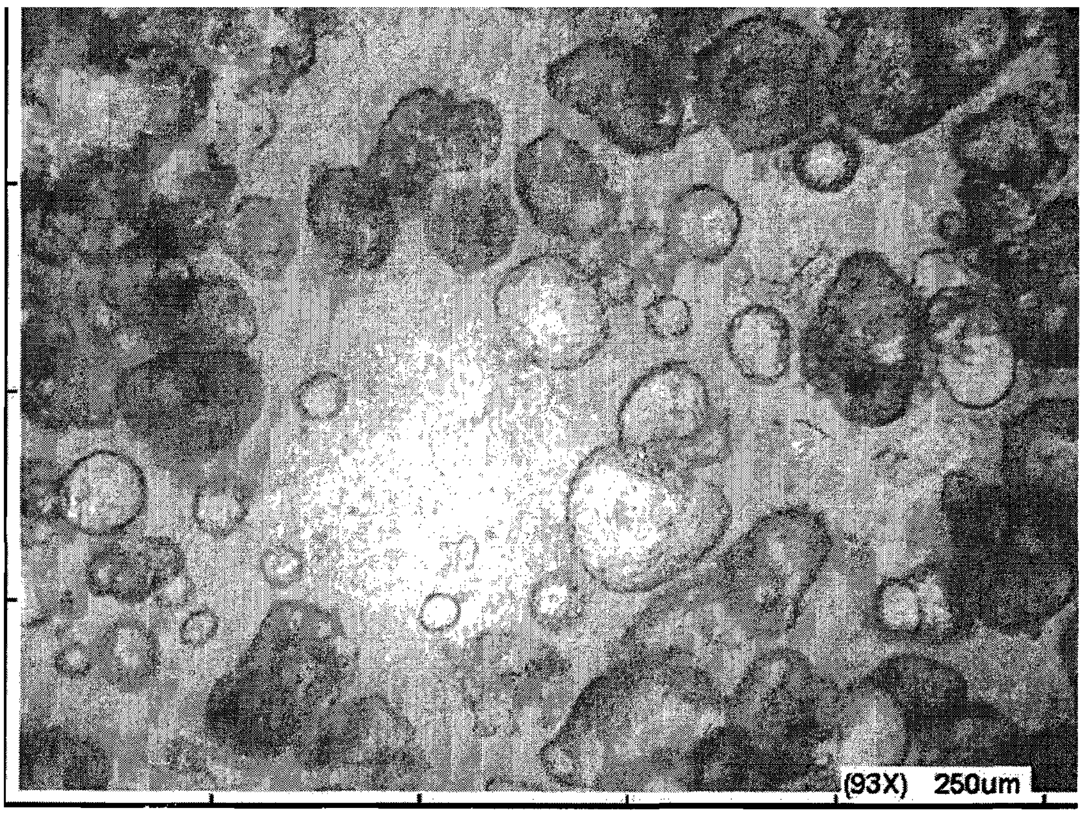

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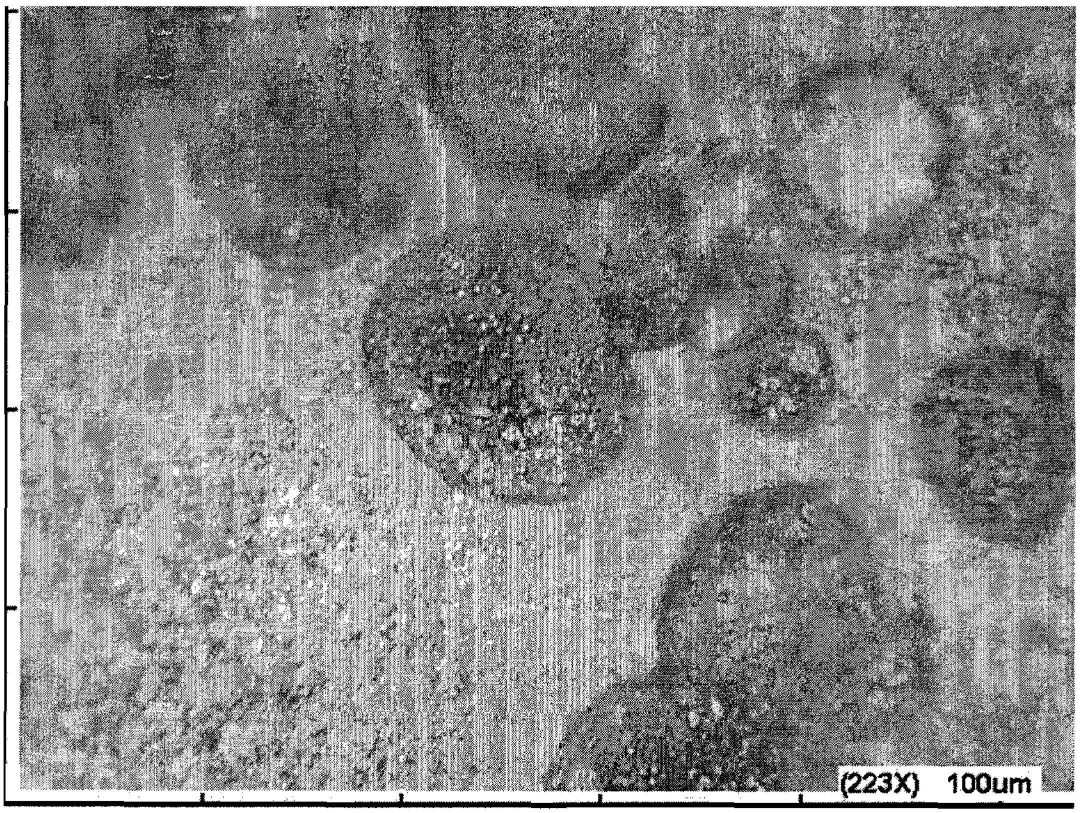

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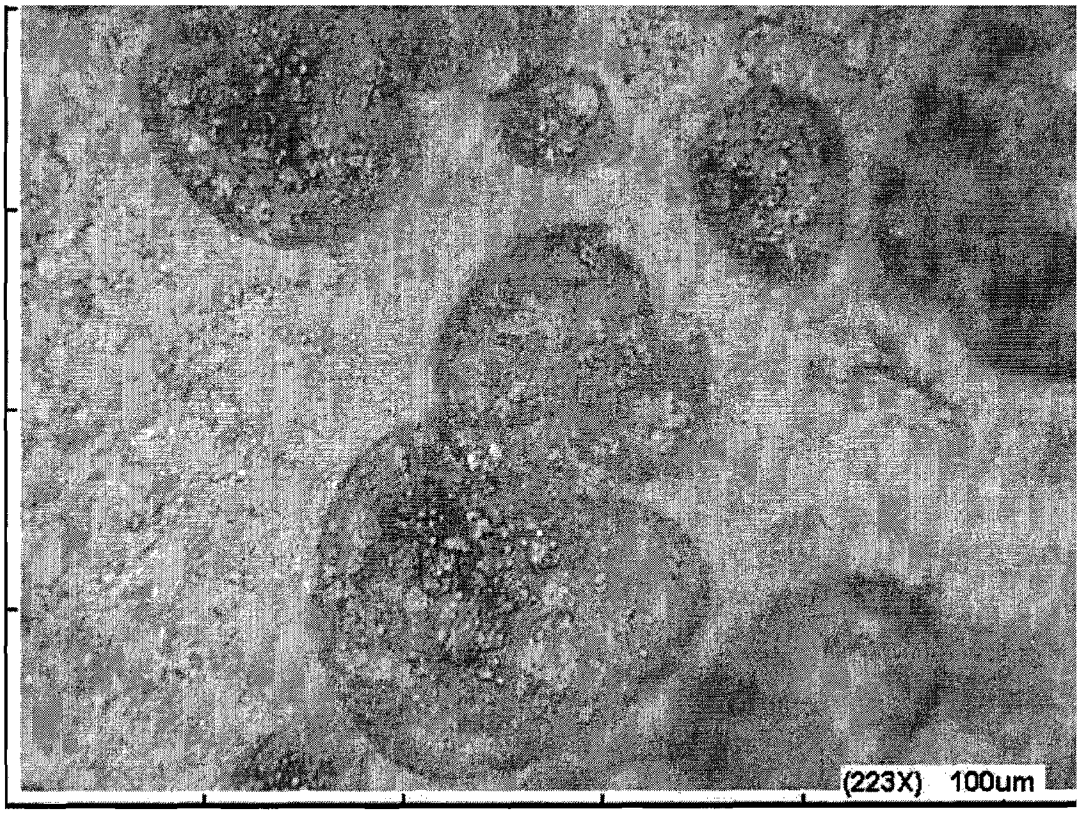

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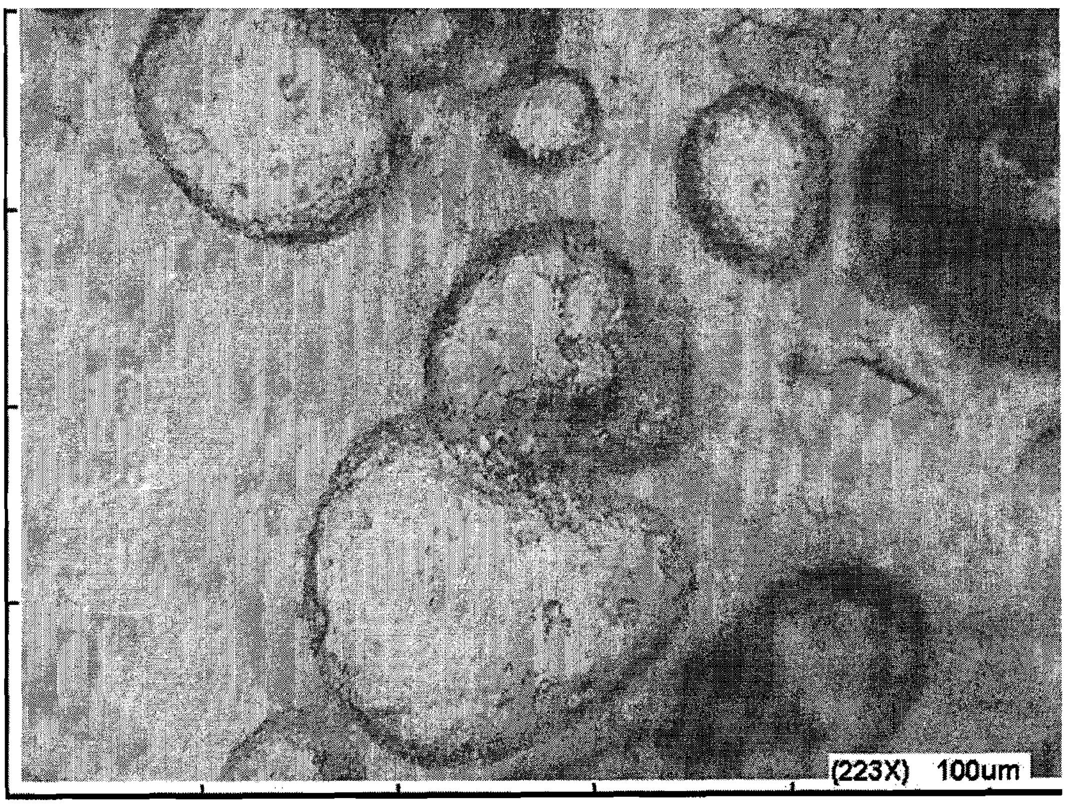

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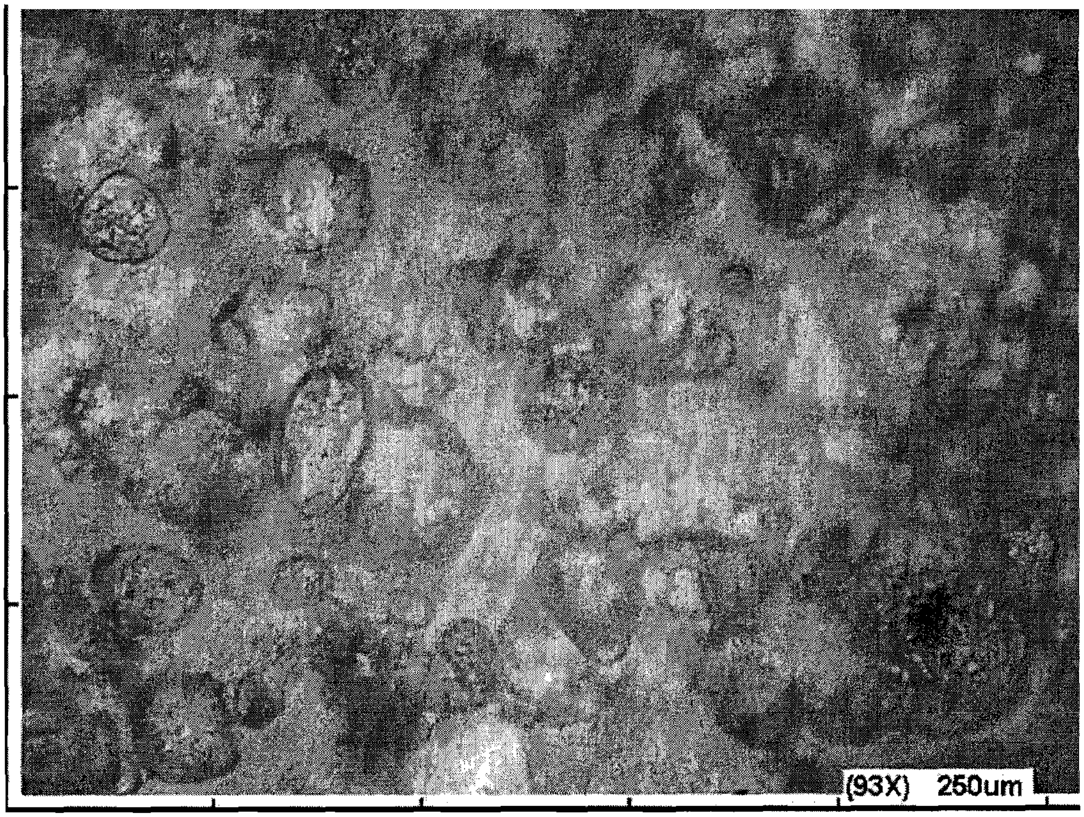

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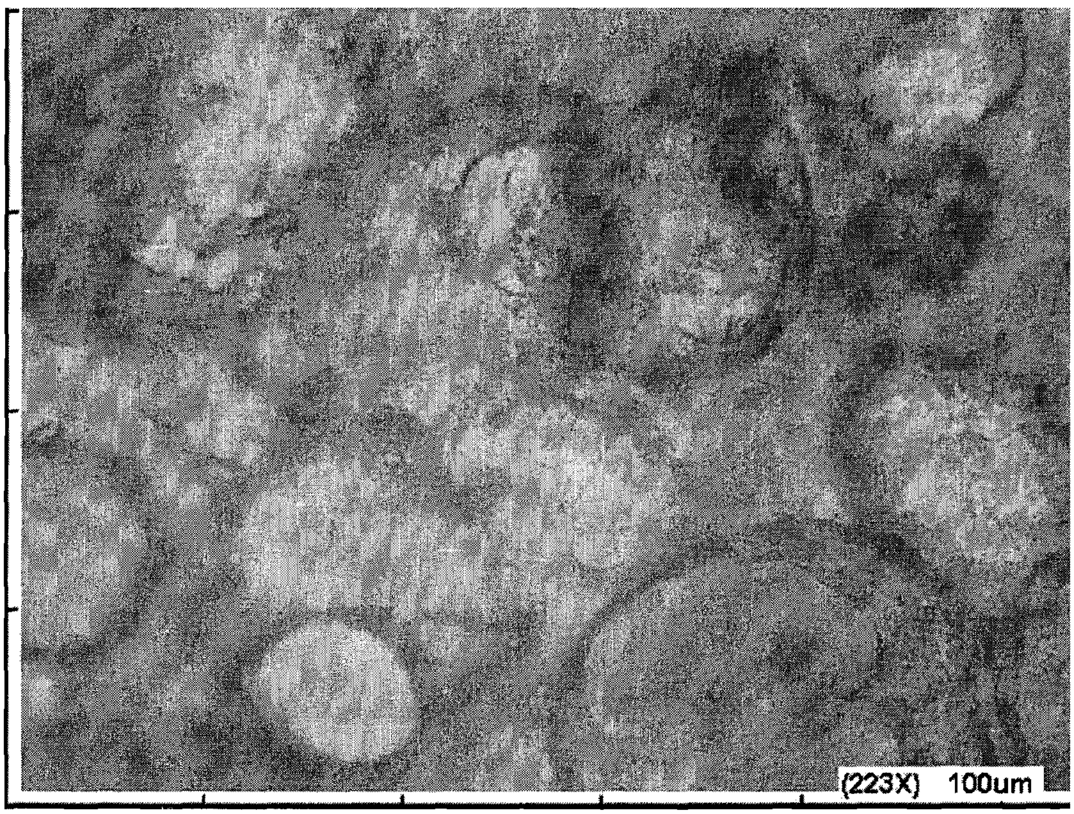

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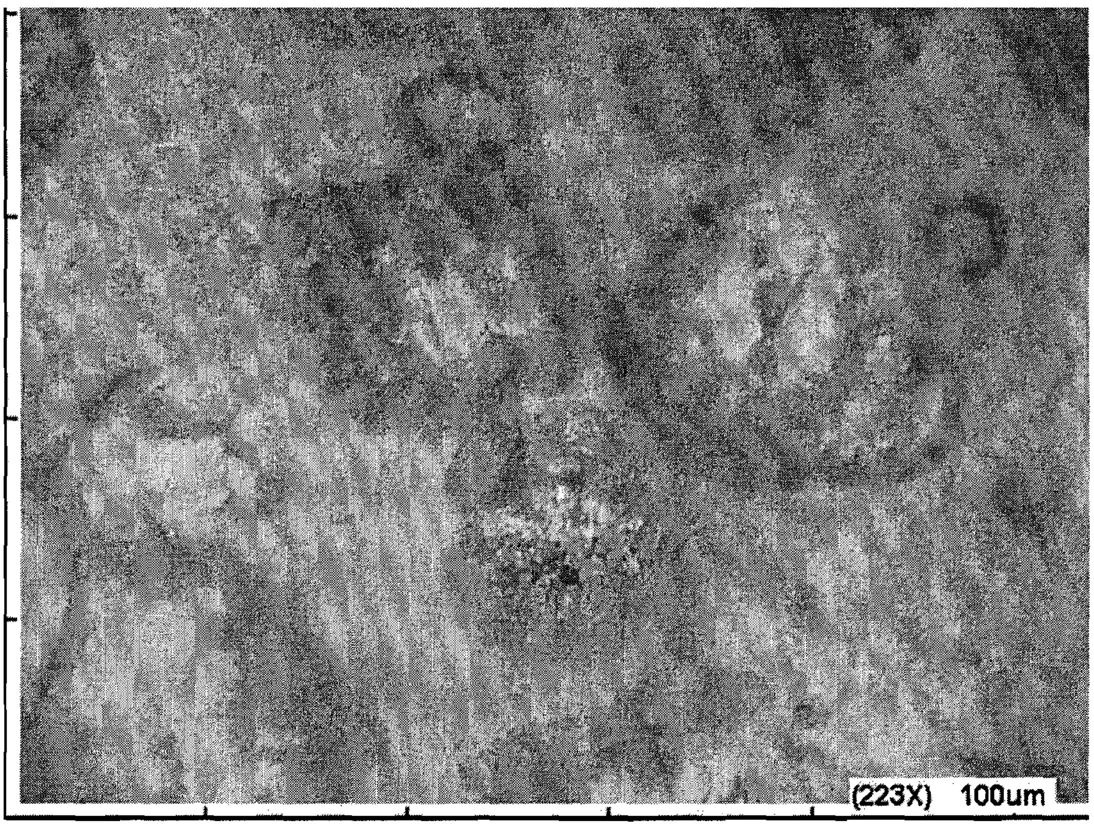

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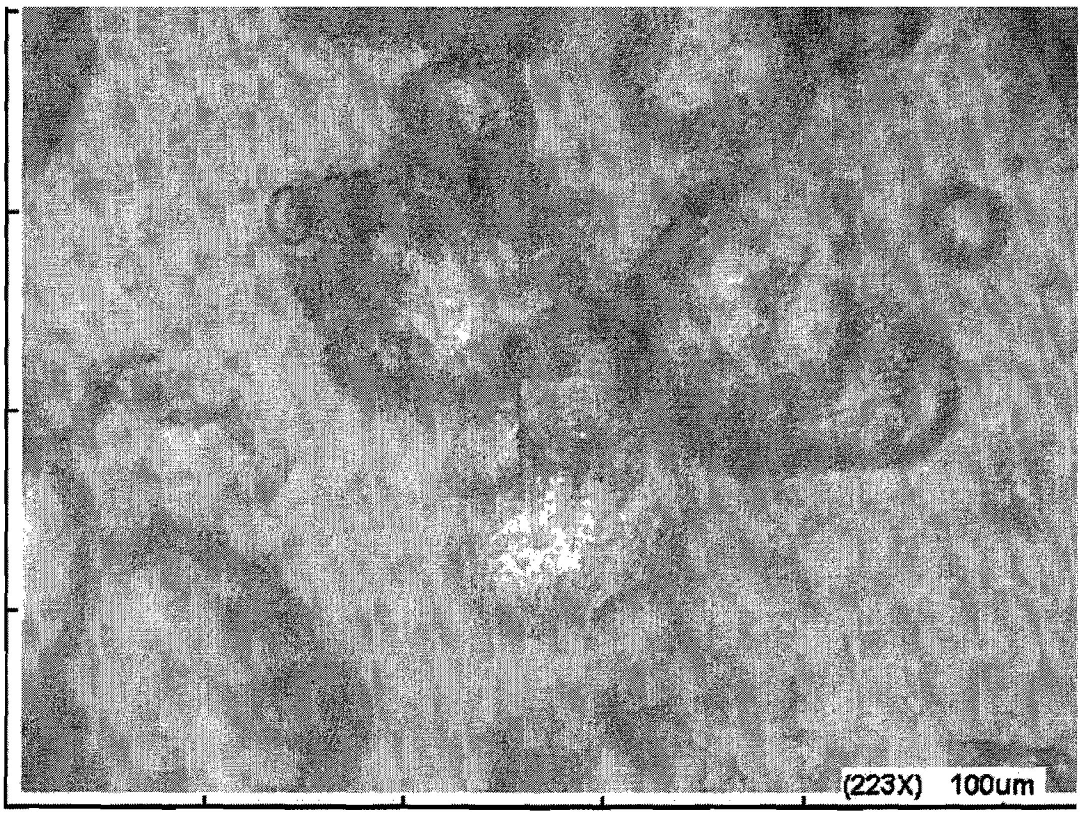


FIG. 25

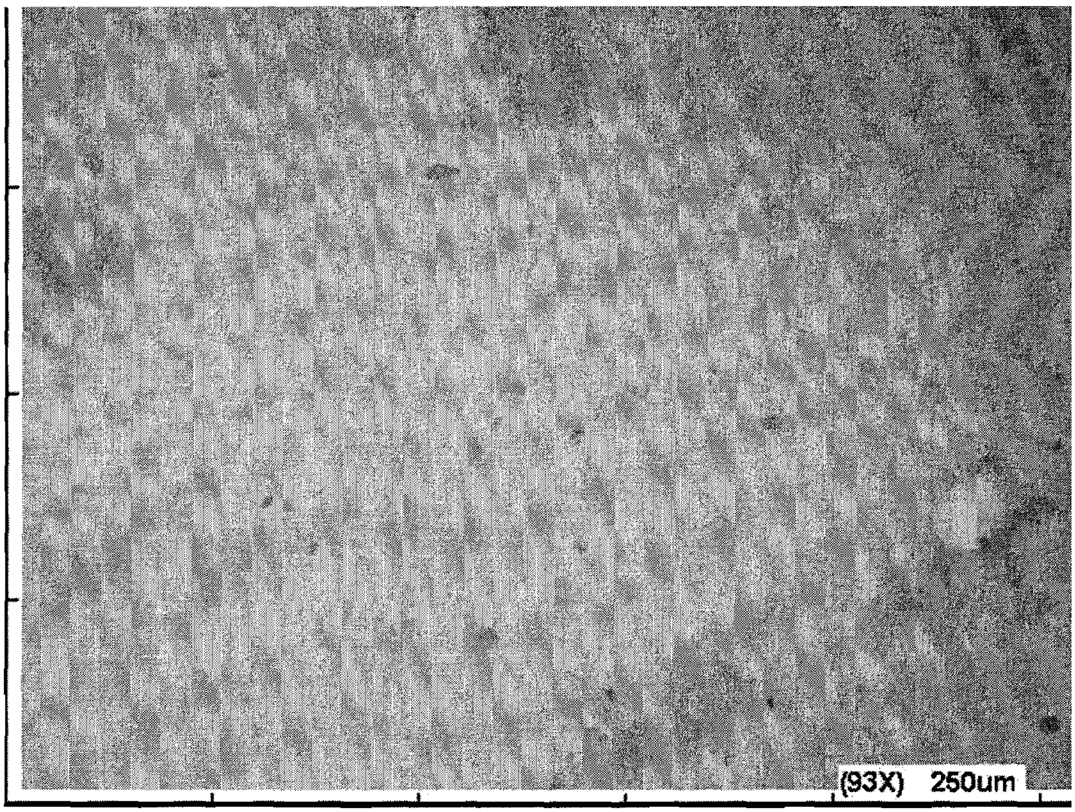


FIG. 26

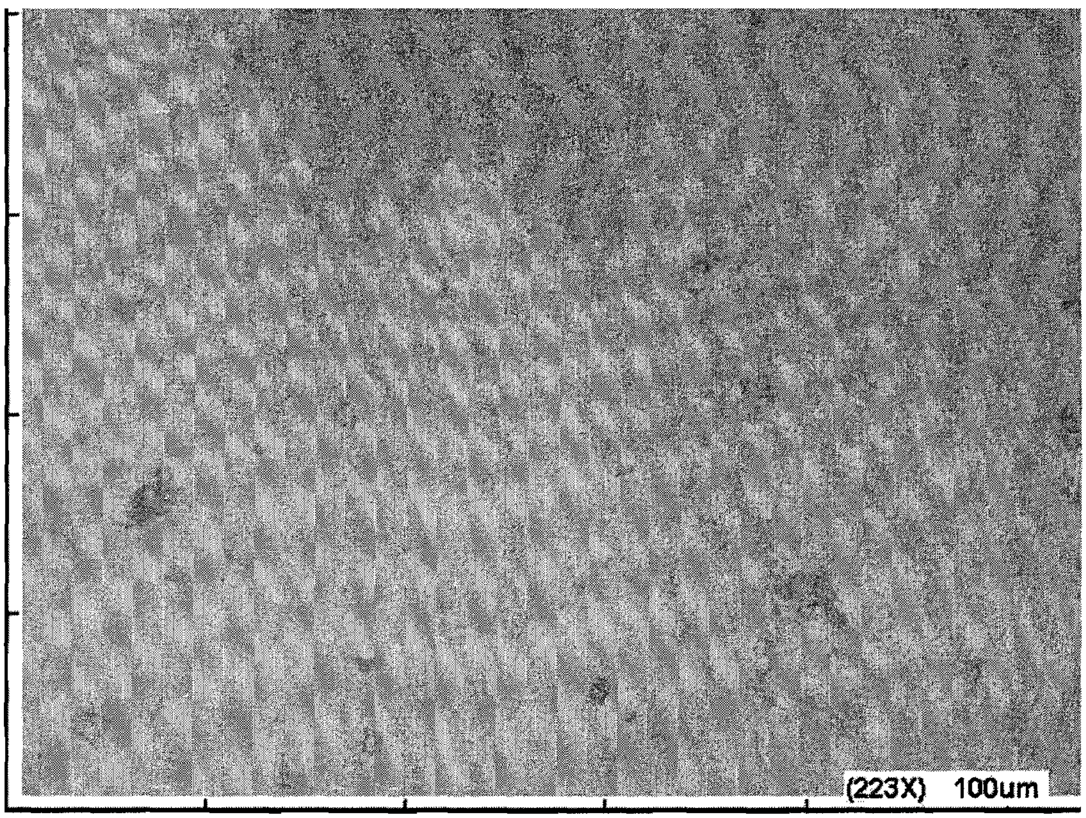


FIG. 27

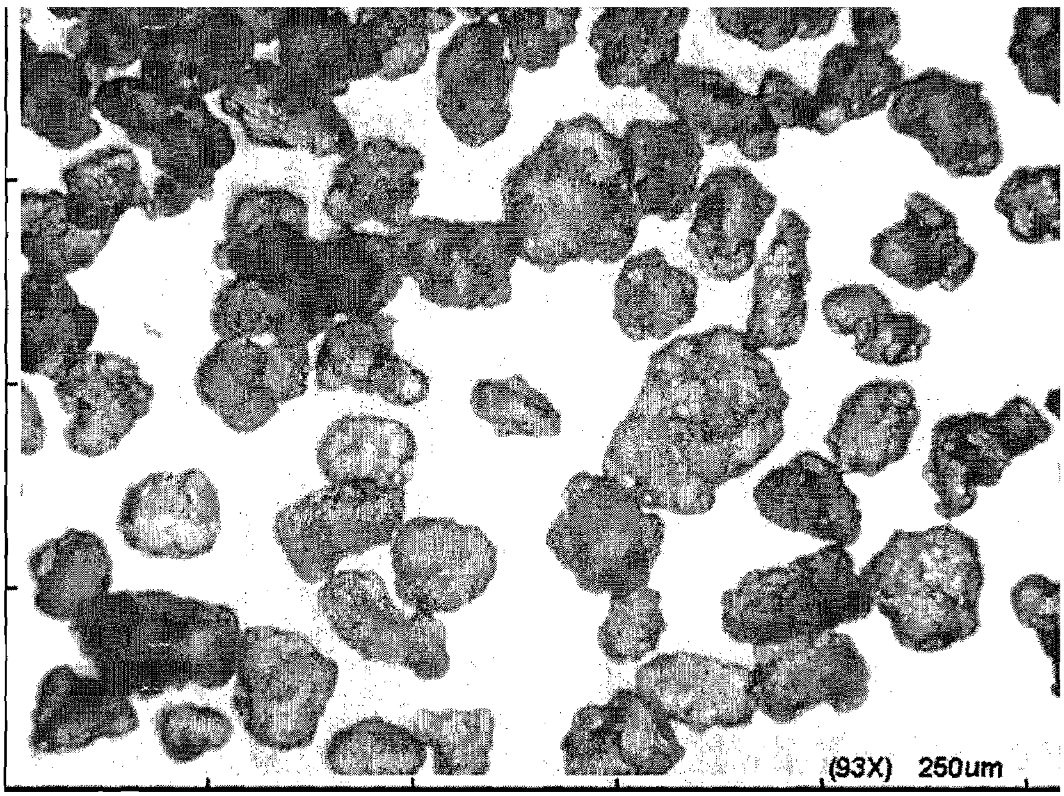


FIG. 28

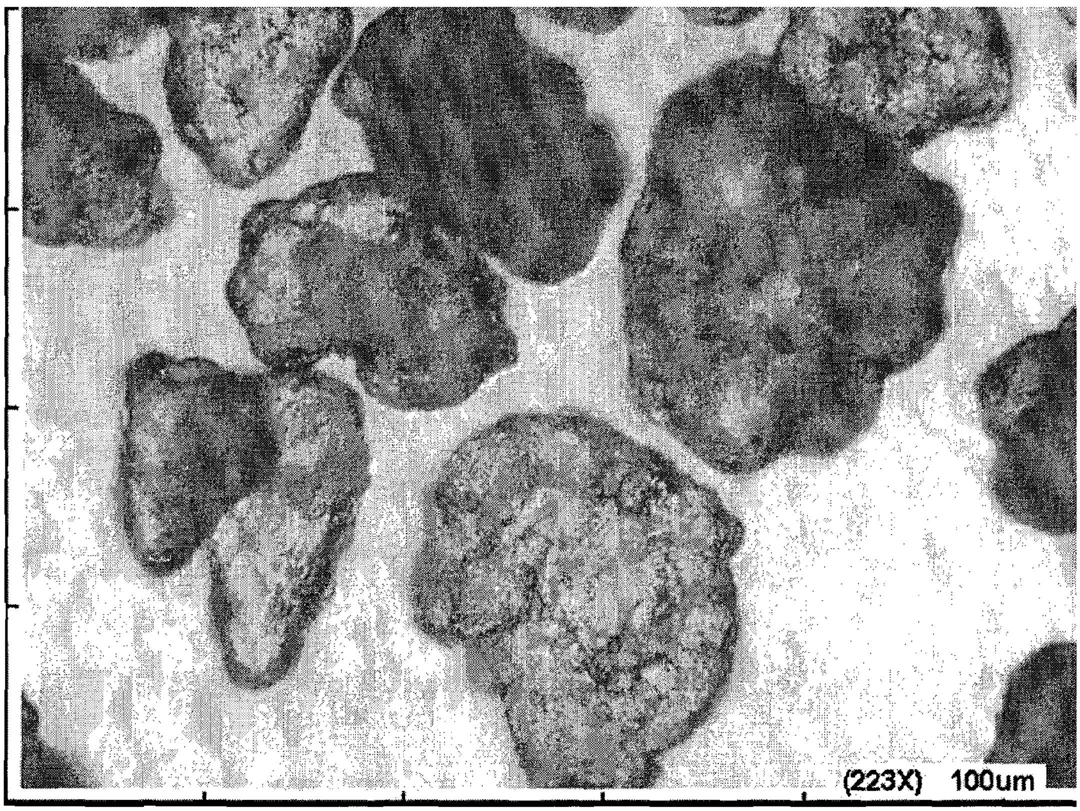
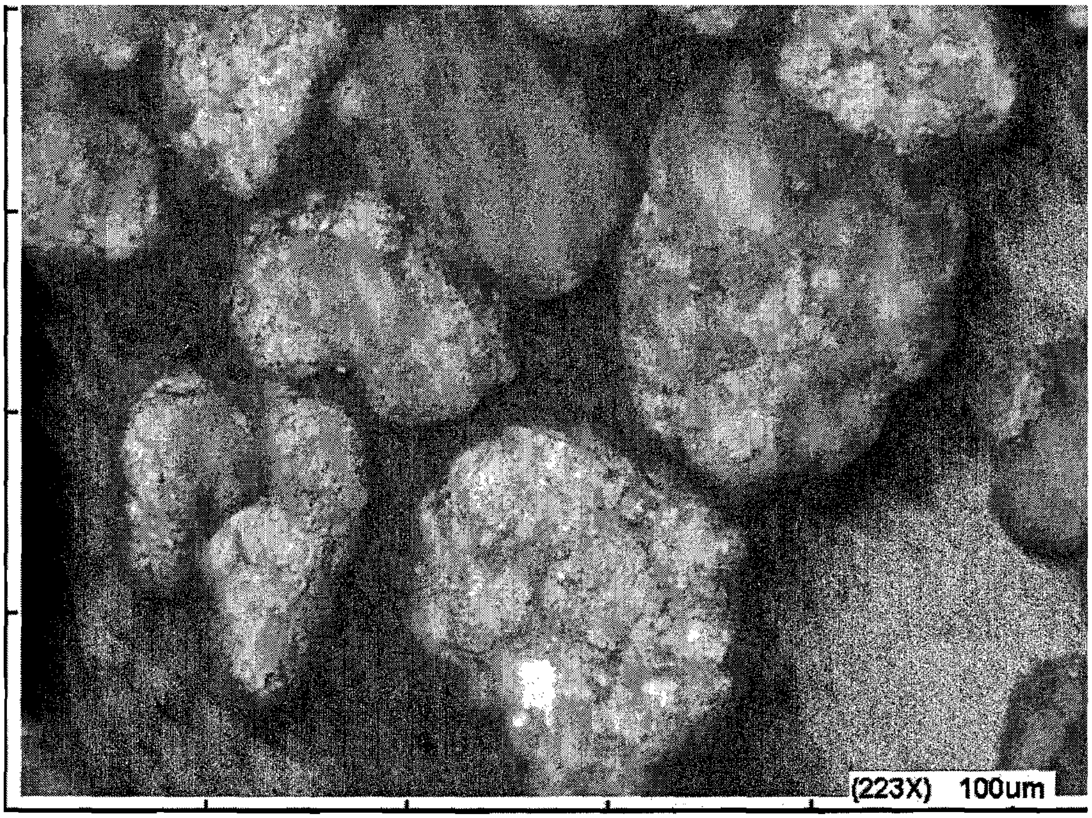


FIG. 29



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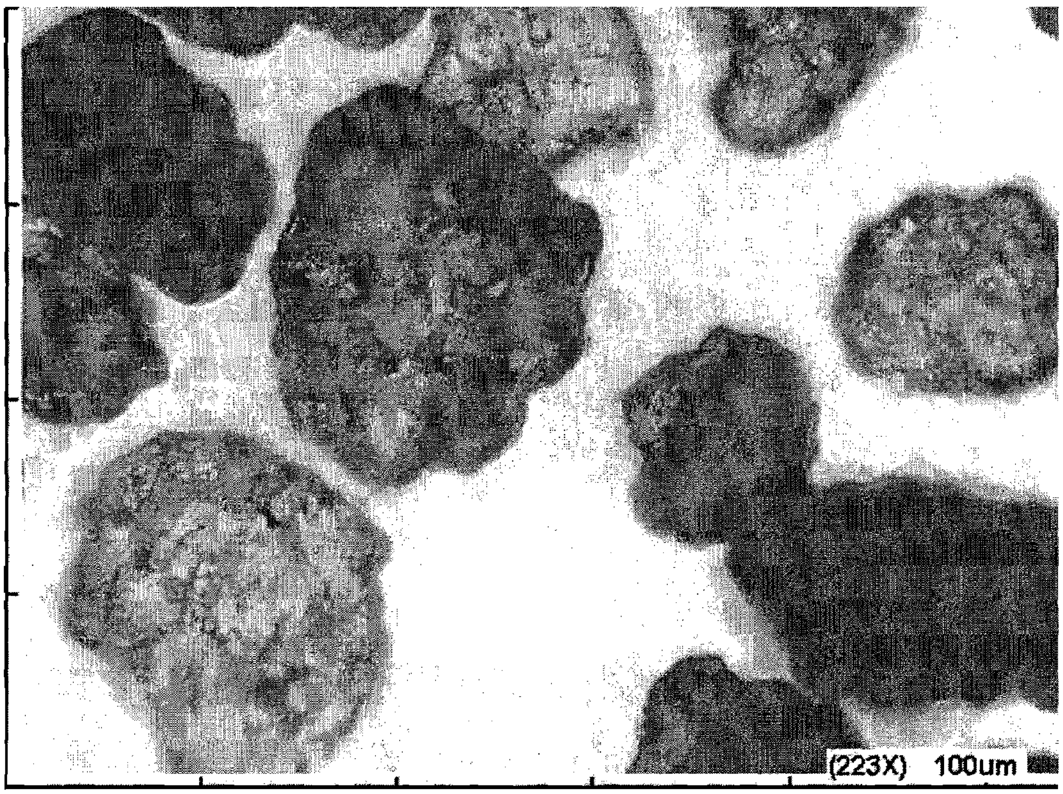

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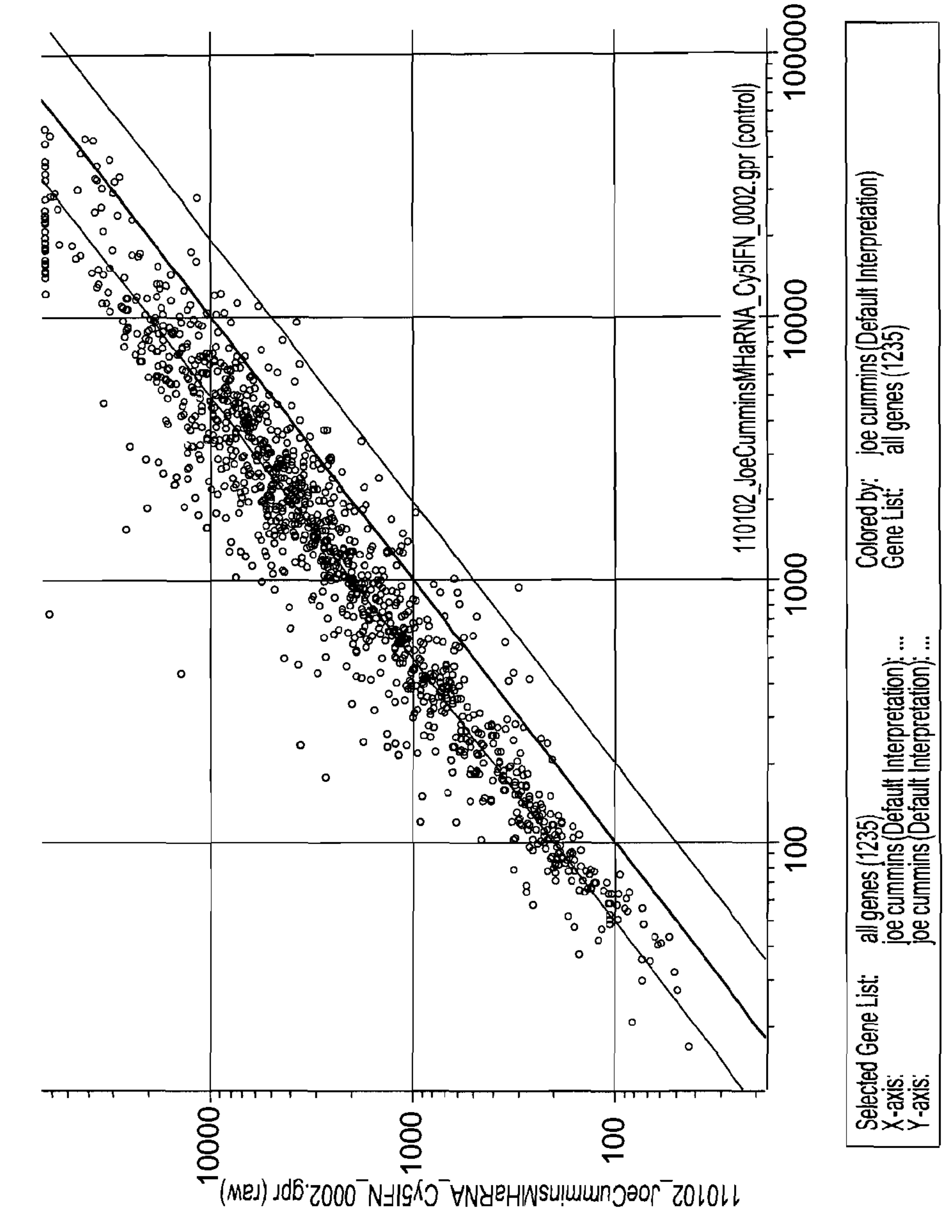

Normalized to GAPDH, most of the ISGs are induced.

FIG. 32

1101 02_JoeCumminsMHaRNA- Cy5IFN- 0002.gpr

Normali.	t-test p-\	Raw	Control	Common	Genbank	Map	Chror	Fun	Keywords
84.981	0.0037	63217.5	743.905	hemoglobin, epsilon 1	H79534	11	11		ISG
31.519	0.009	13927.5	441.874	v-jun avian sarcoma virus 17 oncogene	W96134	11	11		ISG
16.689	0.0192	25923	1553.28	CD69 antigen (p60, early T-cell activati(	NM_0017812p	13	12		ISG
15.267	0.0168	3612.5	236.618	regulator of G-protein signalling 1	AA017544	1	1		ISG
15.097	0.0222	2677.5	177.357	ESTs, Weakly similar to 1207289A reve	BF589173		0		ISG
11.022	0.0271	20701	1878.21	cold shock domain protein A	AA465019	12	12		ISG
8.6706	0.0592	4329.5	499.333	nasopharyngeal carcinoma susceptibility	AA504162	16	16		ISG
7.8361	0.0499	3699.5	472.107	interferon, gamma	AA969504	12	12		ISG
7.6992	0.0473	25074	3256.69	nuclear factor of kappa light polypeptide	W55872	14	14		ISG
7.6909	0.0459	920	119.623	early growth response 2 (Krox-20 (Dros(	AA446027	10	10		ISG
7.3832	0.0587	7531	1020.01	phorbol-12-myristate-13-acetate-inducel	AA458838	18	18		ISG
7.3285	0.0485	1770.5	241.591	interleukin 8	AA 102526	4	4		ISG
7.0928	0.0503	33673.5	4747.59	synaptonemal complex protein 1	NM_00317	1	1		ISG
6.6697	0.0623	2963	444.246	v-fos FBJ murine osteosarcoma viral or	NM_0052514q	24	14		ISG
6.5273	0.0567	10378	1589.94	Homo sapiens, clone IMAGE:3357927,	AA669531	17	17		ISG
6.319	0.0672	8145.5	1289.05	ESTs	T49610	17	17		ISG
6.1247	0.0662	4008.5	654.478	complement component 4-binding prote	T621 00	1	1		ISG
6.0223	0.0642	907	150.608	pyridoxal (pyridoxine, vitamin 86) kinas	AA158035	21	21		NOGRW
5.7239	0.0691	11852.5	2070.69	ESTs, Weakly similar to ubiquitous	TPFT47454	2	2		ISG
5.6889	0.0698	7907.5	1389.98	hypothetical protein FLJ21817 simiiartc	H89563	5	5		ISG
5.6855	0.0707	5575	980.557	IMAGE EST	T49086		0		ISG
5.5452	0.0729	7083	1277.32		T57938		0		ISG
5.5284	0.0754	6782.5	1226.85	malic enzyme 1, NADP(+)-dependent, c	AA669689	6q12	6		ISG
5.4536	0.0747	6200.5	1136.96	betaine-homocysteine methyitransferasf	T58958	5	5		ISG
5.341	0.0847	2714	508.147	guanosine monophosphate reductase	AA406242	6	6		ISG
5.2945	0.0816	12961.5	2448.12	amphiphysin (Stiff-Mann syndrome with	AA620426	7	7		ISG
5.2806	0.0802	4844.5	917.408	collagen, type VI, alpha 2	Stratagene	21	21		ISG
5.2499	0.0796	9429	1796.04	placental growth factor, vascular endoth	AA130714	14	14		ISG
5.2416	0.0799	4123	786.592	ESTs, Weakly similar to hypothetical pro	T60926	12	12		ISG
5.1731	0.0874	1337.5	258.55	related to the Nterminus oftre	AA281057	10p13	10		ISG
5.1566	0.0872	1234	239.304	KIAA0125 gene product	H65343	15	15		ISG
4.9288	0.0875	1567	317.926	cysteine and glycine-rich protein 3 (card	AA195959	11	11		ISG
4.9005	0.088	13022	2657.27	IMAGE EST	T62998		0		ISG
4.8357	0.0899	8366	1730.04	KIAA0763 gene product	AA775952	3pter-:	3		ISG
4.7066	0.0972	12658	2689.42	zinc finger protein 81 (HFZ20)	298304	X	0		ISG
4.6765	0.0951	4931.5	1054.54	Homo sapiens clone FLC0675 PR0287'	AA962465	22	22		ISG
4.5575	0.0992	1072	235.215	ESTs	AA873507	13	13		ISG
4.5361	0.1082	2120.5	467.477	helicase-moi	AA521474	14	14		ISG
4.5151	0.1015	2732.5	605.191	CCAAT/enhancer binding protein (C/EB	AA043506	8	8		ISG
4.5135	0.1008	9961.5	2207.03	ESTs. Moderately similar to putative Ra	AA996156	20	20		ISG
4.4582	0.1031	5056	1134.08	RuvB (E coli homolog)-like 1	AI023590	3	3		ISG
4.4506	0.1169	1911.5	429.488	helicase-moi	AA069444	14	14		ISG
4.4227	0.1054	4999.5	1130.41	phospholipase A2, group VII (platelet-ae	H65030		0		ISG
4.3695	0.1065	673.5	154.137	EST	H30012		0		ISG
4.3652	0.1062	9252	2119.5	intermediate filament protein syncoilin	AA486224	1	1		ISG
4.356	0.1091	952.5	218.662	related to the N terminus oftre	AI361386	10p13	10		ISG
4.3358	0.1075	10323.5	2381.01	prostaglandin-endoperoxide synthase 2	AA644211	1	1		ISG
4.3291	0.1096	5352.5	1236.39	Ras-GTPase activating protein SH3 dor	AI040381	4	4		ISG
4.2285	0.114	12949.5	3062.4	ribosomal protein L 15	AA434088	3	3		HSKP

FIG. 33A

4.2184	0.1138	5411	1282.7	vaccinia related kinase	1AA112979	14	14	ISG
4.2128	0.113	1789.5	424.775	collagen, type VIII, alpha 2	AA780815	1	1	NOT ISG
4.108	0.1174	16170	3936.2	solute carrier family 3 (activators of diba	AA630794	11	11	ISG
4.0832	0.1204	4434	1085.9	betaine-homocysteine methyltransferas(	T58958	5	5	ISG
4.0739	0.1196	4373	1073.43	STAT induced STAT inhibitor 3	NM_00395	17q25	17	ISG
4.0251	0.1433	7193.5	1787.16	7-60 protein	AA86521		0	ISG
4.0202	0.1235	16372	4072.42	cartilage linking protein 1	AA115902	5q143	5	ISG
3.9885	0.1234	2452	614.762	cystic fibrosis transmembrane conducta	NM_00049	7	7	ISG
3.9567	0.1273	12993	3283.8	filamin B, beta (actin-binding protein-27	AA486238	3	3	ISG
3.9374	0.1316	5613	1425.58	lipoprotein lipase	AA633835	8	8	ISG
3.8862	0.1293	5779.5	1487.18	membrane protein of cholinergic synapt	AA669603	17	17	ISG
3.8781	0.1294	1614	416.181	KIAA0125 gene product	H65343	15	15	ISG
3.874	0.1303	11188.5	2888.07	Homo sapiens clone FLC0675 PR0287'	AA781508	22	22	ISG
3.7916	0.1344	11484.5	3028.96	IMAGE EST	T55958		0	ISG
3.7797	0.1352	12168	3219.28	caspase 7, apoptosis-related cysteine pl	T50828	10	10	ISG
3.7644	0.1363	8575.5	2278.03	biliverdin reductase A	AA192419	7	7	ISG
3.7578	0.143	3153.5	839.193	RALBP1 associated Eps domain contair	T72336	X	0	ISG
3.7536	0.1371	12248.5	3263.17	tudor repeat associatorwith PCTAIRE 2	T52694		0	ISG
3.6982	0.1404	2649	716.296	protein phosphatase 3 (formerly 2B), ca	AA682631	4	4	ISG
3.6475	0.1442	2901	795.331	mouse double minute 2, human homolo	AA214617	12q14	12	ISG
3.6225	0.1472	3147	868.748	RNA binding motif, single stranded inter	AA456629	12	12	ISG
3.6072	0.1577	1329.5	368.57	TERA protein	AA906997	12	12	ISG
3.6021	0.147	515	142.972	ESTs	T89980		0	ISG
3.5884	0.148	7055.5	1966.2	tudor repeat associatorwith PCTAIRE 2	Stratagene placl		0	ISG
3.5744	0.1513	2309	645.974	complement component 1, r subcompor	T69603	12	12	ISG
3.5663	0.1559	1900.5	532.906	guanine nucleotide binding protein (G pi	H30255	19	19	ISG
3.5407	0.1586	1220	344.562	dual specificity phosphatase 1	NM_00441	5q34	5	ISG
3.5193	0.1527	4877	1385.77	Epstein-Barr virus induced gene 2 (lymr	AI123732	13	13	ISG
3.5011	0.1547	775	221.356	reversion-inducing-cysteine-rich protein	R26225	9p13-I	9	ISG
3 .5001	0.1548	889.5	254.136	ESTs	R67218	4	4	ISG
3.4914	*0.1559*	*1889*	*541.038*	BCL2/adenovirus E1 B 19kD interacting	NM_OO405	14q11	14	ISG
3.4692	0.1625	1984	571.886	KIAA0440 protein	AA417567	14q24	14	ISG
3.4562	0.164	4419	1278.58	polymerase (DNA directed), gamma	AA188761	15q25	15	HSKP
3.4446	0.1588	11331.5	3289.66	tropomyosin 1 (alpha)	W58092	15	15	ISG
3.4396	0.1663	20336	5912.32	ESTs	AL520050		0	ISG
3.423	0.1602	26322	7689.65	mouse double minute 2, human homolo	AI014368	12q14	12	ISG
3.4083	*0.1679*	632.5	185.578	KIAA0226 gene product	N36389	3	3	ISG
3.3921	0.1691	7686.5	2265.97	ESTs, Highly similar to NK-TUMOR RE.	AA279667		0	ISG
3.3891	0.1631	7019.5	2071.23	mitochondrial ribosomal protein L37	AA488652	1	1	HSKP
3.3833	0.1653	1009.5	298.376	immunoglobulin lambda-like polypeptidl	W73790	22	22	ISG
3.3832	0.1686	5069	1498.28	KIAA0089 protein	AA485401	3	3	ISG
3.3739	0.1644	12566.5	3724.59	Novel human gene mapping to chomost	AA488718	13	13	ISG
3.3636	0.1671	12969	3855.73	damage-specific DNA binding protein 1	AA608679	11	11	ISG
3.3267	0.1693	1460.5	439.019	transcription factor 8 (represses interleu	NM_03075	10p11	10	ISG
3.3219	0.1693	2084	627.351	aryl hydrocarbon receptor	AA181307	7	7	ISG
3.3135	0.1696	13928	4203.46	Homo sapiens NADH dehydrogenase (u	AA608515		0	ISG
3.2886	0.1719	8775.5	2668.47	isocitrate dehydrogenase 2 (NADP+), m	AA679907	15	15	ISG
3.2836	0.1726	7116.5	2167.29	defensin, alpha 5, Paneth cell-specific	M97925	8	8	ISG
3.275	0.173	17415.5	5317.65	von Hippel-Lindau syndrome	H73054	3p26-1	3	ISG
3.275	0.1734	4833.5	1475.88	Homo sapiens cDNA: FLJ22783 fis, clol	T59940	15	15	ISG
3.2677	0.1746	3809	1165.67	small inducible cytokine A3 (homologou	AA677522	17	17	ISG

FIG. 33B

3.2611	0.1748	6484	1988.29	Homo sapiens cDNA: FLJ23269 fis, clol	AA026686	2	2	ISG
3.2609	0.1744	5263.5	1614.11	ribosomal protein S24	N27154	10	10	HSKP
3.2463	0.1759	7559.5	2328.67	ESTs	T 90697		0	ISG
3.2458	0.176	16125.5	4968.14	sin3-associated polypeptide, 30kD	T87622	4q33-c	4	ISG
3.2269	0.178	818	253.498	protein kinase C, iota	T579570			ISG
3.2264	0.178	18430	5712.32	KIAA0160 protein	AI201344	17	17	ISG
3.2193	0.1784	23151.5	7191.38	ribosomal protein S13	AA629641	11	11	HSKP
3.2187	0.1784	22020.5	6841.53	60S acidic ribosomal protein PO	R89308	1	1	HSKP
3.2125	0.1848	1930	600.78	eukaryotic translation initiation factor 3,	AI017388	10	10	ISG
3.1794	0.1888	21608	6796.28	alda-keto reductase family 1, member E	AA701963	7	7	ISG
3.1679	0.1857	981	309.668	mucin 6, gastric	U97698	11	11	ISG
3.1625	0.1847	1101.5	348.301	casein kinase 1, delta	AI002588	17	17	ISG
3.1614	0.1844	9116.5	2883.68	mitochondrial ribosomal protein	L3H05820	3	3	HSKP
3.1497	0.1858	13506.5	4288.24	HCR (a-helix coiled-coil rod homologue;	R37026	6	6	ISG
3.1487	0.1879	7727.5	2454.19	40S ribosomal protein S27 isoform	AA156054	15	15	HSKP
3.1468	0.1907	4831	1535.23	chemokine (C-C motif) receptor	6N57964	6	6	ISG
3.142	0.1863	26450.5	8418.44	transcription termination factor, RNA po	AA709143	9	9	HSKP
3.1396	0.1864	8453	2692.42	breast cancer 1, early onset	H90415		0	ISG
3.1297	0.1929	648.5	207.207	mouse double minute 2, human homolo	R80235	12q14	12	ISG
3.1077	0.1934	3570	1148.77	L-3-hydroxyacyl-Coenzyme A dehydrog	T65407	4q22-(	14	ISG
3.1074	0.1906	18441	5934.6	peptidylprolyl isomerase C (cyclophilin (	AA676404	5	5	ISG
3.0865	0.1922	6710	2174	KIAA1001 protein	H50253	17	17	ISG
3.0789	0.1931	1701	552.472	Homo sapiens mRNA; cDNA DKFZp564	AA404994		0	ISG
3.0559	0.2033	3388	1108.67	ribosomal protein S11	AA461501	19	19	HSKP
3.0496	0.2079	2771	908.639	RAD23 (S. cerevisiae) homolog	AAA476274	19	19	ISG
3.0494	0.1963	18412.5	6038.06	splicing factor 3a, subunit 3, 60kD	R17811	1	1	ISG
3.035	0.1981	10403	3427.63	hydroxyacyl-Coenzyme A dehydrogenaO	NM_00449	X	0	ISG
3.0321	0.1983	11859	3911.21	protein phosphatase 2 (formerly 2A), reg	NM_00271	3q22.3	3	ISG
3.0287	0.2097	34258	11311.1	ribosomal protein S6 kinase, 90kD, poly	R95841	X	0	HSKP
3.0236	0.2007	4435	1466.77	L-3-hydroxyacyl-Coenzyme A dehydrog	T65407	4q22-(	4	ISG
3.0153	0.2169	18183.5	6030.5	inhibitor of DNA binding 2, dominant neg	NM_00216	2p25	2	ISG
3.0105	0.201	12364.5	4107.18	enoyl-Coenzyme A, hydratase/3-hydrox	R02373	3	3	ISG
3.007	0.2013	831	276.355	alpha2,3-sialyltransferase	AA181306	3q13.	3	ISG
3.0008	0.2025	5226.5	1741.69	ribosomal protein, large, PO	H73623	12	12	ISG
2.9975	0.2029	1848.5	616.689	ribosomal protein S23	H71857	5	5	ISG
2.9755	0.2073	958.5	322.127	Interleukin 4			0	ISG
2.9751	0.2052	13734	4616.25	ESTs	AA166617	10	10	ISG
2.9722	0.2165	4981.5	1676.02	heat shock 10kD protein 1 (chaperonin	AA448396	14	14	ISG
2.9708	0.2058	10366.5	3489.46	KIAA0471 gene product	AA279023	17	17	ISG
2.9576	0.2081	2227	752.966	ESTs	AA701026		0	ISG
2.9574	0.2108	1197	404.749	natriuretic peptide receptor C/guanylate	AI222701	5	5	ISG
2.9544	0.2077	31105	10528.5	interferon (alpha, beta and omega) rece	N59150	21	21	ISG
2.9312	0.2107	26030	8880.39	nuclear cap binding protein, 80kD	AA757918	9	9	ISG
2.9179	0.2125	21756	7456.15	ESTs	H20808		0	ISG
2.9155	0.2135	21764.5	7465.1	transforming growth factor, beta receptc	AA487034	3	3	ISG
2.9145	0.2135	6857	2352.68	lysosomal-associated membrane protein	NM_01439	3	3	ISG
2.9143	0.2153	5172	1774.7	hypothetical protein FLB6421	AA418724	7q33	7	ISG
2.9133	0.2145	3530.5	1211.84	KIAA0694 gene product	AI653069		0	ISG
2.9124	0.2132	55084.5	18913.5	peroxisome proliferative activated recep	NM_OO623	6	6	ISG
2.9098	0.2136	8364.5	2874.6	interferon regulatory factor 4	AA825491	6	6	ISG
2.9026	0.2153	17286	5955.35	stimulated trans-acting factor (50 kDa)	AA083407	11	11	ISG

FIG. 33C

2.9021	0.2145	14884.5	5128.94	ribosomal protein L26 homolog	W94107	5	5	HSKP
2.9006	0.2164	9639	3323.08	fibrinogen, gamma polypeptide	NM_02187	4	4	ISG
2.8965	0.216	4567	1576.74	eukaryotic translation elongation factor'	AA620477	7	7	ISG
2.8958	0.2154	798	275.57	TATA box binding protein (TBP)-associc	AA677306	Xq13.	0	HSKP
2.8936	0.2183	5342.5	1846.34	alanyl-tRNA synthetase	AA156571	16	16	ISG
2.8863	0.2166	4473	1549.71	Homo sapiens agrin precursor mRNA,	AA773358	1	1	ISG
2.8816	0.2172	2119	735.348	ribosomal protein L32	N53394	3	3	HSKP
2.8811	0.2173	1709	593.181	small inducible cytokine A3 (homologou	AA416584	17	17	ISG
2.8786	0.2252	2238.5	777.63	ribosomal protein S29	N93715	14	14	ISG
2.8693	0.2195	2450.5	854.042	EST	R06326		0	ISG
2.8683	0.2193	11065	3857.66	Hemoglobin, alpha 2	T565282	16	16	ISG
2.8641	0.2214	32368	11301.1	eukaryotic translation initiation factor 3,	AA669674	8	8	ISG
2.8618	0.2324	5644	1972.19	mal, T-cell differentiation protein	AA227594	2	2	ISG
2.8557	0.2232	16526	5787.05	ribosomal protein L36a	AA669359	14	14	HSKP
2.8552	0.221	521.5	182.648	RNA binding motif protein 9	H03903	22q13	22	ISG
2.841	0.2242	1422.5	500.711	hypothetical protein DKFZp547D155	AL512758		0	ISG
2.834	0.2249	4779	1686.33	modulator recognition factor I	AA789301	2	2	ISG
2.8274	0.2277	13507	4777.22	egf-like module containing, mucin-like, I	AA157797	19	19	ISG
2.818	0.2328	2764.5	980.998	asparagine synthetase	AA894927	7	7	ISG
2.813	0.2269	27172	9659.56	lectin, galactoside-binding, soluble, 1 (g	NM_00230	22	22	ISG
2.8106	0.2354	16494	5868.53	ribosomal protein L1Oa	R01139	6	6	HSKP
2.8099	0.2297	25422	9047.41	ribosomal protein S24	AI005519	10	10	HSKP
2.8059	0.2316	1637.5	583.599	ribosomal protein S6 kinase, 70kD, poly	AA425446	17	17	HSKP
2.8059	0.2283	36245	12917.6	ribosomal protein L21	AA464743	13	13	HSKP
2.8004	0.229	10155.5	3626.5	heat shock transcription factor 1	NM_00552	8	8	ISG
2.7912	0.2303	11841	4242.32	thrombospondin 1	AA464630	15	15	ISG
2.7911	0.2335	1779.5	637.552	nasopharyngeal carcinoma susceptibility	AA94059	16	16	ISG
2.7882	0.2308	15639	5609	ribosomal protein L39	N54526	X	0	HSKP
2.7875	0.2314	25378	9104.06	ribosomal protein L35	AA625634	6	6	ISG
2.7872	0.2307	1764.5	633.074	tetratricopeptide repeat domain 3	AA007509	21	21	ISG
2.7848	0.2372	18165	6522.81	ribosomal protein S10	AI611010	6	6	ISG
2.7841	0.2364	9032.5	3244.3	farnesyl diphosphate synthase (farnesyl	T65790	1	1	ISG
2.7825	0.2324	15894	5712.06	xanthene dehydrogenase	R09503	2	2	ISG
2.78	0.2431	5283.5	1900.56	inhibitor of DNA binding 2, dominant ne	NM_00216	2p25	2	ISG
2.7726	0.2529	46107.5	16630	delta sleep inducing peptide, immunorea	AB025432	Xq22.:	0	ISG
2.7709	0.2333	4259	1537.03	myeloid/lymphoid or mixed-lineage leuk.	AA057425	11	11	ISG
2.7628	0.2355	9476	3429.91	apolipoprotein L	AF323540	22	22	ISG
2.7587	0.239	5131	1859.95	ELK4, ETS-domain protein (SRF access	H61758	1	1	ISG
2.7508	0.2362	45752.5	16632.4	zinc finger protein 91 (HPF7, HTF10)	NM_OO343	19	19	ISG
2.7495	0.2364	65463	23808.8	ribosomal protein S23	N73091	5	5	HSKP
2.749	0.2366	1083	393.959	adenylate cyclase 2 (brain)	N45141	5	5	NOGRW
2.7468	0.2474	7583	2760.63	ras homolog gene family, member B	AA495846	2	2	ISG
2.7468	0.2373	21519.5	7834.44	inhibitor of DNA binding 2, dominant ne	NM_00216	2p25	2	ISG
2.7383	0.2544	5356	1955.97	chemokine (C-C motif) receptor 7	NM_00183	17	17	ISG
2.7367	0.2402	521.5	190.561	EST	N62914	1	1	ISG
2.7346	0.2426	1053	385.069	hydroxymethylbifane synthase	R06321	11	11	ISG
2.7341	0.2391	636.5	232.798	nerve growth factor, beta polypeptide	T56316	1	1	ISG
2.7335	0.2471	1987.5	727.086	ligase I, DNA, ATP-dependent	AA291715	19q13	19	HSKP
2.7326	0.2409	5486.5	2007.76	ESTs	H63361	5	5	ISG
2.7085	0.2505	4368.5	1612.88	SC35-interacting protein 1	H78241	12	12	ISG
2.7082	0.2458	9726.5	3591.45	stem-loop (histone) binding protein	AA629558	4	4	ISG

FIG. 33D

2.6924	0.2464	35767	13284.6	ribosomal protein L7a	H23421	9	9	ISG
2.6917	0.2458	620.5	230.522	RNA binding motif protein 9	AA454681	22q13	22	ISG
2.6844	0.2488	818.5	304.906	ATPase, Ca++ transporting, plasma me	N93024	1	1	ISG
2.6819	0.2632	5977.5	2228.84	nuclear antigen Sp100	AA447481	2	2	ISG
2.6717	0.2492	1025.5	3 83.843	serine (or cysteine) proteinase inhibitor,	N75719	7	7	ISG
2.6661	0.2511	4569	1713.73	11H7			0	
2.6423	0.2541	3830	1449.47	ribosomal protein S25	AA779404	11	11	HSKP
2.6422	0.2548	22780	8621.53	protein tyrosine phosphatase, receptor t	NM_00283	20p13	20	ISG
2.6344	0.2572	585.5	222.25	zinc finger protein 85	AI253261		0	ISG
2.627	0.2596	2732.5	1040.17	enolase 2, (gamma, neuronal)	AA450189	12	12	ISG
2.6258	0.2603	14783	5629.99	ubiquitin-like 1 (sentrin)	AA488626	2	2	ISG
2.6203	0.2587	1594.5	608.51	pyridoxal (pyridoxine, vitamin B6) kinas	AA158035	21	21	NOGRW
2.6201	0.2581	2669.5	1018.86	immunoglobulin heavy constant mu	H73590	14	14	ISG
2.6164	0.2627	4296	1641.92	Human mRNA for KIAAO099 gene, com	T56948	1	1	ISG
2.6154	0.2596	8979	3433.17	60S ribosomal protein L30 isolog	AA063398	15	15	HSKP
2.6083	0.2606	562.5	215.66	general transcription factor IIA, 1 (37kD	NM_01585	14	14	ISG
2.6052	0.2616	1024	393.058	zinc finger protein 84 (HPF2)	AA922661	5	5	ISG
2.6027	0.2622	1730	664.688	ribosomal protein L5	N80631	1	1	ISG
2.5905	0.2756	7759.5	2995.33	cytochrome c	R52654	7	7	ISG
2.589	0.2657	814.5	314.6	HIR (histone cell cycle regulation defect	W94880	22	22	ISG
2.5852	0.2648	889	343.875	Homo sapiens clone 23632 mRNA sequ	AA418387		0	ISG
2.585	0.2655	2566	992.643	interleukin 6 (interferon, beta 2)	N98591	7	7	ISG
2.5825	0.2667	4782	1851.66	bromodomain-containing 2	H72520	6	6	ISG
2.5814	0.2652	6480.5	2510.5	Homo sapiens clone FLC0675 PR0287'	R41407	22	22	ISG
2.5779	0.2664	16317	6329.59	runt-related transcription factor 3	N67778	1p36	1	ISG
2.5767	0.2666	5467	25407.1	ribosomal protein S23	N73091	5	5	ISG
2.5762	0.2668	6790.5	2635.85	Peroxisomal acyl-coenzyme A oxidase I	T62985	17	17	ISG
2.5758	0.2665	577	224.012	ESTs	T88698	14	14	ISG
2.5706	0.2672	16949.5	6593.59	lymphotoxin beta (TNF superfamily, me	AI351740		0	ISG
2.5697	0.2697	37902.5	14749.8	ESTs	H28545	7	7	ISG
2.5682	0.2677	2039	793.944	translocase of outer mitochondrial mem	AA088722	3	3	ISG
2.566	0.2778	31810.5	12397.1	ribosomal protein S4, Y-linked	T69468	Y	0	HSKP
2.5627	0.2722	3807	1485.54	lymphocyte antigen 6 complex, lo cus E	AA865464	8	8	ISG
2.5475	0.2773	3364.5	1320.72	growth arrest and DNA-damage-inducib	AA504354	19p13	19	ISG
2 .544	0. 2741	924.5	363.408	hypothetical protein	AL079292		0	ISG
2.5415	0.2734	19433	7646.34	adenosine deaminase, RNA-specific	AA600189	1	1	ISG
2.5377	0.2736	3852.5	1518.13	Homo sapiens clone 23632 mRNA sequ	N49250		0	ISG
2.537	0.276	1046.5	412.49	S100 calcium-binding protein A 11 (calgi	N29374	1	1	ISG
2.5228	0.2802	27262	10806.4	guanine nucleotide binding protein (G pl	AA487912	1	1	ISG
2.522	0.2771	7898.5	3131.84	MHC class I polypeptide-related sequen	NM_00593	6	6	ISG
2.518	0.2784	11115.5	4414.46	2',5'-oligoadenylatesynthetase 1 (40-46	AA146773	12q24	12	ISG
2.5169	0.2796	47251	18773.7	CD68 antigen	NM_OO125	17p13	17	ISG
2.5169	0.2781	915.5	363.748	IDN3 protein	N62911	5	5	ISG
2.5121	0.2823	20808.5	8283.16	splicing factor, arginine/serine-rich 2	AA454585	17	17	ISG
2.5087	0.2802	1017	405.389	guanine nucleotide binding protein (G pl	AA701654	19	19	ISG
2.5082	0.2847	5064.5	2019.18	adenovirus 5 E1A binding protein	AA598473		0	ISG
2.5028	0.2892	559.5	223.547	hypothetical protein MGC3036	AA976044	7	7	ISG
2.502	0.2807	43177.5	17257.5	van Hippel-Lindau syndrome	R54177	3p26-j	3	ISG

FIG. 33E

PROCESS FOR MAKING AN INGESTIBLE FILM

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a continuation-in-part of; (a) PCT/US02/32575, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (2) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002; (b) PCT/US02/32594, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/414,276, filed Sep. 27, 2002, (2) U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002; and (c) PCT/US02/32542, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/371,940, filed Apr. 11, 2002, (2) U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002; and claims benefit to U.S. Provisional Application No. 60/443,741 filed Jan. 30, 2003, the contents all of which are incorporated herein by reference.

FIELD OF THE INVENTION

The invention relates to rapidly dissolving films and methods of their preparation. The films contain an active ingredient that is evenly distributed throughout the film. The even or uniform distribution is achieved by controlling one or more parameters, and particularly the elimination of air pockets prior to and during film formation and the use of a drying process that reduces aggregation or conglomeration of the components in the film as it forms into a solid structure. The drying process further permits exposure of the film to temperatures above that at which the active ingredient typically would degrade without loss of a desired level of activity.

BACKGROUND OF THE RELATED TECHNOLOGY

Active ingredients, such as drugs or pharmaceuticals, may be prepared in a tablet form to allow for accurate and consistent dosing. However, this form of preparing and dispensing medications has many disadvantages including that a large proportion of adjuvants that must be added to obtain a size able to be handled, that a larger medication form requires additional storage space, and that dispensing includes counting the tablets which has a tendency for inaccuracy. In addition, many persons, estimated to be as much as 28% of the population, have difficulty swallowing tablets. While tablets may be broken into smaller pieces or even crushed as a means of overcoming swallowing difficulties, this is not a suitable solution for many tablet or pill forms. For example, crushing or destroying the tablet or pill form to facilitate ingestion, alone or in admixture with food, may also destroy the controlled release properties.

As an alternative to tablets and pills, films may be used to carry active ingredients such as drugs, pharmaceuticals, and the like. However, historically films and the process of making drug delivery systems therefrom have suffered from a number of unfavorable characteristics that have not allowed them to be used in practice.

Films that incorporate a pharmaceutically active ingredient are disclosed in expired U.S. Pat. No. 4,136,145 to Fuchs, et al. ("Fuchs"). These films may be formed into a sheet, dried and then cut into individual doses. The Fuchs disclosure alleges the fabrication of a uniform film, which includes the combination of water-soluble polymers, surfactants, flavors, sweeteners, plasticizers and drugs. These allegedly flexible films are disclosed as being useful for oral, topical or enteral use. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and ear areas.

Examination of films made in accordance with the process disclosed in Fuchs, however, reveals that such films suffer from the aggregation or conglomeration of particles, i.e., self-aggregation, making them inherently non-uniform. This result can be attributed to Fuchs' process parameters, which although not disclosed likely include the use of relatively long drying times, thereby facilitating intermolecular attractive forces, convection forces, air flow and the like to form such agglomeration.

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

The problems of self-aggregation leading to non-uniformity of a film were addressed in U.S. Pat. No. 4,849,246 to Schmidt ("Schmidt"). Schmidt specifically pointed out that the methods disclosed by Fuchs did not provide a uniform film and recognized that that the creation of a non-uniform film necessarily prevents accurate dosing, which as discussed above is especially important in the pharmaceutical area. Schmidt abandoned the idea that a mono-layer film, such as described by Fuchs, may provide an accurate dosage form and instead attempted to solve this problem by forming a multi-layered film. Moreover, his process is a multi-step process that adds expense and complexity and is not practical for commercial use.

Other U.S. Patents directly addressed the problems of particle self-aggregation and non-uniformity inherent in conventional film forming techniques. In one attempt to overcome non-uniformity, U.S. Pat. No. 5,629,003 to Horstmann et al. and U.S. Pat. No. 5,948,430 to Zerbe et al. incorporated additional ingredients, i.e. gel formers and polyhydric alcohols respectively, to increase the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film. These methods have the disadvantage of requiring additional components, which translates to additional cost and manufacturing steps. Furthermore, both methods employ the use the conventional time-consuming drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The long length of drying time aids in promoting the aggregation of the active and other adjuvant, notwithstanding the use of viscosity modifiers. Such processes also run the risk of exposing the active, i.e., a drug, or vitamin C, or other components to prolonged exposure to moisture and elevated temperatures, which may render it ineffective or even harmful.

In addition to the concerns associated with degradation of an active during extended exposure to moisture, the conventional drying methods themselves are unable to provide uniform films. The length of heat exposure during conventional processing, often referred to as the "heat history", and the manner in which such heat is applied, have a direct effect on the formation and morphology of the resultant film product. Uniformity is particularly difficult to achieve via conventional drying methods where a relatively thicker film, which is well-suited for the incorporation of a drug active, is desired. Thicker uniform films are more difficult to achieve because the surfaces of the film and the inner portions of the film do not experience the same external conditions simultaneously during drying. Thus, observation of relatively thick films made from such conventional processing shows a non-uniform structure caused by convection and intermolecular forces and requires greater than 10% moisture to remain flexible. The amount of free moisture can often interfere over time with the drug leading to potency issues and therefore inconsistency in the final product.

Conventional drying methods generally include the use of forced hot air using a drying oven, drying tunnel, and the like. The difficulty in achieving a uniform film is directly related to the Theological properties and the process of water evaporation in the film-forming composition. When the surface of an aqueous polymer solution is contacted with a high temperature air current, such as a film-forming composition passing through a hot air oven, the surface water is immediately evaporated forming a polymer film or skin on the surface. This seals the remainder of the aqueous film-forming composition beneath the surface, forming a barrier through which the remaining water must force itself as it is evaporated in order to achieve a dried film. As the temperature outside the film continues to increase, water vapor pressure builds up under the surface of the film, stretching the surface of the film, and ultimately ripping the film surface open allowing the water vapor to escape. As soon as the water vapor has escaped, the polymer film surface reforms, and this process is repeated, until the film is completely dried. The result of the repeated destruction and reformation of the film surface is observed as a "ripple effect" which produces an uneven, and therefore non-uniform film. Frequently, depending on the polymer, a surface will seal so tightly that the remaining water is difficult to remove, leading to very long drying times, higher temperatures, and higher energy costs.

Other factors, such as mixing techniques, also play a role in the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval. Air can be trapped in the composition during the mixing process or later during the film making process, which can leave voids in the film product as the moisture evaporates during the drying stage. The film frequently collapse around the voids resulting in an uneven film surface and therefore, non-uniformity of the final film product. Uniformity is still affected even if the voids in the film caused by air bubbles do not collapse. This situation also provides a non-uniform film in that the spaces, which are not uniformly distributed, are occupying area that would otherwise be occupied by the film composition. None of the above-mentioned patents either addresses or proposes a solution to the problems caused by air that has been introduced to the film.

Therefore, there is a need for methods and compositions for film products, which use a minimal number of materials or components, and which provide a substantially non-self-aggregating uniform heterogeneity throughout the area of the films. Desirably, such films are produced through a selection of a polymer or combination of polymers that will provide a desired viscosity, a film-forming process such as reverse roll coating, and a controlled, and desirably rapid, drying process which serves to maintain the uniform distribution of non-self-aggregated components without the necessary addition of gel formers or polyhydric alcohols and the like which appear to be required in the products and for the processes of prior patents, such as the aforementioned Horstmann and Zerbe patents. Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product.

SUMMARY OF THE INVENTION

In one aspect of the present invention there is provided a process for making a film having a substantially uniform distribution of components and a desired level of an active component, which includes the steps of combining a polymer component, polar solvent and an active component to form a matrix with a uniform distribution of the components; forming a film from the matrix; providing a surface having top and bottom sides; feeding the film onto the top side of the surface; and drying the film by applying heat to the bottom side of the surface and exposing the film to a temperature above a degradation temperature of the active component, wherein the active component is maintained at the desired level.

In another aspect of the present invention, there is provided a film product containing a desired level of an active component formed by the steps of: combining a polymer, a polar solvent and an active component to form a material with a non-self-aggregating uniform heterogeneity; forming the material into a film; and drying the film at a temperature above a degradation temperature of the active component, wherein the active component is maintained at the desired level.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a side view of a package containing a unit dosage film of the present invention.

FIG. **2** shows a top view of two adjacently coupled packages containing individual unit dosage forms of the present invention, separated by a tearable perforation.

FIG. **3** shows a side view of the adjacently coupled packages of FIG. **2** arranged in a stacked configuration.

FIG. **4** shows a perspective view of a dispenser for dispensing the packaged unit dosage forms, dispenser containing the packaged unit dosage forms in a stacked configuration.

FIG. **5** is a schematic view of a roll of coupled unit dose packages of the present invention.

FIG. **6** is a schematic view of an apparatus suitable for preparation of a pre-mix, addition of an active, and subsequent formation of the film.

FIG. **7** is a schematic view of an apparatus suitable for drying the films of the present invention.

FIG. **8** is a sequential representation of the drying process of the present invention.

FIG. **9** is a photographic representation of a film dried by conventional drying processes.

FIG. **10** is a photographic representation of a film dried by conventional drying processes.

FIG. **11** is a photographic representation of a film dried by conventional drying processes.

FIG. **12** is a photographic representation of a film dried by conventional drying processes.

FIG. **13** is a photographic representation of a film dried by conventional drying processes.

FIG. **14** is a photographic representation of a film dried by conventional drying processes.

FIG. **15** is a photographic representation of a film dried by conventional drying processes.

FIG. **16** is a photographic representation of a film dried by conventional drying processes.

FIG. **17** is a photographic representation of a film dried by the inventive drying process.

FIG. **18** is a photographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **19** is a photographic representation of a film containing fat coated dried by the inventive drying process.

FIG. **20** is a photographic representation of a film containing fat coated dried by the inventive drying process.

FIG. **21** is a photographic representation of a film containing fat coated dried by the inventive drying process.

FIG. **22** is a photographic representation of a film containing fat coated dried by the inventive drying process.

FIG. **23** is a photographic representation of a film containing fat coated dried by the inventive drying process.

FIG. **24** is a photographic representation of a film containing fat coated dried by the inventive drying process.

FIG. **25** is a photographic representation of a film containing fat coated dried by the inventive drying process.

FIG. **26** is a photographic representation of fat coated particles not in film, or 9 minutes at 80° C.

FIG. **27** is a photographic representation of fat coated particles not in film, or 9 minutes at 80° C.

FIG. **28** is a photographic representation of fat coated particles at room temperature prior to processing.

FIG. **29** is a photographic representation of fat coated particles at room temperature prior to processing.

FIG. **30** is a photographic representation of fat coated particles at room temperature prior to processing.

FIG. **31** is a photographic representation of fat coated particles at room temperature prior to processing.

FIG. **32** is a graphical representation of a microarray on the blood of a human after ingestion by the human of a film of the present invention containing a bovine derived protein.

FIG. **33** is a table of the data represented in the graph of FIG. **32**.

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of the present invention the term non-self-aggregating uniform heterogeneity refers to the ability of the films of the present invention, which are formed from one or more components in addition to a polar solvent, to provide a substantially reduced occurrence of, i.e. little or no, aggregation or conglomeration of components within the film as is normally experienced when films are formed by conventional drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The term heterogeneity, as used in the present invention, includes films that will incorporate a single component, such as a polymer, as well as combinations of components, such as a polymer and an active. Uniform heterogeneity includes the substantial absence of aggregates or conglomerates as is common in conventional mixing and heat drying methods used to form films.

Furthermore, the films of the present invention have a substantially uniform thickness, which is also not provided by the use of conventional drying methods used for drying water-based polymer systems. The absence of a uniform thickness detrimentally affects uniformity of component distribution throughout the area of a given film.

The film products of the present invention are produced by a combination of a properly selected polymer and a polar solvent, optionally including an active ingredient as well as other fillers known in the art. These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process. Examples of controlled drying processes include, but are not limited to, the use of the apparatus disclosed in U.S. Pat. No. 4,631,837 to Magoon ("Magoon"), herein incorporated by reference, as well as hot air impingement across the bottom substrate and bottom heating plates. Another drying technique for obtaining the films of the present invention is controlled radiation drying, in the absence of uncontrolled air currents, such as infrared and radio frequency radiation (i.e. microwaves).

The objective of the drying process is to provide a method of drying the films that avoids complications, such as the noted "rippling" effect, that are associated with conventional drying methods and which initially dry the upper surface of the film, trapping moisture inside. In conventional oven drying methods, as the moisture trapped inside subsequently evaporates, the top surface is altered by being ripped open and then reformed. These complications are avoided by the present invention, and a uniform film is provided by drying the bottom surface of the film first or otherwise preventing the formation of polymer film formation (skin) on the top surface of the film prior to drying the depth of the film. This may be achieved by applying heat to the bottom surface of the film with substantially no top air flow, or alternatively by the introduction of controlled microwaves to evaporate the water or other polar solvent within the film, again with substantially no top air flow. Yet alternatively, drying may be achieved by using balanced fluid flow, such as balanced air flow, where the bottom and top air flows are controlled to provide a uniform film. In such a case, the air flow directed at the top of the film should not create a condition which would cause movement of particles present in the wet film, due to forces generated by the air currents. Additionally, air currents directed at the bottom of the film should desirably be controlled such that the film does not lift up due to forces from the air. Uncontrolled air currents, either above or below the film, can create non-uniformity in the final film products. The humidity level of the area surrounding the top surface may also be appropriately adjusted to prevent premature closure or skinning of the polymer surface.

This manner of drying the films provides several advantages. Among these are the faster drying times and a more uniform surface of the film, as well as uniform distribution of components for any given area in the film. In addition, the faster drying time allows viscosity to quickly build within the film, further encouraging a uniform distribution of components and decrease in aggregation of components in the final film product. Desirably, the drying of the film will occur within about ten minutes or fewer, or more desirably within about five minutes or fewer.

The present invention yields exceptionally uniform film products when attention is paid to reducing the aggregation of the compositional components. By avoiding the introduction of and eliminating excessive air in the mixing process, selecting polymers and solvents to provide a controllable viscosity and by drying the film in a rapid manner from the bottom up, such films result.

The products and processes of the present invention rely on the interaction among various steps of the production of the films in order to provide films that substantially reduce the self-aggregation of the components within the films. Specifically, these steps include the particular method used to form the film, making the composition mixture to prevent air bubble inclusions, controlling the viscosity of the film forming composition and the method of drying the film. More particularly, a greater viscosity of components in the mixture is particularly useful when the active is not soluble in the selected polar solvent in order to prevent the active from settling out. However, the viscosity must not be too great as to hinder or prevent the chosen method of casting, which desirably includes reverse roll coating due to its ability to provide a film of substantially consistent thickness.

In addition to the viscosity of the film or film-forming components or matrix, there are other considerations taken into account by the present invention for achieving desirable film uniformity. For example, stable suspensions are achieved which prevent solid (such as drug particles) sedimentation in non-colloidal applications. One approach provided by the present invention is to balance the density of the particulate (ρ_p) and the liquid phase (ρ_1) and increase the viscosity of the liquid phase (μ). For an isolated particle, Stokes law relates the terminal settling velocity (Vo) of a rigid spherical body of radius (r) in a viscous fluid, as follows:

$$V_o=(2gr^r)(\rho_p-\rho_1)/9\mu$$

At high particle concentrations, however, the local particle concentration will affect the local viscosity and density. The viscosity of the suspension is a strong function of solids volume fraction, and particle-particle and particle-liquid interactions will further hinder settling velocity.

Stokian analyses has shown that the incorporation of a third phase, dispersed air or nitrogen, for example, promotes suspension stability. Further, increasing the number of particles leads to a hindered settling effect based on the solids volume fraction. In dilute particle suspensions, the rate of sedimentation, v, can be expressed as:

$$v/V_o=1/(1+\kappa\phi)$$

where κ=a constant, and ϕ is the volume fraction of the dispersed phase. More particles suspended in the liquid phase results in decreased velocity. Particle geometry is also an important factor since the particle dimensions will affect particle-particle flow interactions.

Similarly, the viscosity of the suspension is dependent on the volume fraction of dispersed solids. For dilute suspensions of non-interaction spherical particles, an expression for the suspension viscosity can be expressed as:

$$\mu/\mu_o=1+2.5\phi$$

where μ_o is the viscosity of the continuous phase and ϕ is the solids volume fraction. At higher volume fractions, the viscosity of the dispersion can be expressed as:

$$\mu/\mu_o=1+2.5\phi+C_1\phi^2+C_2\phi^3+ \ldots$$

where C is a constant.

The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a viscoelastic non-Newtonian fluid with low yield stress values. This is the equivalent of producing a high viscosity continuous phase at rest. Formation of a viscoelastic or a highly structured fluid phase provides additional resistive forces to particle sedimentation. Further, flocculation or aggregation can be controlled minimizing particle-particle interactions. The net effect would be the preservation of a homogeneous dispersed phase.

The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size, and volume fraction. The particle size distribution of the dispersed phase needs to be controlled by selecting the smallest realistic particle size in the high viscosity medium, i.e., <500 μm. The presence of a slight yield stress or elastic body at low shear rates may also induce permanent stability regardless of the apparent viscosity. The critical particle diameter can be calculated from the yield stress values. In the case of isolated spherical particles, the maximum shear stress developed in settling through a medium of given viscosity can be given as

$$\tau_{max}=3V\mu/2r$$

For pseudoplastic fluids, the viscosity in this shear stress regime may well be the zero shear rate viscosity at the Newtonian plateau.

A stable suspension is an important characteristic for the manufacture of a pre-mix composition which is to be fed into the film casting machinery film, as well as the maintenance of this stability in the wet film stage until sufficient drying has occurred to lock-in the particles and matrix into a sufficiently solid form such that uniformity is maintained. For viscoelastic fluid systems, a rheology that yields stable suspensions for extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. A desirable property for the films is shear thinning or pseudoplasticity, whereby the viscosity decreases with increasing shear rate. Time dependent shear effects such as thixotropy are also advantageous. Structural recovery and shear thinning behavior are important properties, as is the ability for the film to self-level as it is formed.

The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt %, in a viscoelastic fluid matrix with acceptable viscosity values throughout a broad shear rate range. During mixing, pumping, and film casting, shear rates in the range of $10\text{-}10_5$ sec.$^{-1}$ may be experienced and pseudoplasticity is the preferred embodiment.

In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, viscoelasticity, structural recovery will influence the quality of the film. As an illustrative example, the leveling of shear-thinning pseudoplastic fluids has been derived as

$$\alpha^{(n-1/n)}=\alpha_o^{(n-1/n)}-((n-1)/(2n-1))(\tau/K)^{1/n}(2\pi/\lambda)^{(3+n)/n} h^{(2n+1)/n}t$$

where α is the surface wave amplitude, α_o is the initial amplitude, λ is the wavelength of the surface roughness, and both "n" and "K" are viscosity power law indices. In this example, leveling behavior is related to viscosity, increasing as n decreases, and decreasing with increasing K.

Desirably, the films or film-forming compositions of the present invention have a very rapid structural recovery, i.e. as the film is formed during processing, it doesn't fall apart or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic fluids. Such fluids with consideration of properties, such as viscosity and elasticity, promote thin film formation and uniformity.

Thus, uniformity in the mixture of components depends upon numerous variables. As described herein, viscosity of the components, the mixing techniques and the rheological properties of the resultant mixed composition and wet casted film are important aspects of the present invention. Additionally, control of particle size and particle shape are further considerations. Desirably, the size of the particulate a particle size of 150 microns or less, for example 100 microns or less. Moreover, such particles may be spherical, substantially spherical, or non-spherical, such as irregularly shaped particles or ellipsoidally shaped particles. Ellipsoidally shaped particles or ellipsoids are desirable because of their ability to maintain uniformity in the film forming matrix as they tend to settle to a lesser degree as compared to spherical particles.

A number of techniques may be employed in the mixing stage to prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed. Additionally, the speed of the mixture is desirably controlled to prevent cavitation of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film. Desirably, the inventive process first forms a masterbatch of film-forming components without active ingredients such as drug particles or volatile materials such as flavor oils. The actives are added to smaller mixes of the masterbatch just prior to casting. Thus, the masterbatch pre-mix can be allowed to stand for a longer time without concern for instability in drug or other ingredients.

When the matrix is formed including the film-forming polymer and polar solvent in addition to any additives and the active ingredient, this may be done in a number of steps. For example, the ingredients may all be added together or a pre-mix may be prepared. The advantage of a pre-mix is that all ingredients except for the active may be combined in advance, with the active added just prior to formation of the film. This is especially important for actives that may degrade with prolonged exposure to water, air or another polar solvent.

FIG. **6** shows an apparatus **20** suitable for the preparation of a pre-mix, addition of an active and subsequent formation of a film. The pre-mix or master batch **22**, which includes the film-forming polymer, polar solvent, and any other additives except a drug active is added to the master batch feed tank **24**. The components for pre-mix or master batch **22** are desirably formed in a mixer (not shown) prior to their addition into the master batch feed tank **24**. Then a predetermined amount of the master batch is controllably fed via a first metering pump **26** and control valve **28** to either or both of the first and second mixers, **30**, **30'**. The present invention, however, is not limited to the use of two mixers, **30**, **30'**, and any number of mixers may suitably be used. Moreover, the present invention is not limited to any particular sequencing of the mixers **30**, **30'**, such as parallel sequencing as depicted in FIG. **6**, and other sequencing or arrangements of mixers, such as series or combination of parallel and series, may suitably be used. The required amount of the drug or other ingredient, such as a flavor, is added to the desired mixer through an opening, **32**, **32'**, in each of the mixers, **30**, **30'**. Desirably, the residence time of the pre-mix or master batch **22** is minimized in the mixers **30**, **30'**. While complete dispersion of the drug into the pre-mix or master batch **22** is desirable, excessive residence times may result in leaching or dissolving of the drug, especially in the case for a soluble drug. Thus, the mixers **30**, **30'** are often smaller, i.e. lower residence times, as compared to the primary mixers (not shown) used in forming the pre-mix or master batch **22**. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan **36** through the second metering pumps, **34**, **34'**. The metering roller **38** determines the thickness of the film **42** and applies it to the application roller. The film **42** is finally formed on the substrate **44** and carried away via the support roller **46**.

While the proper viscosity uniformity in mixture and stable suspension of particles, and casting method are important in the initial steps of forming the composition and film to promote uniformity, the method of drying the wet film is also important. Although these parameters and properties assist uniformity initially, a controlled rapid drying process ensures that the uniformity will be maintained until the film is dry.

The wet film is then dried using controlled bottom drying or controlled microwave drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film **48** as described herein. Controlled bottom drying or controlled microwave drying advantageously allows for vapor release from the film without the disadvantages of the prior art. Conventional convection air drying from the top is not employed because it initiates drying at the top uppermost portion of the film, thereby forming a barrier against fluid flow, such as the evaporative vapors, and thermal flow, such as the thermal energy for drying. Such dried upper portions serve as a barrier to further vapor release as the portions beneath are dried, which results in non-uniform films. As previously mentioned some top air flow can be used to aid the drying of the films of the present invention, but it must not create a condition that would cause particle movement or a rippling effect in the film, both of which would result in non-uniformity. If top air is employed, it is balanced with the bottom air drying to avoid non-uniformity and prevent film lift-up on the carrier belt. A balance top and bottom air flow may be suitable where the bottom air flow functions as the major source of drying and the top air flow is the minor source of drying. The advantage of some top air flow is to move the exiting vapors away from the film thereby aiding in the overall drying process. The use of any top air flow or top drying, however, must be balanced by a number of factors including, but not limited, to rheological properties of the composition and mechanical aspects of the processing. Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot break, distort or otherwise physically disturb the surface of the composition. Moreover, air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions. For thin or low viscosity compositions, low air velocity must be used. For thick or high viscosity compositions, higher air velocities may be used. Furthermore, air velocities are desirable low so as to avoid any lifting or other movement of the film formed from the compositions.

Moreover, the films of the present invention may contain particles that are sensitive to temperature, such as flavors, which may be volatile, or drugs, which may have a low degradation temperature. In such cases, the drying temperature may be decreased while increasing the drying time to adequately dry the uniform films of the present invention. Furthermore, bottom drying also tends to result in a lower internal film temperature as compared to top drying. In bottom drying, the evaporating vapors more readily carry heat away from the film as compared to top drying which lowers the internal film temperature. Such lower internal film temperatures often result in decreased drug degradation and decreased loss of certain volatiles, such as flavors.

During film preparation, it may be desirable to dry films at high temperatures. High heat drying produces uniform films, and leads to greater efficiencies in film production. Films containing sensitive active components, however, may face degradation problems at high temperatures. Degradation is the "decomposition of a compound . . . exhibiting well-defined intermediate products." The American Heritage Dictionary of the English Language (4^{th} ed. 2000). Degradation of an active component is typically undesirable as it may cause instability, inactivity, and/or decreased potency of the active component. For instance, if the active component is a drug or bioactive material, this may adversely affect the safety or efficacy of the final pharmaceutical product. Additionally, highly volatile materials will tend to be quickly released from this film upon exposure to conventional drying methods.

Degradation of an active component may occur through a variety of processes, such as, hydrolysis, oxidation, and light degradation, depending upon the particular active component. Moreover, temperature has a significant effect on the rate of such reactions. The rate of degradation typically doubles for every 10° C. increase in temperature. Therefore, it is commonly understood that exposing an active component to high temperatures will initiate and/or accelerate undesirable degradation reactions.

Proteins are one category of useful active ingredients that will degrade, denature, or otherwise become inactive when they are exposed to high temperatures for extended periods of time. Proteins serve a variety of functions in the body such as enzymes, structural elements, hormones and immunoglobulins. Examples of proteins include enzymes such as pancreatin, trypsin, pancrelipase, chymotrypsin, hyaluronidase, sutilains, streptokinaw, urokinase, altiplase, papain, bromelainsdiastase, structural elements such as collagen and albumin, hormones such as thyroliberin, gonadoliberin, adrenocorticottropin, corticotrophin, cosyntropin, sometrem, somatropion, prolactin, thyrotropin, somatostatin, vasopressin, felypressin, lypressin, insulin, glucagons, gastrin, pentagastrin, secretin, cholecystokinin-pancreozymin, and immunomodulators which may include polysaccharides in addition to glycoproteins including cytokines which are useful for the inhibition and prevention of malignant cell growth such as tumor growth. A suitable method for the production of some useful glycoproteins is disclosed in U.S. Pat. No. 6,281,337 to Cannon-Carlson, et al., which in incorporated herein in its entirety.

Temperatures that approach 100° C. will generally cause degradation of proteins as well as nucleic acids. For example some glycoproteins will degrade if exposed to a temperature of 70° C. for thirty minutes. Proteins from bovine extract are also known to degrade at such low temperatures. DNA also begins to denature at this temperature.

Applicants have discovered, however, that the films of the present invention may be exposed to high temperatures during the drying process without concern for degradation, loss of activity or excessive evaporation due to the inventive process for film preparation and forming. In particular, the films may be exposed to temperatures that would typically lead to degradation, denaturization, or inactivity of the active component, without causing such problems. According to the present invention, the manner of drying may be controlled to prevent deleterious levels of heat from reaching the active component.

As discussed herein, the flowable mixture is prepared to be uniform in content in accordance with the teachings of the present invention. Uniformity must be maintained as the flowable mass was formed into a film and dried. During the drying process of the present invention, several factors produce uniformity within the film while maintaining the active component at a safe temperature, i.e., below its degradation temperature. First, the films of the present invention have an extremely short heat history, usually only on the order of minutes, so that total temperature exposure is minimized to the extent possible. The films are controllably dried to prevent aggregation and migration of components, as well as preventing heat build up within. Desirably, the films are dried from the bottom. Controlled bottom drying, as described herein, prevents the formation of a polymer film, or skin, on the top surface of the film. As heat is conducted from the film bottom upward, liquid carrier, e.g., water, rises to the film surface. The absence of a surface skin permits rapid evaporation of the liquid carrier as the temperature increases, and thus, concurrent evaporative cooling of the film. Due to the short heat exposure and evaporative cooling, the film components such as drag or volatile actives remain unaffected by high temperatures. In contrast, skinning on the top surface traps liquid carrier molecules of increased energy within the film, thereby causing the temperature within the film to rise and exposing active components to high, potentially deleterious temperatures.

Second, thermal mixing occurs within the film due to bottom heating and absence of surface skinning. Thermal mixing occurs via convection currents in the film. As heat is applied to the bottom of the film, the liquid near the bottom increases in temperature, expands, and becomes less dense. As such, this hotter liquid rises and cooler liquid takes its place. While rising, the hotter liquid mixes with the cooler liquid and shares thermal energy with it, i.e., transfers heat. As the cycle repeats, thermal energy is spread throughout the film.

Robust thermal mixing achieved by the controlled drying process of the present invention produces uniform heat diffusion throughout the film. In the absence of such thermal mixing, "hot spots" may develop. Pockets of heat in the film result in the formation of particle aggregates or danger areas within the film and subsequent non-uniformity. The formation of such aggregates or agglomerations is undesirable because it leads to non-uniform films in which the active may be randomly distributed. Such uneven distribution may lead to large differences in the amount of active per film, which is problematic from a safety and efficacy perspective.

Furthermore, thermal mixing helps to maintain a lower overall temperature inside the film. Although the film surfaces may be exposed to a temperature above that at which the active component degrades, the film interior may not reach this temperature. Due to this temperature differential, the active does not degrade.

FIG. **8** is a sequential representation of the drying process of the present invention. After mechanical mixing, the film may be placed on a conveyor for continued thermal mixing during the drying process. At the outset of the drying process, depicted in Section A, the film **1** preferably is heated from the bottom **10** as it is travels via conveyor (not shown). Heat may be supplied to the film by a heating mechanism, such as, but not limited to, the dryer depicted in FIG. **7**. As the film is heated, the liquid carrier, or volatile ("V"), begins to evaporate, as shown by upward arrow **50**. Thermal mixing also initiates as hotter liquid, depicted by arrow **30**, rises and cooler liquid, depicted by arrow **40**, takes its place. Because no skin forms on the top surface **20** of the film **1**, as shown in Section B the volatile liquid continues to evaporate **50** and thermal mixing **30/40** continues to distribute thermal energy throughout the film. Once a sufficient amount of the volatile liquid has evaporated, thermal mixing has produced uniform heat diffusion throughout the film **1**. The resulting dried film **1** is a visco-elastic solid, as depicted in Section C. The components desirably are locked into a uniform distribution throughout the film. Although minor amounts of liquid carrier, i.e., water, may remain subsequent to formation of the visco-elastic, the film may be dried further without movement of the particles, if desired.

Furthermore, particles or particulates may be added to the film-forming composition or matrix after the composition or matrix is cast into a film. For example, particles may be added to the film **42** prior to the drying of the film **42**. Particles may be controllably metered to the film and disposed onto the film through a suitable technique, such as through the use of a doctor blade (not shown) which is a device which marginally or softly touches the surface of the film and controllably disposes the particles onto the film surface. Other suitable, but non-limiting, techniques include the use of an additional roller to place the particles on the film surface, spraying the particles onto the film surface, and the like. The particles may be placed on either or both of the opposed film surfaces, i.e., the top and/or bottom film surfaces. Desirably, the particles are securably disposed onto the film, such as being embedded into the film. Moreover, such particles are desirably not fully encased or fully embedded into the film, but remain exposed to the surface of the film, such as in the case where the particles are partially embedded or partially encased.

The particles may be any useful organoleptic agent, cosmetic agent, pharmaceutical agent, or combinations thereof. Desirably, the pharmaceutical agent is a taste-masked or a controlled-release pharmaceutical agent. Useful organoleptic agents include flavors and sweeteners. Useful cosmetic agents include breath freshening or decongestant agents, such as menthol, including menthol crystals.

Although the inventive process is not limited to any particular apparatus for the above-described desirable drying, one particular useful drying apparatus **50** is depicted in FIG. **7**. Drying apparatus **50** is a nozzle arrangement for directing hot fluid, such as but not limited to hot air, towards the bottom of the film **42** which is disposed on substrate **44**. Hot air enters the entrance end **52** of the drying apparatus and travels vertically upward, as depicted by vectors **54**, towards air deflector **56**. The air deflector **56** redirects the air movement to minimize upward force on the film **42**. As depicted in FIG. **7**, the air is tangentially directed, as indicated by vectors **60** and **60'**, as the air passes by air deflector **56** and enters and travels through chamber portions **58** and **58'** of the drying apparatus **50**. With the hot air flow being substantially tangential to the film **42**, lifting of the film as it is being dried is thereby minimized. While the air deflector **56** is depicted as a roller, other devices and geometries for deflecting air or hot fluid may suitable be used. Furthermore, the exit ends **62** and **62'** of the drying apparatus **50** are flared downwardly. Such downward flaring provides a downward force or downward velocity vector, as indicated by vectors **64** and **64'**, which tend to provide a pulling or drag effect of the film **42** to prevent lifting of the film **42**. Lifting of the film **42** may not only result in non-uniformity in the film or otherwise, but may also result in non-controlled processing of the film **42** as the film **42** and/or substrate **44** lift away from the processing equipment.

Monitoring and control of the thickness of the film also contributes to the production of a uniform film by providing a film of uniform thickness. The thickness of the film may be monitored with gauges such as Beta Gauges. A gauge may be coupled to another gauge at the end of the drying apparatus, i.e. drying oven or tunnel, to communicate through feedback loops to control and adjust the opening in the coating apparatus, resulting in control of uniform film thickness.

The film products are generally formed by combining a properly selected polymer and polar solvent, as well as any active ingredient or filler as desired. Desirably, the solvent content of the combination is at least about 30% by weight of the total combination. The matrix formed by this combination is formed into a film, desirably by roll coating, and then dried, desirably by a rapid and controlled drying process to maintain the uniformity of the film, more specifically, a non-self-aggregating uniform heterogeneity. The resulting film will desirably contain less than about 10% by weight solvent, more desirably less than about 8% by weight solvent, even more desirably less than about 6% by weight solvent and most desirably less than about 2%. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, methylene chloride, or any combination thereof.

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

Film-Forming Polymers

The polymer may be water soluble, water swellable, water insoluble, or a combination of one or more either water soluble, water swellable or water insoluble polymers. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water soluble polymers include, but are not limited to, pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium aginate, polyethylene glycol, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water insoluble polymers include, but are not limited to, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof.

As used herein the phrase "water soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water swellable polymers. The materials useful with the present invention may be water soluble or water swellable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water soluble or water swellable at pressures less than atmospheric pressure. Desirably, the water soluble polymers are water soluble or water swellable having at least 20 percent by weight water uptake. Water swellable polymers having a 25 or greater percent by weight water uptake are also useful. Films or dosage forms of the present invention formed from such water soluble polymers are desirably sufficiently water soluble to be dissolvable upon contact with bodily fluids.

Other polymers useful for incorporation into the films of the present invention include biodegradable polymers, copolymers, block polymers and combinations thereof. Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly(lactic acid) (PLA), polydioxanoes, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy) propane acid and sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly(lactic acid)/poly (glycolic acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic acid), copolymers of polyurethane and poly(lactic acid), copolymers of α-amino acids, copolymers of α-amino acids and caproic acid, copolymers of α-benzyl glutamate and polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene, polyhydroxy-alkanoates and mixtures thereof. Binary and ternary systems are contemplated.

Other specific polymers useful include those marketed under the Medisorb and Biodel trademarks. The Medisorb materials are marketed by the Dupont Company of Wilmington, Del. and are generically identified as a "lactide/glycolide co-polymer" containing "propanoic acid, 2-hydroxy-polymer with hydroxy-polymer with hydroxyacetic acid." Four such polymers include lactide/glycolide 100 L, believed to be 100% lactide having a melting point within the range of 338°-347° F. (170°-175° C.); lactide/glycolide 100 L, believed to be 100% glycolide having a melting point within the range of 437°-455° F. (225°-235° C.); lactide/glycolide 85/15, believed to be 85% lactide and 15% glycolide with a melting point within the range of 338°-347° F. (170°-175° C.); and lactide/glycolide 50/50, believed to be a copolymer of 50% lactide and 50% glycolide with a melting point within the range of 338°-347° F. (170°-175° C.).

The Biodel materials represent a family of various polyanhydrides which differ chemically.

Although a variety of different polymers may be used, it is desired to select polymers to provide a desired viscosity of the mixture prior to drying. For example, if the active or other components are not soluble in the selected solvent, a polymer that will provide a greater viscosity is desired to assist in maintaining uniformity. On the other hand, if the components are soluble in the solvent, a polymer that provides a lower viscosity may be preferred.

The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process.

The viscosity may be adjusted based on the selected active depending on the other components within the matrix. For example, if the component is not soluble within the selected solvent, a proper viscosity may be selected to prevent the component from settling which would adversely affect the uniformity of the resulting film. The viscosity may be adjusted in different ways. To increase viscosity of the film matrix, the polymer may be chosen of a higher molecular weight or crosslinkers may be added, such as salts of calcium, sodium and potassium. The viscosity may also be adjusted by adjusting the temperature or by adding a viscosity increasing component. Components that will increase the viscosity or stabilize the emulsion/suspension include higher molecular weight polymers and polysaccharides and gums, which include without limitation, alginate, carrageenan, hydroxypropyl methyl cellulose, locust bean gum, guar gum, xanthan gum, dextran, gum arabic, gellan gum and combinations thereof.

It has also been observed that certain polymers which when used alone would ordinarily require a plasticizer to achieve a flexible film, can be combined without a plasticizer and yet achieve flexible films. For example, HPMC and HPC when used in combination provide a flexible, strong film with the appropriate plasticity and elasticity for manufacturing and storage. No additional plasticizer or polyalcohol is needed for flexibility.

Controlled Release Films

The term "controlled release" is intended to mean the release of active at a pre-selected or desired rate. This rate will vary depending upon the application. Desirable rates include fast or immediate release profiles as well as delayed, sustained or sequential release. Combinations of release patterns, such as initial spiked release followed by lower levels of sustained release of active are contemplated. Pulsed drug releases are also contemplated.

The polymers that are chosen for the films of the present invention may also be chosen to allow for controlled disintegration of the active. This may be achieved by providing a substantially water insoluble film that incorporates an active that will be released from the film over time. This may be accomplished by incorporating a variety of different soluble or insoluble polymers and may also include biodegradable polymers in combination. Alternatively, coated controlled release active particles may be incorporated into a readily soluble film matrix to achieve the controlled release property of the active inside the digestive system upon consumption.

Films that provide a controlled release of the active are particularly useful for buccal, gingival, sublingual and vaginal applications. The films of the present invention are particularly useful where mucosal membranes or mucosal fluid is present due to their ability to readily wet and adhere to these areas.

The convenience of administering a single dose of a medication which releases active ingredients in a controlled fashion over an extended period of time as opposed to the administration of a number of single doses at regular intervals has long been recognized in the pharmaceutical arts. The advantage to the patient and clinician in having consistent and uniform blood levels of medication over an extended period of time are likewise recognized. The advantages of a variety of sustained release dosage forms are well known. However, the preparation of a film that provides the controlled release of an active has advantages in addition to those well-known for controlled release tablets. For example, thin films are difficult to inadvertently aspirate and provide an increased patient compliance because they need not be swallowed like a tablet. Moreover, certain embodiments of the inventive films are designed to adhere to the buccal cavity and tongue, where they controllably dissolve. Furthermore, thin films may not be crushed in the manner of controlled release tablets which is a problem leading to abuse of drugs such as Oxycontin.

The actives employed in the present invention may be incorporated into the film compositions of the present invention in a controlled release form. For example, particles of drug may be coated with polymers such as ethyl cellulose or polymethacrylate, commercially available under brand names such as Aquacoat ECD and Eudragit E-100, respectively. Solutions of drug may also be absorbed on such polymer materials and incorporated into the inventive film compositions. Other components such as fats and waxes, as well as sweeteners and/or flavors may also be employed in such controlled release compositions.

The actives may be taste-masked prior to incorporation into the film composition, as set forth in co-pending PCT application titled, Uniform Films For Rapid Dissolve Dosage Form Incorporating Taste-Masking Compositions, (based on U.S. Provisional Application No. Express Mail Label No.: EU552991605 US of the same title, filed Sep. 27, 2003,) the entire subject matter of which is incorporated by reference herein.

Actives

When an active is introduced to the film, the amount of active per unit area is determined by the uniform distribution of the film. For example, when the films are cut into individual dosage forms, the amount of the active in the dosage form can be known with a great deal of accuracy. This is achieved because the amount of the active in a given area is substantially identical to the amount of active in an area of the same dimensions in another part of the film. The accuracy in dosage is particularly advantageous when the active is a medicament, i.e. a drug.

The active components that may be incorporated into the films of the present invention include, without limitation pharmaceutical and cosmetic actives, drugs, medicaments, antigens or allergens such as ragweed pollen, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

A wide variety of medicaments, bioactive active substances and pharmaceutical compositions may be included in the dosage forms of the present invention. Examples of useful drugs include ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

Examples of medicating active ingredients contemplated for use in the present invention include antacids, H_2-antagonists, and analgesics. For example, antacid dosages can be prepared using the ingredients calcium carbonate alone or in combination with magnesium hydroxide, and/or aluminum hydroxide. Moreover, antacids can be used in combination with H_2-antagonists.

Analgesics include opiates and opiate derivatives, such as oxycodone (available as Oxycontin®), ibuprofen, aspirin, acetaminophen, and combinations thereof that may optionally include caffeine.

Other preferred drugs for other preferred active ingredients for use in the present invention include anti-diarrheals such as immodium AD, anti-histamines, anti-tussives, decongestants, vitamins, and breath fresheners. Common drugs used alone or in combination for colds, pain, fever, cough, congestion, runny nose and allergies, such as acetaminophen, chlorpheniramine maleate, dextromethorphan, pseudoephedrine HCl and diphenhydramine may be included in the film compositions of the present invention.

Also contemplated for use herein are anxiolytics such as alprazolam (available as Xanax®); anti-psychotics such as clozopin (available as Clozaril®) and haloperidol (available as Haldol®); non-steroidal anti-inflammatories (NSAID's) such as dicyclofenacs (available as Voltaren®) and etodolac (available as Lodine®), anti-histamines such as loratadine (available as Claritin®), astemizole (available as Hismanal™), nabumetone (available as Relafen®), and Clemastine (available as Tavist®); anti-emetics such as granisetron hydrochloride (available as Kytril®) and nabilone (available as Cesamet™); bronchodilators such as Bentolin®, albuterol sulfate (available as Proventil®); anti-depressants such as fluoxetine hydrochloride (available as Prozac®), sertraline hydrochloride (available as Zoloft®), and paroxtine hydrochloride (available as Paxil®); anti-migraines such as Imigra®, ACE-inhibitors such as enalaprilat (available as Vasotec®), captopril (available as Capoten®) and lisinopril (available as Zestril®); anti-Alzheimer's agents, such as nicergoline; and Ca^{H}-antagonists such as nifedipine (available as Procardia® and Adalat®), and verapamil hydrochloride (available as Calan®).

Erectile dysfunction therapies include, but are not limited to, drugs for facilitating blood flow to the penis, and for effecting autonomic nervous activities, such as increasing parasympathetic (cholinergic) and decreasing sympathetic (adrenersic) activities. Useful non-limiting drugs include sildenafils, such as Viagra®, tadalafils, such as Cialis®, vardenafils, apomorphines, such as Uprima®, yohimbine hydrochlorides such as Aphrodyneg, and alprostadils such as Caverject®.

The popular H_2-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidien, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

Active antacid ingredients include, but are not limited to, the following: aluminum hydroxide, dihydroxyaluminum aminoacetate, aminoacetic acid, aluminum phosphate, dihydroxyaluminum sodium carbonate, bicarbonate, bismuth aluminate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, bismuth subsilysilate, calcium carbonate, calcium phosphate, citrate ion (acid or salt), amino acetic acid, hydrate magnesium aluminate sulfate, magaldrate, magnesium aluminosilicate, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, milk solids, aluminum mono-ordibasic calcium phosphate, tricalcium phosphate, potassium bicarbonate, sodium tartrate, sodium bicarbonate, magnesium aluminosilicates, tartaric acids and salts.

The pharmaceutically active agents employed in the present invention may include allergens or antigens, such as , but not limited to, plant pollens from grasses, trees, or ragweed; animal danders, which are tiny scales shed from the skin and hair of cats and other furred animals; insects, such as house dust mites, bees, and wasps; and drugs, such as penicillin.

An anti-oxidant may also be added to the film to prevent the degradation of an active, especially where the active is photosensitive.

Cosmetic active agents may include breath freshening compounds like menthol, other flavors or fragrances, especially those used for oral hygiene, as well as actives used in dental and oral cleansing such as quaternary ammonium bases. The effect of flavors may be enhanced using flavor enhancers like tartaric acid, citric acid, vanillin, or the like.

Also color additives can be used in preparing the films. Such color additives include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors are dyes, their corresponding lakes, and certain natural and derived colorants. Lakes are dyes absorbed on aluminum hydroxide.

Other examples of coloring agents include known azo dyes, organic or inorganic pigments, or coloring agents of natural origin. Inorganic pigments are preferred, such as the oxides or iron or titanium, these oxides, being added in concentrations ranging from about 0.001 to about 10%, and preferably about 0.5 to about 3%, based on the weight of all the components.

Flavors may be chosen from natural and synthetic flavoring liquids. An illustrative list of such agents includes volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids, oleoresins or extracts derived from plants, leaves, flowers, fruits, stems and combinations thereof. A non-limiting representative list of examples includes mint oils, cocoa, and citrus oils such as lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot or other fruit flavors.

The films containing flavorings may be added to provide a hot or cold flavored drink or soup. These flavorings include, without limitation, tea and soup flavorings such as beef and chicken.

Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral i.e., alphacitral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), tolyl aldehyde (cherry, almond), 2,6-dimethyloctanol (green fruit), and 2-dodecenal (citrus, mandarin), combinations thereof and the like.

The sweeteners may be chosen from the following non-limiting list: glucose (corn syrup), dextrose, invert sugar, fructose, and combinations thereof; saccharin and its various salts such as the sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; *Stevia Rebaudiana* (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, and the like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methyl-1-1-1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof, and natural intensive sweeteners, such as Lo Han Kuo. Other sweeteners may also be used.

When the active is combined with the polymer in the solvent, the type of matrix that is formed depends on the solubilities of the active and the polymer. If the active and/or polymer are soluble in the selected solvent, this may form a solution. However, if the components are not soluble, the matrix may be classified as an emulsion, a colloid, or a suspension.

Dosages

The film products of the present invention are capable of accommodating a wide range of amounts of the active ingredient. The films are capable of providing an accurate dosage amount (determined by the size of the film and concentration of the active in the original polymer/water combination) regardless of whether the required dosage is high or extremely low. Therefore, depending on the type of active or pharmaceutical composition that is incorporated into the film, the active amount may be as high as about 300 mg, desirably up to about 150 mg or as low as the microgram range, or any amount therebetween.

The film products and methods of the present invention are well suited for high potency, low dosage drugs. This is accomplished through the high degree of uniformity of the films. Therefore, low dosage drugs, particularly more potent racemic mixtures of actives are desirable.

Anti-Foaming and De-Foaming Compositions

Anti-foaming and/or de-foaming components may also be used with the films of the present invention. These components aid in the removal of air, such as entrapped air, from the film-forming compositions. As described above, such entrapped air may lead to non-uniform films. Simethicone is one particularly useful anti-foaming and/or de-foaming agent. The present invention, however, is not so limited and other anti-foam and/or de-foaming agents may suitable be used.

Simethicone is generally used in the medical field as a treatment for gas or colic in babies. Simethicone is a mixture of fully methylated linear siloxane polymers containing repeating units of polydimethylsiloxane which is stabilized with trimethylsiloxy end-blocking unites, and silicon dioxide. It usually contains 90.5-99% polymethylsiloxane and 4-7% silicon dioxide. The mixture is a gray, translucent, viscous fluid which is insoluble in water.

When dispersed in water, simethicone will spread across the surface, forming a thin film of low surface tension. In this way, simethicone reduces the surface tension of bubbles air located in the solution, such as foam bubbles, causing their collapse. The function of simethicone mimics the dual action of oil and alcohol in water. For example, in an oily solution any trapped air bubbles will ascend to the surface and dissipate more quickly and easily, because an oily liquid has a lighter density compared to a water solution. On the other hand, an alcohol/water mixture is known to lower water density as well as lower the water's surface tension. So, any air bubbles trapped inside this mixture solution will also be easily dissipated. Simethicone solution provides both of these advantages. It lowers the surface energy of any air bubbles that trapped inside the aqueous solution, as well as lowering the surface tension of the aqueous solution. As the result of this unique functionality, simethicone has an excellent anti-foaming property that can be used for physiological processes (anti-gas in stomach) as well as any for external processes that require the removal of air bubbles from a product.

In order to prevent the formation of air bubbles in the films of the present invention, the mixing step can be performed under vacuum. However, as soon as the mixing step is completed, and the film solution is returned to the normal atmosphere condition, air will be re-introduced into or contacted with the mixture. In many cases, tiny air bubbles will be again trapped inside this polymeric viscous solution. The incorporation of simethicone into the film-forming composition either substantially reduces or eliminates the formation of air bubbles.

Simethicone may be added to the film-forming mixture as an anti-foaming agent in an amount from about 0.01 weight percent to about 5.0 weight percent, more desirably from about 0.05 weight percent to about 2.5 weight percent, and most desirably from about 0.1 weight percent to about 1.0 weight percent.

Optional Components

A variety of other components and fillers may also be added to the films of the present invention. These may include, without limitation, surfactants; plasticizers which assist in compatibilizing the components within the mixture; polyalcohols; anti-foaming agents, such as silicone-containing compounds, which promote a smoother film surface by releasing oxygen from the film; and thermo-setting gels such as pectin, carageenan, and gelatin, which help in maintaining the dispersion of components.

The variety of additives that can be incorporated into the inventive compositions may provide a variety of different functions. Examples of classes of additives include excipients, lubricants, buffering agents, stabilizers, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, anti-adherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers, elastomers and mixtures thereof. These additives may be added with the active ingredient(s).

Useful additives include, for example, gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, grape seed proteins, whey proteins, whey protein isolates, blood proteins, egg proteins, acrylated proteins, water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, xanthan gum, gellan gum, gum arabic and related gums (gum ghatti, gum karaya, gum tragancanth), pectin, water-soluble derivatives of cellulose: alkylcelluloses hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcelulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose (HPMC); carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethylcellulose and their alkali metal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols, polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVY/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate, crosslinked gelatin, shellac, water soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; and other similar polymers.

Such extenders may optionally be added in any desired amount desirably within the range of up to about 80%, desirably about 3% to 50% and more desirably within the range of 3% to 20% based on the weight of all components.

Further additives may be inorganic fillers, such as the oxides of magnesium aluminum, silicon, titanium, etc. desirably in a concentration range of about 0.02% to about 3% by weight and desirably about 0.02% to about 1% based on the weight of all components.

Further examples of additives are plasticizers which include polyalkylene oxides, such as polyethylene glycols, polypropylene glycols, polyethylene-propylene glycols, organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate, triacetin, polysorbate, cetyl alcohol, propylene glycol, sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, and the like, added in concentrations ranging from about 0.5% to about 30%, and desirably ranging from about 0.5% to about 20% based on the weight of the polymer.

There may further be added compounds to improve the flow properties of the starch material such as animal or vegetable fats, desirably in their hydrogenated form, especially those which are solid at room temperature. These fats desirably have a melting point of 50° C. or higher. Preferred are tri-glycerides with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}-fatty acids. These fats can be added alone without adding extenders or plasticizers and can be advantageously added alone or together with mono- and/or di-glycerides or phosphatides, especially lecithin. The mono- and di-glycerides are desirably derived from the types of fats described above, i.e. with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}-fatty acids.

The total amounts used of the fats, mono-, di-glycerides and/or lecithins are up to about 5% and preferably within the range of about 0.5% to about 2% by weight of the total composition

It is further useful to add silicon dioxide, calcium silicate, or titanium dioxide in a concentration of about 0.02% to about 1% by weight of the total composition. These compounds act as texturizing agents.

These additives are to be used in amounts sufficient to achieve their intended purpose. Generally, the combination of certain of these additives will alter the overall release profile of the active ingredient and can be used to modify, i.e. impede or accelerate the release.

Lecithin is one surface active agent for use in the present invention. Lecithin can be included in the feedstock in an amount of from about 0.25% to about 2.00% by weight. Other surface active agents, i.e. surfactants, include, but are not limited to, cetyl alcohol, sodium lauryl sulfate, the Spans™ and Tweens™ which are commercially available from ICI Americas, Inc. Ethoxylated oils, including ethoxylated castor oils, such as Cremophor® EL which is commercially available from BASF, are also useful. Carbowax™ is yet another modifier which is very useful in the present invention. Tweens™ or combinations of surface active agents may be used to achieve the desired hydrophilic-lipophilic balance ("HLB"). The present invention, however, does not require the use of a surfactant and films or film-forming compositions of the present invention may be essentially free of a surfactant while still providing the desirable uniformity features of the present invention.

As additional modifiers which enhance the procedure and product of the present invention are identified, Applicants intend to include all such additional modifiers within the scope of the invention claimed herein.

Other ingredients include binders which contribute to the ease of formation and general quality of the films. Non-limiting examples of binders include starches, pregelatinize starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinyloxoazolidone, and polyvinylalcohols.

Forming the Film

The films of the present invention must be formed into a sheet prior to drying. After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired, the combination is formed into a sheet or film, by any method known in the art such as extrusion, coating, spreading, casting or drawing the multi-component matrix. If a multi-layered film is desired, this may be accomplished by co-extruding more than one combination of components which may be of the same or different composition. A multi-layered film may also be achieved by coating, spreading, or casting a combination onto an already formed film layer.

Although a variety of different film-forming techniques may be used, it is desirable to select a method that will provide a flexible film, such as reverse roll coating. The flexibility of the film allows for the sheets of film to be rolled and transported for storage or prior to being cut into individual dosage forms. Desirably, the films will also be self-supporting or in other words able to maintain their integrity and structure in the absence of a separate support. Furthermore, the films of the present invention may be selected of materials that are edible or ingestible.

Coating or casting methods are particularly useful for the purpose of forming the films of the present invention. Specific examples include reverse roll coating, gravure coating, immersion or dip coating, metering rod or meyer bar coating, slot die or extrusion coating, gap or knife over roll coating, air knife coating, curtain coating, or combinations thereof, especially when a multi-layered film is desired.

Roll coating, or more specifically reverse roll coating, is particularly desired when forming films in accordance with the present invention. This procedure provides excellent control and uniformity of the resulting films, which is desired in the present invention. In this procedure, the coating material is measured onto the applicator roller by the precision setting of the gap between the upper metering roller and the application roller below it. The coating is transferred from the application roller to the substrate as it passes around the support roller adjacent to the application roller. Both three roll and four roll processes are common.

The gravure coating process relies on an engraved roller running in a coating bath, which fills the engraved dots or lines of the roller with the coating material. The excess coating on the roller is wiped off by a doctor blade and the coating is then deposited onto the substrate as it passes between the engraved roller and a pressure roller.

Offset Gravure is common, where the coating is deposited on an intermediate roller before transfer to the substrate.

In the simple process of immersion or dip coating, the substrate is dipped into a bath of the coating, which is normally of a low viscosity to enable the coating to run back into the bath as the substrate emerges.

In the metering rod coating process, an excess of the coating is deposited onto the substrate as it passes over the bath roller. The wire-wound metering rod, sometimes known as a Meyer Bar, allows the desired quantity of the coating to remain on the substrate. The quantity is determined by the diameter of the wire used on the rod.

In the slot die process, the coating is squeezed out by gravity or under pressure through a slot and onto the substrate. If the coating is 100% solids, the process is termed "Extrusion" and in this case, the line speed is frequently much faster than the speed of the extrusion. This enables coatings to be considerably thinner than the width of the slot.

The gap or knife over roll process relies on a coating being applied to the substrate which then passes through a "gap" between a "knife" and a support roller. As the coating and substrate pass through, the excess is scraped off.

Air knife coating is where the coating is applied to the substrate and the excess is "blown off" by a powerful jet from the air knife. This procedure is useful for aqueous coatings.

In the curtain coating process, a bath with a slot in the base allows a continuous curtain of the coating to fall into the gap between two conveyors. The object to be coated is passed along the conveyor at a controlled speed and so receives the coating on its upper face.

Drying the Film

The drying step is also a contributing factor with regard to maintaining the uniformity of the film composition. A controlled drying process is particularly important when, in the absence of a viscosity increasing composition or a composition in which the viscosity is controlled, for example by the selection of the polymer, the components within the film may have an increased tendency to aggregate or conglomerate. An alternative method of forming a flmn with an accurate dosage, that would not necessitate the controlled drying process, would be to cast the films on a predetermined well. With this method, although the components may aggregate, this will not result in the migration of the active to an adjacent dosage form, since each well may define the dosage unit per se.

When a controlled or rapid drying process is desired, this may be through a variety of methods. A variety of methods may be used including those that require the application of heat. The liquid carriers are removed from the film in a manner such that the uniformity, or more specifically, the non-self-aggregating uniform heterogeneity, that is obtained in the wet film is maintained.

Desirably, the film is dried from the bottom of the film to the top of the film. Desirably, substantially no air flow is present across the top of the film during its initial setting period, during which a solid, visco-elastic structure is formed. This can take place within the first few minutes, e.g. about the first 0.5 to about 4.0 minutes of the drying process. Controlling the drying in this manner, prevents the destruction and reformation of the film's top surface, which results from conventional drying methods. This is accomplished by forming the film and placing it on the top side of a surface having top and bottom sides. Then, heat is initially applied to the bottom side of the film to provide the necessary energy to evaporate or otherwise remove the liquid carrier. The films dried in this manner dry more quickly and evenly as compared to air-dried films, or those dried by conventional drying means. In contrast to an air-dried film that dries first at the top and edges, the films dried by applying heat to the bottom dry simultaneously at the center as well as at the edges. This also prevents settling of ingredients that occurs with films dried by conventional means.

The temperature at which the films are dried is about 100° C. or less, desirably about 90° C. or less, and most desirably about 80° C. or less.

Another method of controlling the drying process, which may be used alone or in combination with other controlled methods as disclosed above includes controlling and modifying the humidity within the drying apparatus where the film is being dried. In this manner, the premature drying of the top surface of the film is avoided.

Additionally, it has also been discovered that the length of drying time can be properly controlled, i.e. balanced with the heat sensitivity and volatility of the components, and particularly the flavor oils and drugs. The amount of energy, temperature and length and speed of the conveyor can be balanced to accommodate such actives and to minimize loss, degradation or ineffectiveness in the final film.

A specific example of an appropriate drying method is that disclosed by Magoon. Magoon is specifically directed toward a method of drying fruit pulp. However, the present inventors have adapted this process toward the preparation of thin films.

The method and apparatus of Magoon are based on an interesting property of water. Although water transmits energy by conduction and convection both within and to its surroundings, water only radiates energy within and to water. Therefore, the apparatus of Magoon includes a surface onto which the fruit pulp is placed that is transparent to infrared radiation. The underside of the surface is in contact with a temperature controlled water bath. The water bath temperature is desirably controlled at a temperature slightly below the boiling temperature of water. When the wet fruit pulp is placed on the surface of the apparatus, this creates a "refractance window." This means that infrared energy is permitted to radiate through the surface only to the area on the surface occupied by the fruit pulp, and only until the fruit pulp is dry. The apparatus of Magoon provides the films of the present invention with an efficient drying time reducing the instance of aggregation of the components of the film.

The films may initially have a thickness of about 500 μm to about 1,500 μm, or about 20 mils to about 60 mils, and when dried have a thickness from about 3 μm to about 250 μm, or about 0.1 mils to about 10 mils. Desirably, the dried films will have a thickness of about 2 mils to about 8 mils, and more desirably, from about 3 mils to about 6 mils.

Uses of Thin Films

The thin films of the present invention are well suited for many uses. The high degree of uniformity of the components of the film makes them particularly well suited for incorporating pharmaceuticals. Furthermore, the polymers used in construction of the films may be chosen to allow for a range of disintegration times for the films. A variation or extension in the time over which a film will disintegrate may achieve control over the rate that the active is released, which may allow for a sustained release delivery system. In addition, the films may be used for the administration of an active to any of several body surfaces, especially those including mucous membranes, such as oral, anal, vaginal, ophthalmological, the surface of a wound, either on a skin surface or within a body such as during surgery, and similar surfaces.

The films may be used to orally administer an active. This is accomplished by preparing the films as described above and introducing them to the oral cavity of a mammal. This film may be prepared and adhered to a second or support layer from which it is removed prior to use, i.e. introduction to the oral cavity. An adhesive may be used to attach the film to the support or backing material which may be any of those known in the art, and is preferably not water soluble. If an adhesive is used, it will desirably be a food grade adhesive that is ingestible and does not alter the properties of the active. Mucoadhesive compositions are particularly useful. The film compositions in many cases serve as mucoadhesives themselves.

The films may be applied under or to the tongue of the mammal. When this is desired, a specific film shape, corresponding to the shape of the tongue may be preferred. Therefore the film may be cut to a shape where the side of the film corresponding to the back of the tongue will be longer than the side corresponding to the front of the tongue. Specifically, the desired shape may be that of a triangle or trapezoid. Desirably, the film will adhere to the oral cavity preventing it from being ejected from the oral cavity and permitting more of the active to be introduced to the oral cavity as the film dissolves.

Another use for the films of the present invention takes advantage of the films' tendency to dissolve quickly when introduce to a liquid. An active may be introduced to a liquid by preparing a film in accordance with the present invention, introducing it to a liquid, and allowing it to dissolve. This may be used either to prepare a liquid dosage form of an active, or to flavor a beverage.

The films of the present invention are desirably packaged in sealed, air and moisture resistant packages to protect the active from exposure oxidation, hydrolysis, volatilization and interaction with the environment. Referring to FIG. **1**, a packaged pharmaceutical dosage unit **10**, includes each film **12** individually wrapped in a pouch or between foil and/or plastic laminate sheets **14**. As depicted in FIG. **2**, the pouches **10**, **10'** can be linked together with tearable or perforated joints **16**. The pouches **10**, **10'** may be packaged in a roll as depicted in FIG. **5** or stacked as shown in FIG. **3** and sold in a dispenser **18** as shown in FIG. **4**. The dispenser may contain a full supply of the medication typically prescribed for the intended therapy, but due to the thinness of the film and package, is smaller and more convenient than traditional bottles used for tablets, capsules and liquids. Moreover, the films of the present invention dissolve instantly upon contact with saliva or mucosal membrane areas, eliminating the need to wash the dose down with water.

Desirably, a series of such unit doses are packaged together in accordance with the prescribed regimen or treatment, e.g., a 10-90 day supply, depending on the particular therapy. The individual films can be packaged on a backing and peeled off for use.

The features and advantages of the present invention are more fully shown by the following examples which are provided for purposes of illustration, and are not to be construed as limiting the invention in any way.

EXAMPLES

Examples A-I

Water soluble thin film compositions of the present invention are prepared using the amounts described in Table 1.

TABLE 1

	Weight (g)								
Ingredient	A	B	C	D	E	F	G	H	I
Hydroxypropylmethyl cellulose		1.76		1.63	32.00		3.67		32.00
Peppermint oil		0.90	1.0	1.05		8.0	2.67		
Sweetener	0.15	0.15	0.22	0.10		4.6	1.53	0.15	
Polyvinylpyrrolidone		0.94		1.05		7.0	2.33		
Tween 80[1]	0.5	0.5	2.0	0.65	11.80		1.35	0.5	11.80
Simethicone[2]	0.2	0.2	0.15	0.30	1.80		0.21	0.2	1.80
Listerine[3]	83.35							83.35	
Methylcellulose	6.0								
Cornstarch[4]			1.75						
Agar			1.25						
Water		42.24	93.63	39.22	768.0	280.0	88.24		768.0
Loratadine[5]					19.2				19.2
Pullulan[6]								6.0	
Ibuprofen									38.4

[1] Available from ICI Americas
[2] Available from OSI
[3] Available from Pfizer, Inc. including thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), menthol (0.042%), water (up to 72.8%), alcohol (26.9%), benzoic acid, poloxamer 407, sodium benzoate, and caramel color
[4] Available from Grain Processing Corporation as Pure Cote B792
[5] Available from Schering Corporation as Claritin
[6] Available from Hayashibara Biochemical Laboratories, Inc., Japan

The ingredients of inventive compositions A-I were combined by mixing until a uniform mixture acheived. The compositions were then formed into a film by reverse roll coating. These films were then dried on the top side of an infrared transparent surface, the bottom side of which was in contact with a heated water bath at approximately 99° C. No external thermal air currents were present above the film. The films were dried to less than about 6% by weight in about 4 to 6 minutes. The films were flexible, self-supporting and provided a uniform distribution of the components within the film.

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

Uniformity was also measured by first cutting the film into individual dosage forms. Twenty-five dosage forms of substantially identical size were cut from the film of inventive composition above (E) above from random locations throughout the film. Then eight of these dosage forms were randomly selected and additively weighed. The additive weights of eight randomly selected dosage forms, are as shown in Table 2 below:

TABLE 2

Sample	Additive Weight (g) Trial 1	Trial 2
1	0.04	0.04
2	0.08	0.08
3	0.12	0.12
4	0.16	0.16
5	0.20	0.20
6	0.24	0.24
7	0.28	0.28
8	0.32	0.32

The individual dosages were consistently 0.04 gm, which shows that the distribution of the component within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages forms from the same film of substantially equal dimensions, will contain the same mass.

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

When the films formed from inventive compositions A-H are placed on the tongue, they rapidly dissolve, releasing the active ingredient. Similarly, when they are placed in water, the films rapidly dissolve which provides a flavored drink when the active is chosen to be a flavoring.

Examples J-L

Thin films that have a controlled degradation time and include combinations of water soluble and water insoluble polymers and water soluble films that allow controlled release of an active are prepared using approximately the amounts described in Table 3.

TABLE 3

Ingredient	Weight (g) J	K	L
Hydroxypropylmethyl cellulose		1.0	1.0
Tween 80[1]	0.7	0.7	0.7
Water			5.0
Aquacoat ECD[2]	17.0	17.0	17.5
Peppermint oil	1.0	0.4	1.1

[1]Available from ICI Americas
[2]A 30% by weight aqueous dispersion of ethyl cellulose available from FMC

The components of inventive compositions J-L were combined and formed into films using the methods for preparing inventive compositions A-I above. These films were also flexible, self-supporting and provided a uniform distribution of active which permits accuracy in dosing.

The uniformity of the films prepared from inventive compositions J-L may also be tested by either visual means measuring the weights of individual dosage films, or by dissolving the films and testing for the amount of active as described above.

Examples M-O

An alternative method of preparing films which provides an accurate dosing may be used for any of inventive compositions A-I. The method begins with first combining the ingredients with mixing. The combination of ingredients is then divided among individual wells or molds. In such a method, aggregation of the components during drying is prevented by the individual wells.

TABLE 4

Ingredient	Weight % M	N	O
5% Methylcellulose Solution[1]	73.22	44.22	74.22
Raspberry Flavor	3.28	3.28	3.28
Sweetener Blends	1.07	1.07	1.07
Tween-80[2]	2.47	2.47	2.47
Polyvinylpyrrolidone	3.30	3.30	3.30
Ethanol 95%	8.24	8.24	8.24
Propylene Glycol	1.65	1.65	1.65
Calcium Carbonate	4.12	4.12	4.12
Cornstarch[3]	1.65	1.65	1.65
Red Dye[4]	1.00		
Corn Syrup[5]		30.00	

[1]Available from Dow Chemical Co. as Methocel K35
[2]Available from ICI Americas
[3]Available from Grain Processing Corporation as Pure Cote B792
[4]Available from McCormick
[5]Available from Bestfoods, Inc. as Karo Syrup

The ingredients in the above Table 4 were combined and formed into a film by casting the combination of ingredients onto the glass surface and applying heat to the bottom side of the glass. This provided inventive compositions M-O.

The film of composition M was examined both prior to and after drying for variations in the shading provided by the red dye. The film was examined both under sunlight and by incandescent bulb light. No variations in shade or intensity of color were observed.

Further testing of the films of composition M included testing of absorption which is directly related to concentration. The film was cut into segments each measuring 1.0 in. by 0.75 in., which were consecutively assigned numbers. Approximately 40 mg of the scrap material from which the segments were cut was dissolved in about 10 ml of distilled water and then quantitatively transferred to a 25 ml volumetric flask and brought to volume. The solution was centrifuged and scanned at 3 nm intervals from 203-1200 nm. The frequency of maximum absorption was found to be 530 nm. The solution was then re-centrifuged at a higher RPM (for the same length of time) and re-scanned, which demonstrated no change in the % transmission or frequency.

Each of the segments were weighed to 0.1 mg and then dissolved in 10 ml distilled water and transferred quantitatively to a 25 ml volumetric flask and brought to volume with distilled water. Each segment solution was then centrifuged as above, and then scanned, at first from 203-1200 nm and later from only 500 nm to 550 nm at a 1 nm scanning speed. The value recorded was the % transmission at the lowest wave length, which was most frequently 530 nm.

The absorption values are shown in Table 5 below:

TABLE 5

Segment	mg/% A
1-2	1.717
3-4	1.700
5-6	1.774
7*	1.701
9-10	1.721
11-12	1.729
13-14	1.725
15-16	1.713

*segment 8 was lost

The overall average absorption was 1.724. Of the 15 segments tested, the difference between the highest and lowest values was 0.073 units, or 4% based on the average. This shows excellent control over the uniformity of the dye within the composition because the absorption is directly proportional to the concentration of the dye within each segment.

The film of inventive composition N provided a very flexible film. This film was able to be stretched and exhibited a very high tensile strength.

After forming the film of inventive composition O, the film was removed from the glass by very rapidly stripping the length of the glass with a razor. This provided very tightly wound "toothpick-like" dosage forms. Each dosage form consistently weighed 0.02 g. This demonstrates the uniformity of the dosage forms as well as the superior self-supporting properties of the films.

Examples P-W

Compositions P-W were prepared to demonstrate the interaction among various conditions in production of films as they relate to the present invention. The ingredients in the below Table 6 were combined and formed into a film using the process parameters listed in Table 7 below, prepared in a 6 m drying tunnel designed to incorporate bottom drying of the films. Each of the examples shows the effect of different ingredient formulations and processing techniques on the resultant film products.

TABLE 6

	Weight (g)							
Ingredient	P	Q	R	S	T	U	V	W
Hydroxypropylmethyl cellulose	320	320	320	320	320	320	345	345
Water	1440	1440	1440	1440		1440	999	999
Sweetener						60	60	45
Mint Flavor						80	80	
Propylene Glycol	50	50	50	100	100	100	100	69.3
Xanthan	22		11	11.23	10	10	10	6.9
Water/Ethanol(60/40)					1440			
Orange Flavor								42

TABLE 7

	Film Thickness (Micron)	Top[1] v (m/sec)	Bot.[1] v (m/sec)	T[1] (° C.)	Top[2] v (m/sec)
P1	100	0	22	75	0
P2	350	0	22	75	0
P3	350	0	40	75	0
P4	350	0	40	75	0
P5	350	10	40	75	10
Q	350	0	40	75	10
R	350	0	40	85	10
S1	250	0	40	100	0
S2	300	0	40	100	0
S3	350	0	40	100	0
T1	250	0	40	100	0
T2	350	0	40	100	0
U1	300	0	40	100	0
U2	250	0	40	100	0
U3	300	0	40	100	0
V1	300	0	40	100	0
V2	300	0	40	100	0
V3	300	0	40	100	0
W1	300	0	40	93	0
W2	250	0	40	90	0
W3	200	0	40	90	0

	Bot.[2] v (m/sec)	T[2] (° C.)	Film Weight (g)	Coater Speed m/min	% Moisture
P1	23	60	109	5	>20
P2	23	60	n/a	5	>20
P3	40	60	161	3	>20
P4	40	75	191	3	>20
P5	40	75	253	3	>20
Q	40	75	n/a	3	>20
R	0	85		2.5	>20
S1	40	90	163	1.5	<5
S2	40	90	193	1.5	<5
S3	40	90	225	1.5	<5
T1	40	90	64	1.5	<5
T2	40	90	83	1.5	<5
U1	40	90	208	1.5	20
U2	40	90	177	1.5	20
U3	40	90	212	1.3	20
V1	40	90	237	1.3	20
V2	40	100	242	1.3	20
V3	40	100	221	1	6
W1	40	90	220	1.3	5
W2	40	90	199	1.3	5
W3	40	90	169	1.3	5

[1]First Heater Section (3 m)
[2]Second Heater Section (3 m)

In Table 7, each of the process parameters contributes to different properties of the films. Film thickness refers to the distance between the blade and the roller in the reverse roll coating apparatus. Bottom velocity and top velocity refer to the speed of air current on the bottom and top sides of the film, respectively. The film weight is a measure of the weight of a circular section of the substrate and the film of 100 cm^2.

Compositions P-R show the effects of visco-elastic properties on the ability to coat the film composition mixture onto the substrate for film formation. Composition P displayed a stringy elastic property. The wet film would not stay level, the coating was uneven, and the film did not dry. In Composition Q, substantially the same formulation as P was used however the xanthan was not included. This product coated the substrate but would not stay level due to the change in the visco-elastic properties of the wet foam. Composition R was prepared using substantially the same formulation, but incorporated one-half of the amount of xanthan of Composition P. This formulation provided a composition that could be evenly coated. Compositions P-Q demonstrate the importance of proper formulation on the ability of the film matrix to conform to a particular coating technique.

The films produced from Composition S contained a large amount of air in the films. This is shown by the dried film thickness which was the same despite that variation in the coated thickness as in Table 7. Microscopic examination of the film revealed a large number of air bubbles in the film. In order to correct for the addition of air in the films, care must be taken in the mixing process to avoid air inclusion.

Composition T included a change in the solvent to 60/40 water ethanol. Composition T was stirred slowly for 45 min. to deaerate the mixture. The dried weight film products T1 and T2 were consistent with the increase in solids from T1 to T2. The films dried much faster with less than 5% moisture. With the particular combination of ingredients in Composition T, the substitution of part ethanol for part water allowed the film to dry more quickly. The elimination of air from the film as a result of the slow stirring also contributed to the uniformity of the final film product and the faster drying time.

Only water was used as a solvent in Composition U. The dried weight of the U1-U3 changed consistently in accordance with the change in coating thickness indicating that no air bubbles were present. However, these films contained 20% moisture upon exit from the oven, unlike the films of Composition T, which included part ethanol and dried completely.

The amount of solids was increased and the amount of water was decreased in Compositions V1 and V2. The dried weight was greater than U1-U3 due to the increase in solids, however the films still contained 20% moisture upon exit from the oven, similar to Composition U.

The coating line speed was reduced for Composition V3, to prevent premature drying of the exposed top film surface. This film product dried to 6% moisture.

While increasing the amount of solids improved the film weight, longer drying times were required. This was due to the surface of the film sealing preventing easy removal of the water. Therefore, for Compositions W1-W3, the temperature in the first 3 m section of the dryer was decreased. This prevented the premature drying of the top surface of the films. Even at greater film thicknesses, the films were dried to 5% moisture even at faster coater line speeds.

Examples X-AA

TABLE 8

	Weight (g)			
Ingredient	X	Y	Z	AA
Loratadine	104.69			
Zomig		52.35		
Paxil			104.69	
Hydroxypropyl methylcellulose	320	320	320	150
Sweetener blend	60	60	60	0.4
Simethicone	1.5	1.5	1.5	1.5
Propylene glycol	100	100	100	
Water	1440	1440	1440	790
Cream essence				0.4
Polyvinyl pyrrolidinone				4
Ethanol				40
Cocoa				55.2
Polyoxyl-40-stearate				7

Compositions X, Y and Z of Table 8 were taste mask coated using a Glatt coater and Eudragit E-100 polymethacrylate polymer as the coating. The coating was spray coated at a 20% level. Therefore 10 mg of drug 12.5 mg of the final dry product must be weighed.

The base formula which excluded the drug additive was mixed with care to not incorporate air. After initial mixing the formula was slowly mixed to deaerate over 30 min. During this time the drug was weighed and prepared for addition to the base mix.

For Composition X, the Loratadine (80% drug) was added slowly to the mix with stirring. After 5 min. of stirring, the total mix was added to the pan of a three roll coater set (reverse roll coater) at 30 micron coating thickness.

The process bottom temperature was set at 90° C. with no top heat or air, the bottom air velocity was set at 40 m/sec., and the line speed was set at 1.3 m/min. Total drying time for the film was 4.6 min.

The liquid was coated at 30 microns and dried in the oven in less than 5 min. The film was flexible and a 1"×0.75" piece weighed 70 mg and contained 10 mg of Loratadine.

The experiment was repeated for Compositions Y and Z, Zomig and Paxil, respectively. Both produced flexible films with the target weight of 70 mg containing 5 mg of Zomig and 70 mg containing 10 mg of Paxil, respectively.

The products were sweet without any noticeable drug aftertaste.

The ingredients of Composition AA were mixed in order to reduce air captured in the fluid matrix. After mixing 45 g of loratadine coated at a 80% active level and 20% coating using Eudragit E-100, this mixture was added slowing with mixing until the drug was evenly dispersed, approximately 5 min. The liquid was then deposited into the 3 roll coater (reverse roll coater) and coated at 30 microns at a line speed of 1.3 m/min. The oven temperature was set at 90° C. to apply air and heat to the bottom only, with an air velocity set at 40 m/sec. The dried film was 0.005 inch. thick (5 mil) and was cut into 1 in.×0.75 in. pieces weighing 70 mg+/−0.7 mg, demonstrating the uniformity of the composition of the film. The film was flexible with 5% moisture, free of air bubbles, and had uniform drug distribution as seen under the light microscope, as well as shown by the substantially identical weight measurements of the film pieces.

Examples BA-BI

The incorporation of the anti-foaming/de-foaming agent (i.e., simethicone) provided a film that not only provided a uniform film that substantially reduced or eliminated air bubbles in the film product, but also provided other benefits. The films displayed more desirable organoleptic properties. The films had an improved texture that was less "paper-like" provided a better mouth-feel to the consumer.

The compositions in Table 9 were prepared (including the addition of simethicone in inventive compositions BA-BG) and mixed under vacuum to remove air bubbles.

The resultant uncut films of inventive compositions BA-BG exhibited uniformity in content particularly with respect to the insoluble active, as well as unit doses of ¾" by 1" by 5 mils cut therefrom. The inventive compositions also were observed to have a smooth surface, absent of air bubbles. The significantly higher amounts of simethicone present in inventive compositions BF-BG also provided a very uniform film, but not significantly improved from that of inventive compositions BA-BE.

By contrast, comparative examples BH-BI were observed to have a rougher surface, exhibiting the inclusion of air bubbles in the resultant film which provided a less uniform texture and distribution of the ingredients.

TABLE 9

Ingredient	BA	BB	BC	BD	BE	BF	BG	BH	BI
Hydroxypropylmethyl cellulose	0	3.77	3.70	3.84	0	3.67	0	0	3.84
Peppermint oil	2.94	1.93	2.39	0	0	2.67	2.94	2.67	0
Sweetener	2.20	0.32	0.23	0	0.17	1.53	2.20	1.54	0
Polyvinylpyrrolidone	2.68	2.01	2.39	0	0	2.33	2.68	2.34	0
Tween 80[1]	2.24	1.07	1.48	1.42	0.55	1.35	2.24	0	1.42
Simethicone[2]	0.66	0.42	0.68	0.22	0.22	5.00	2.00	0	0
Listerine[3]	0	0	0	0	92.41	0	0	0	0
Methylcellulose	4.03	0	0	0	0	0	4.03	0	0
Cornstarch[4]	2.68	0	0	0	0	0	2.68	0	0
Water	73.53	90.47	89.14	92.22	0	83.45	72.19	93.46	92.44
Loratadine[5]	4.29	0	0	2.31	0	0	4.29	0	2.31
Pullulan[6]	0	0	0	0	6.65	0	0	0	0
Calcium Carbonate	1.43	0	0	0	0	0	1.43	0	0
Xanthan Gum	0.30	0	0	0	0	0	0.30	0	0
Propylene Glycol	3.02	0	0	0	0	0	3.02	0	0

[1]Available from ICI Americas
[2]Available from OSI
[3]Available from Pfizer, Inc. including thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), menthol (0.042%), water (up to 72.8%), alcohol (26.9%), benzoic acid, poloxamer 407, sodium benzoate, and caramel color
[4]Available from Grain Processing Corporation as Pure Cote B792
[5]Available from Schering Corporation as Claritin
[6]Available from Hayashibara Biochemical Laboratories, Inc., Japan

Examples CA-CC

The following examples of the present invention describe films and film-forming compositions that use an ethoxylated caster oil as a surfactant, or alternatively are free of surfactants, plasticizers and/or polyalcohols. Desirably, the films or film-forming compositions of the present invention are essentially free of surfactants. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of plasticizers. Still furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of polyalcohols. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants and plasticizers. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants, plasticizers and polyalcohols.

TABLE 10

Ingredient	(parts by wt.) CA
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
Xanthan Gum	1.14
SURFACTANT[2]:	2.0
PLASTICIZER[3]:	11.67
ANTI-FOAM AGENT[4]	2.44
OTHER	
Spearmint Flavor	10.43
Loratadine (drug)	16.62
Calcium Carbonate	5.54
Sweetener	9.36

[1]Available from Grain Processing Corporation as Pure Cote B792
[2]Ethoxylated caster oil, Cremophor ® EL available from BASF
[3]Propylene Glycol
[4]Silicone Emulsion

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 45 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over 45 min.

After release of the vacuum, 6 grams of the liquid was added to a coating paper using a 200 micron spiral wound rod and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90° C. until about 5% moisture remained. The formula coated and dried to a film thickness of approx. 60 microns and quickly dissolved in the mouth.

TABLE 11

Ingredient	(parts by wt.) CB
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
PLASTICIZER/SOLVENT[2]:	22.1
ANTI-FOAM AGENT[3]	2.44
OTHER	
Raspberry Flavor	0.3
Calcium Carbonate[4]	30.38
Sweetener	8.36

[1]Available from Grain Processing Corporation as Pure Cote B792
[2]Propylene Glycol
[3]Polydimethyl Siloxane Emulsion
[4]Functioned to mimic drug loading

The above ingredients were added to water at 40% until a homogeneous suspension was made. Vacuum was added over 20 min. starting at 500 mm Hg. and ending at 660 mm Hg. until all air was removed from suspension. Film was made as described in prior experiments. The liquid coated the silicone release substrate and dried to a uniform flexible film. The film passed the 180° bend test without cracking and dissolved in the mouth.

TABLE 12

Ingredient	(parts by wt.) CC
POLYMERS:	
Hydroxypropylmethyl cellulose	7.8
Hydroxypropyl cellulose	7.8
ANTI-FOAM AGENT[1]	0.75
OTHER	
Peppermint & Bittermint Flavor	2.25
Tastemasking Flavor[2]	0.3
Calcium Carbonate[3]	15.2
Sweeteners	0.9

[1]Polydimethyl Siloxane Emulsion
[2]Prosweet from Virginia Dave
[3]Functioned to mimic drug loading

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 20 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner up to 760 mm over 35 min.

After release of the vacuum, the liquid was added to a coating paper using a 350 micron smooth bar and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90° C. until about 4% moisture remained. The formula coated and dried to a film. The film had an acceptable taste and quickly dissolved in the mouth. The taste-masking flavor is an ingredient that affects the taste receptors to mask the receptors from registering a different, typical undesirable, taste. The film passed the 180° bend test without cracking and dissolved in the mouth.

Example CD

The following example of the present invention describe films and film-forming compositions that use a taste-masked, pharmaceutically active agent which also contains flavors and taste-masking aids. A taste-masking flavor is an ingredients that effects taste receptors to mask the receptors from registering a different, typically undesirable, taste.

TABLE 13

Ingredient	(grams) CD
Hydroxypropylmethyl cellulose	4.26
Hydroxypropyl cellulose	1.42
Precipitated calcium Carbonate	1.22
Sweetener[1]	0.6
Taste-Masking flavor[2]	0.08
Taste-masked Acetaminophen[3]	5.86
Cinnamon Flavor	0.9
Spearmint Flavor	0.43
Polydimethylsiloxane emulsion	0.23

[1]Sucralose, available from McNeil Nutritionals
[2]Magna Sweet, available from Mafco Worldwide Corp.
[3]Gutte Enteric, coated acetaminophen, Gatte, LLC

The above ingredients, except for the pharmaceutically active agent and flavors, were added at 35 grams water and stirred until polymers were fully hydrated which took about 20 min. Food coloring (7 drops of red food coloring and 1 drop of yellow fool coloring) was also added. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over about 10 to 20 minutes. The taste-masked Acetaminophen was added to the mix in about 4 minutes was stirring under vacuum. The flavors were then added to the mix in about 4 minutes was stirring under vacuum.

After release of the vacuum, the liquid solution was added to a coating paper using a 350 micron smooth bar. The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90° C. for about 11 minutes until about 3% moisture remained.

The formula coated and dried to a film. The film had an acceptable taste and moderately quickly dissolved in the mouth. The film did not curl on standing. The film passed the 180° bend test without cracking and dissolved in the mouth.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to include all such changes and modifications as fall within the true scope of the invention.

Examples CE-CF

Thin film compositions of the present invention were prepared using the amounts described in Table 14.

TABLE 14

Ingredient	Weight (g)
Hydroxypropylmethyl cellulose	3.92
Pullulan	3.92
Trehalose[1]	3.5
Precipitated Calcium Carbonate	3.85
Propylene Glycol	1.96
Simethicone[2]	0.35
Bovine Extract[3]	32.5
Water	q.s.

[1]Available from Cargill Inc.
[2]Available from Sentry
[3]Available from Amarillo Biosciences Inc.

The above ingredients were combined by mixing until a uniform mixture was achieved. A sufficient amount of water was present in the film compositions prior to drying, i.e., q.s., which may range between about 200 g to about 1000 g. The compositions then were cast into films onto release paper using a K-Control Coater with a 250 micron smooth bar.

In Example CE, the films subsequently were dried in an oven at approximately 80° C. for about 6 minutes. The films were dried to about 4.3 percent moisture. In Example CF, the films were dried in an oven at approximately 60° C. for about 10 minutes. The films were dried to about 5.06 percent moisture. After drying, the protein derived from bovine extract, which was contained in the films, was tested to determine whether or not it remained active. The protein was found to be approximately 100 percent active in the final, dried film products of both Examples CE and CF. Therefore, the heat sensitive active did not substantially degrade or denaturize during the drying process.

Examples CG-CI

Example CG

Thin film compositions of the present invention were prepared using the amounts described in Table 15.

TABLE 15

	Weight (g)	
Ingredient	CG	CH
Hydroxypropylmethyl cellulose	4.59	9.18
Hydroxypropyl cellulose	1.53	3.06
Sucralose[1]	0.7	1.4
Magna Sweet[2]	0.09	0.18
Precipitated calcium carbonate	2.0	4
Fat-coated dextromethorphan hydrobromide	5.96	11.93
Orange concentrate	1.05	2.1
Prosweet MM24[3]	0.18	0.35
Propylene glycol	1.22	2.45
Simethicone[4]	0.18	0.35
Water	32.5	65

[1]Available from McNeil Nutritional
[2]Available from Mafco Worldwide Corp.
[3]Available from Virginia Dare
[4]Available from Sentry

The above ingredients were combined by mixing, and then cast into two films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were subsequently dried according to conventional drying techniques, rather than via the uniform drying process of the present invention. One film was dried in an oven at 80° C. for 9 minutes on a wire rack. The second film was dried in an oven at 80° C. for 9 minutes on a wire screen. Both films were dried to about 2.4 percent moisture.

The resulting dried films showed imprints of the wire rack and screen after drying. In particular, the films exhibited aggregations of particles in both line and diamond configurations, as shown in FIGS. **9-16**. These configurations comprise imprints of wire supports typically used in the drying process. Without uniform heat diffusion, the wire supports conducted heat more intensely at the points of contact with the substrate, leading to increased evaporation at these points. This caused more vigorous mixing, thereby pulling more particles to the contact points. The resulting increased particle density at the contact points is depicted in FIGS. **9-16**.

Example CH

A composition including the ingredients of Example CG was combined and formed into films, as in Example CG. The films were dried by the process of the present invention, under the same time and temperature conditions as in Example CG. In particular, the films were dried in an 80° C. air oven for 9 minutes on trays lined with furnace filters. The films were dried to about 1.89 percent moisture. The resulting films had no streaks, and were homogenous. Due to uniform heat diffusion throughout the film, no particle aggregations developed, as depicted in FIG. **17**.

What is claimed is:

1. A process for making an ingestible film having a substantially uniform distribution of components and a desired level of a pharmaceutical or biological active component, comprising the steps of:

(a) combining a polymer component, water and a pharmaceutical or biological active component to form a matrix with a uniform distribution of said components;

(b) forming a film from said matrix;

(c) providing a conveyor surface having top and bottom sides;

(d) feeding said film onto said top side of said surface; and

(e) drying said film within about 10 minutes or fewer by applying hot air currents to said bottom side of said conveyor surface with substantially no hot air currents on the top side of said surface and exposing said film to a temperature above a degradation temperature of said pharmaceutical or biological active component, wherein said degradation temperature is 70° C. or higher,

wherein said pharmaceutical or biological active component is maintained at said desired level.

2. The process of claim **1**, wherein said drying step maintains a non-self-aggregating uniform heterogeneity of said components throughout said film.

3. The process of claim **1**, wherein said film is flexible when dried.

4. The process of claim **1**, wherein said film is self-supporting.

5. The process of claim **1**, wherein uniform distribution determines the amount of active material component per area.

6. The process of claim **1**, wherein a specific amount of the active material component may be obtained from said film by cutting said film to a predetermined size.

7. A process for making an ingestible film having a substantially uniform distribution of components and a desired level of a pharmaceutical or biological active component, comprising the steps of:

(a) forming a masterbatch premix of a water-soluble polymer component and water;

(b) feeding a predetermined amount of said premix to at least one mixer;

(c) adding a pharmaceutical or biological active component to said at least one mixer;

(d) mixing said pharmaceutical or biological active component and said predetermined amount of said premix to form a matrix having a uniform distribution of components;

(e) forming a film from said matrix;

(f) providing a conveyor surface having top and bottom sides;

(g) feeding said film onto said top side of said surface; and

(h) drying said film by applying heat to said bottom side of said conveyor surface and exposing said film to a temperature above a degradation temperature of said pharmaceutical or biological active component, wherein said degradation temperature is 70° C. or higher,

wherein said drying step further comprises rapidly forming a visco-elastic film within about the first 4.0 minutes by applying hot air currents to said bottom side of said surface in the absence of hot air currents on the ton side of said surface; and

drying said visco-elastic film to form a self-supporting ingestible film,

wherein said pharmaceutical or biological active component is maintained at said desired level.

8. The process of claim 1, wherein said drying of said film reduces the weight percent of said water to about 10% or less.

9. The process of claim 7, wherein said drying of said film reduces the weight percent of said water to about 10% or less.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,357,891 B2
APPLICATION NO. : 10/768809
DATED : April 15, 2008
INVENTOR(S) : Yang et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page Item (74) replace "(74) Attorney, Agent, or Firm - Hoffman & Baron, LLP" with --(74) Attorney, Agent, or Firm - Hoffmann & Baron, LLP--.

Column 3, line 30, replace "...related to the theological properties..." with --...related to the rheological properties...--.

Column 11, line 1, replace "...velocities are desirable low..." with --...velocities are desirably low...--.

Column 27, lines 6-7, replace "...when introduce to a liquid..." with --...when introduced to a liquid...--.

Column 38, line 43, replace "...drop of yellow fool coloring..." with --...drop of yellow food coloring...--.

Column 42, claim 7, lines 7-8, replace "...currents on the ton side of..." with --...currents on the top side of...--.

Signed and Sealed this

Fifteenth Day of July, 2008

JON W. DUDAS
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,357,891 C1
APPLICATION NO. : 90/012098
DATED : August 21, 2012
INVENTOR(S) : Yang et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page, item [73], Assignee: Reexamination Certificate should read: MonoSol Rx, LLC.

Signed and Sealed this
Twenty-third Day of October, 2012

David J. Kappos
Director of the United States Patent and Trademark Office

US007357891C1

(12) **EX PARTE REEXAMINATION CERTIFICATE** (9222nd)

United States Patent

Yang et al.

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(54) **PROCESS FOR MAKING AN INGESTIBLE FILM**

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Related U.S. Application Data

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(51) **Int. Cl.**

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A61K 9/00	(2006.01)
A61K 9/70	(2006.01)
F26B 13/10	(2006.01)
F26B 13/20	(2006.01)

(52) **U.S. Cl.** **264/211.12**; 264/234; 264/260

(58) **Field of Classification Search** .... None
See application file for complete search history.

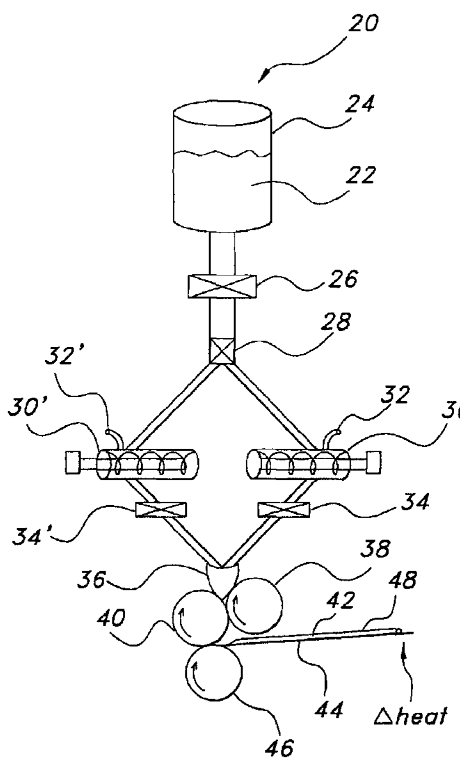
(56) **References Cited**

To view the complete listing of prior art documents cited during the proceeding for Reexamination Control Number 90/012,098, please refer to the USPTO's public Patent Application Information Retrieval (PAIR) system under the Display References tab.

Primary Examiner—Alan Diamond

(57) **ABSTRACT**

The invention relates to film products containing desired levels of active components and methods of their preparation. Desirably, the films disintegrate in water and may be formed by a controlled drying process, or other process that maintains the required uniformity of the film. Desirably, the films may be exposed to temperatures above that at which the active components typically degrade without concern for loss of the desired activity.



EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims **1-9** are cancelled.

New claims **10-28** are added and determined to be patentable.

10. A process for making an ingestible film having a substantially uniform distribution of components and a desired level of a pharmaceutical or biological active component, comprising the steps of: (a) *combining a polymer component, water and a pharmaceutical or biological active component to form a matrix with a uniform distribution of said components;* (b) *forming a film from said matrix;* (c) *providing a conveyor surface having top and bottom sides;* (d) *feeding said film onto said top side of said surface; and* (e) *drying said film within about 10 minutes or fewer by applying hot air currents to said bottom side of said conveyor surface with substantially no hot air currents on the top side of said surface and exposing said film to a temperature above a degradation temperature of said pharmaceutical or biological active component, wherein said degradation temperature is 70° C. or higher, wherein said pharmaceutical or biological active component is maintained at said desired level, wherein said desired level is measured by substantially equally-sized individual unit doses which do not vary by more than 10% of said pharmaceutical or biological active component.*

11. A process for making an ingestible film having a substantially uniform distribution of components and a desired level of a pharmaceutical or biological active component, comprising the steps of: (a) *forming a masterbatch premix of a water-soluble polymer component and water;* (b) *feeding a predetermined amount of said premix to at least one mixer;* (c) *adding a pharmaceutical or biological active component to said at least one mixer;* (d) *mixing said pharmaceutical or biological active component and said predetermined amount of said premix to form a matrix having a uniform distribution of components;* (e) *forming a film from said matrix;* (f) *providing a conveyor surface having top and bottom sides;* (g) *feeding said film onto said top side of said surface; and* (h) *drying said film by applying heat to said bottom side of said conveyor surface and exposing said film to a temperature above a degradation temperature of said pharmaceutical or biological active component, wherein said degradation temperature is 70° C. or higher, wherein said drying step further comprises rapidly forming a visco-elastic film within about the first 4.0 minutes by applying hot air currents to said bottom side of said surface in the absence of hot air currents on the top side of said surface; and drying said visco-elastic film to form a self-supporting ingestible film, wherein said pharmaceutical or biological active component is maintained at said desired level, wherein said desired level is measured by substantially equally-sized individual unit doses which do not vary by more than 10% of said pharmaceutical or biological active component.*

12. The process of claim 10, wherein said matrix is in the form of a solution, emulsion, or suspension.

13. The process of claim 11, wherein said matrix is in the form of a solution, emulsion, or suspension.

14. The process of claim 10, wherein said hot air currents have a temperature of 70° C. to 100° C.

15. The process of claim 10, wherein said hot air currents have a temperature of about 80° C. to about 100° C.

16. The process of claim 11, wherein said step of applying heat comprises applying heat at a temperature of 70° C. to 100° C.

17. The process of claim 11, wherein the step of applying heat comprises applying heat at a temperature of about 80° C. to about 100° C.

18. The process of claim 10, wherein any hot air current velocities on the top side of said surface are insufficient to overcome the inherent viscosity of said film.

19. The process of claim 10, wherein said drying step maintains a non-self-aggregating uniform heterogeneity of said components throughout said film.

20. The process of claim 10, wherein said film is flexible when dried.

21. The process of claim 10, wherein said film is self-supporting.

22. The process of claim 10, wherein said drying of said film reduces the weight percent of said water to about 10% or less.

23. The process of claim 11, wherein said drying step maintains a non-self-aggregating uniform heterogeneity of said components throughout said film.

24. The process of claim 11, wherein said film is flexible when dried.

25. The process of claim 11, wherein said film is self-supporting.

26. The process of claim 11, wherein said drying of said film reduces the weight percent of said water to about 10% or less.

27. The process of claim 10, wherein the step (d) *of feeding said film onto said top side of said surface comprises feeding said film onto the top side of an already-formed film layer.*

28. The process of claim 11, wherein the step (g) *of feeding said film onto said top side of said surface comprises feeding said film onto the top side of an already-formed film layer.*

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