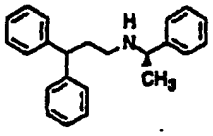
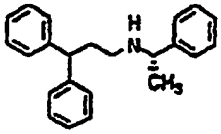
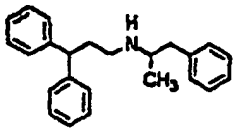
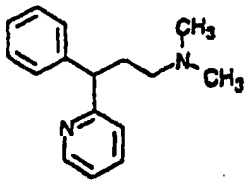
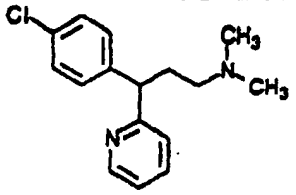
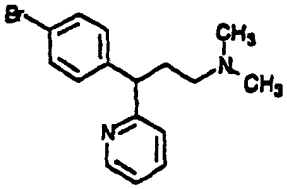
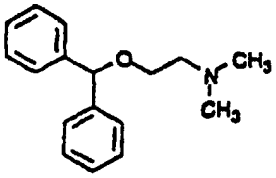
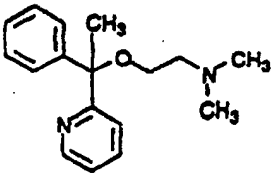
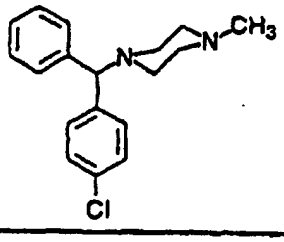
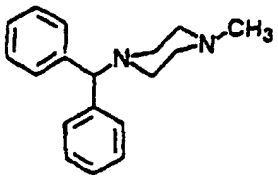
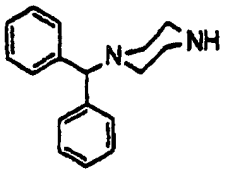
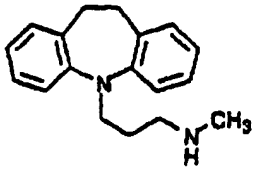
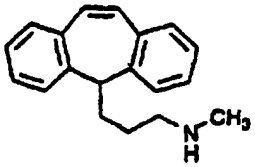
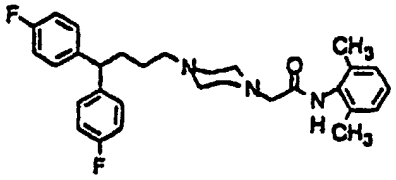
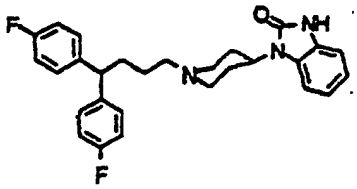
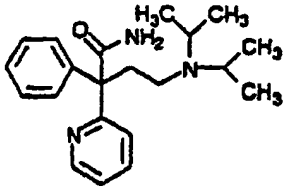
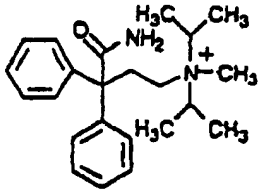
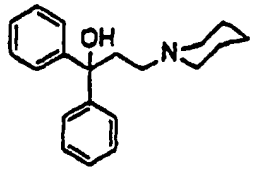
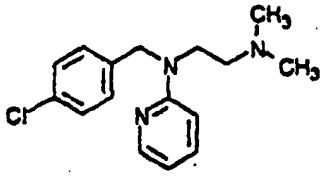
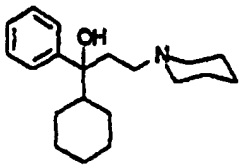
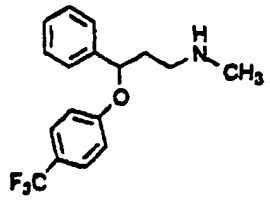
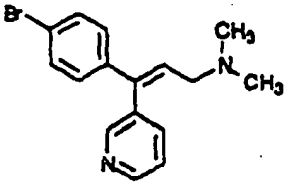
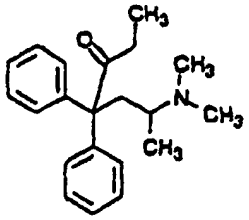
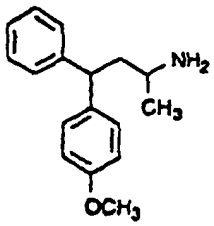
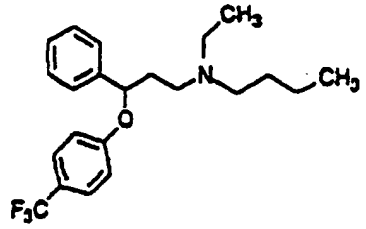
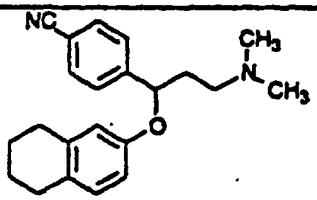
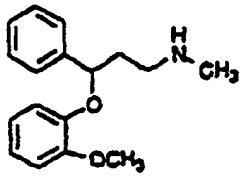
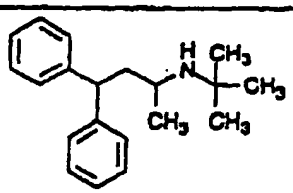
Table 2

Compound and Therapeutic Utility	Structure	IC_{50} (μM) vs. NMDA[a]
(R)-fendiline (calcium channel blocker; coronary vasodilator)		0.719
(S)-fendiline (calcium channel blocker; coronary vasodilator)		0.686
prenylamine (calcium channel blocker; coronary vasodilator)		~10

pheniramine (antihistamine)		22
chlorpheniramine (antihistamine)		>100
brompheniramine (antihistamine)		138
diphenhydramine (antihistamine)		26
doxylamine (antihistamine; hypnotic)		62
chlorcyclizine (antihistamine)		~10
cyclizine (antiemetic)		28

nor-cyclizine (pharmaceutical intermediate)		23
desipramine (antidepressant)		2.3
protriptyline (antidepressant)		≤ 10
lidoflazine (calcium channel blocker; coronary vasodilator)		>30
pimozide (antipsychotic)		>10
disopyramide (antiarrhythmic)		>100
isopropamide (anticholinergic)		87

pridinol (anticholinergic; antiparkinsonian)		10.7
chloropyramine (antihistamine)		76
trihexyphenidyl (anticholinergic; antiparkinsonian)		5.9
fluoxetine (antidepressant)		3.4
zimeldine (antidepressant)		≥ 26
methadone (opiate analgesic)		not tested
Astra compound[b] (antidepressant)		> 30

Novo-Nordisk compound[c] (calcium channel blocker; neuroprotectant)		not tested
Novo-Nordisk compound[d] (calcium channel blocker; neuroprotectant)		28.8
nisoxetine (monoamine uptake inhibitor; antidepressant)		0.894
terodiline (calcium channel blocker; anticholinergic; vasodilator)		not tested

[a]:Inhibition of NMDA/glycine-induced increases in intracellular calcium in cultured rat cerebellar granule cells (RCGC's) (see Example 1).

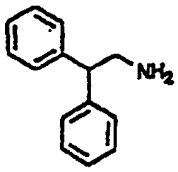
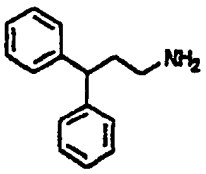
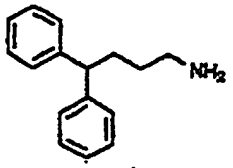
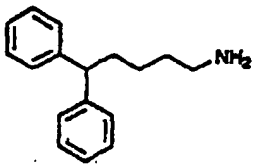
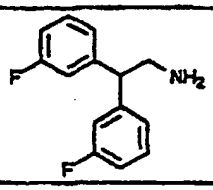
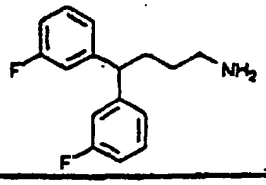
[b]:Disclosed as compound 2 in Table 4 in Marcusson *et al.*, Inhibition of [^{3}H]paroxetine binding by various serotonin uptake inhibitors: structure-activity relationships. *Europ. J. Pharmacol.* 215: 191-198, 1992.

[c]:Disclosed as compound 17 in Jakobsen *et al.*, Aryloxy-phenylpropylamines and their calcium overload blocking compositions and methods of use. U.S. Patent No. 5,310,756, May 10, 1994.

[d]:Disclosed as compound 25 in Jakobsen *et al.*, Aryloxy-phenylpropylamines and their calcium overload blocking compositions and methods of use. U.S. Patent No. 5,310,756, May 10, 1994.

[0337] Structure-activity relationship studies were initiated using Compound **19** (Reference compound) as the lead structure. An examination of the side chain demonstrated that the propyl side chain was optimal for NMDA receptor antagonist potency (Table 3).

Table 3

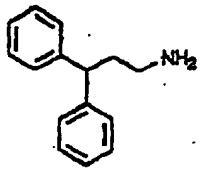
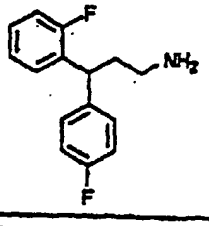
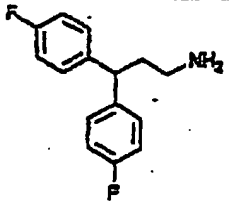
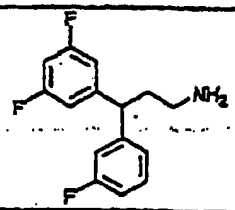
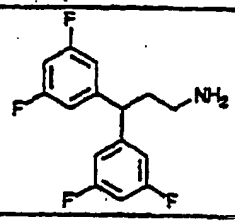
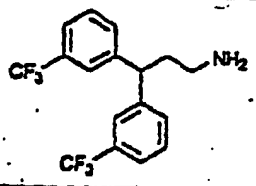
Compound	Structure	IC_{50} (μM) vs. NMDA[a]
2,2-diphenylethylamine		24.5
3,3-diphenylpropylamine (Compound 19)		0.435
4,4-diphenylbutylamine (Compound 70)		1.7
5,5-diphenylpentylamine (Compound 71)		6.4
2,2-bis(3-fluorophenyl)-1-ethylamine (Compound 98)		7.9
4,4-bis(3-fluorophenyl)-1-butylamine (Compound 100)		0.602

[a]: Inhibition of NMDA/glycine-induced increases in intracellular calcium in cultured rat cerebellar granule cells (RCGC's) (see Example 1).

[0338] Further SAR studies examined the optimal pattern of phenyl ring substitution. Initial studies demonstrated

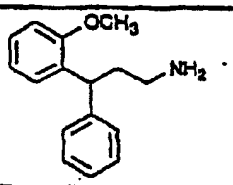
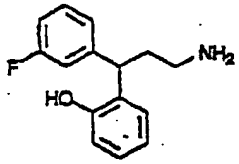
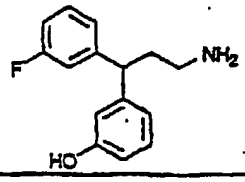
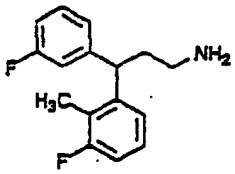
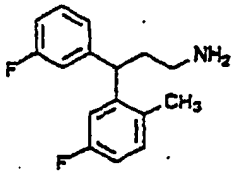
that substitution of a halogen group (fluoro or chloro) at the meta position was optimal for NMDA receptor antagonist potency (Table 4). Increasing the number of fluoro substituents led to an apparent decrease in potency (Table 4).

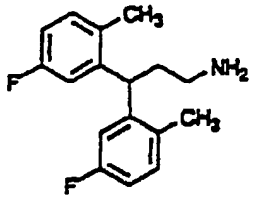
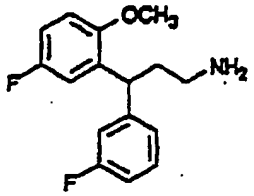
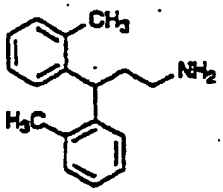
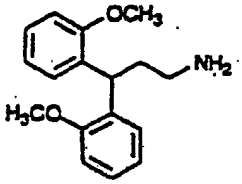
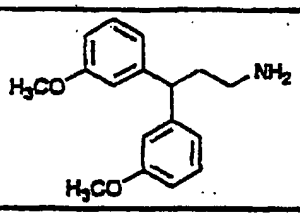
Table 4

Compound	Structure	IC_{50} (μM) vs. NMDA a
3,3-diphenyl-1-propylamine (Compound 19)		0.435
3-(2-fluorophenyl)-3-(4-fluorophenyl)-1-propylamine (Compound 76)		0.730
3,3-bis(4-fluorophenyl)-1-propylamine (Compound 77)		5.5
3-(3,5-difluorophenyl)-3-(3-fluorophenyl)-1-propylamine (Compound 96)		0.187
3,3-bis(3,5,difluorophenyl)-1-propylamine (Compound 97)		0.410
3,3-bis[3-(trifluoromethyl)phenyl]-1-propylamine (Compound 78)		10.2

[a]: Inhibition of NMDA/glycine-induced increases in intracellular calcium in cultured rat cerebellar granule cells (RCGC's) (see Example 1).

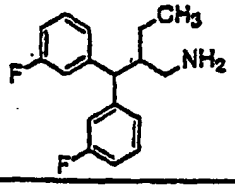
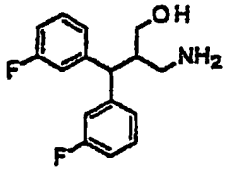
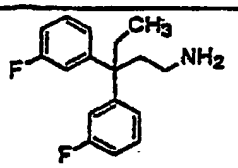
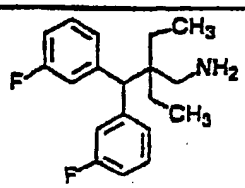
[0339] Replacement of one of the fluoro groups on one phenyl ring with a methyl, methoxy or hydroxy group led to no change or a decrease in the in vitro NMDA receptor antagonist potency. The *ortho* position was optimal for this methyl, methoxy or hydroxy group, and the rank order of potency for this substitution was methyl > methoxy > hydroxy (Table 5). Also illustrated in Table 5 are those compounds possessing the 3,3-bis(3-fluorophenyl) moiety with additional methyl or methoxy substitutions on the phenyl rings, often leading to an increase in NMDA receptor antagonist potency. Table 5 also illustrates those compounds possessing the 3,3-bis(2-methylphenyl) or 3,3-bis(2-methoxyphenyl) moiety in place of the 3,3-bis(3-fluorophenyl) moiety; these substitutions are acceptable, although a decrease in potency is noted.

3-(2-methoxyphenyl)-3-phenyl-1-propylamine (Compound 97)		0.410
3-(2-hydroxyphenyl)-3-(3-fluorophenyl)-1-propylamine (Compound 103)		0.380
3-(3-hydroxyphenyl)-3-3-fluorophenyl)-1-propylamine (Compound 101)		0.912
3-(3-fluorophenyl)-3-(2-methyl-3-fluorophenyl)-1-propylamine (Compound 56)		0.218
3-(3-fluorophenyl)-3-(3-fluoro-6-methylphenyl)-1-propylamine (Compound 57)		0.028

3,3-bis(3-fluoro-6-methylphenyl)-1-propylamine (Compound 58)		0.028
3-(3-fluorophenyl)-3-(3-fluoro-6-methoxyphenyl)-1-propylamine (Compound 61)		0.134
3,3-bis(2-methylphenyl)-1-propylamine (Compound 65)		0.167
3,3-bis(2-methoxyphenyl)-1-propylamine (Compound 62)		0.177
3,3-bis(3-methoxyphenyl)-1-propylamine (Compound 115)		1.9

*:Inhibition of NMDA/glycine-induced increases in intracellular calcium in cultured rat cerebellar granule cells (RCGC's) (see Example 1).

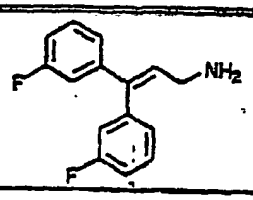
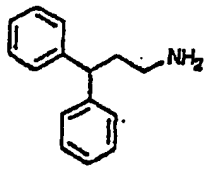
[0340] The next series of SAR experiments investigated the effect of alkyl chain substitutions (branching patterns) on NMDA receptor antagonist potency *in vitro*. The addition of a methyl group on either the α or β carbon on the propyl side chain led to a decrease or no change in potency, respectively (Table 6).

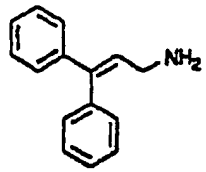
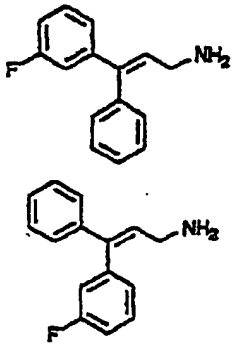
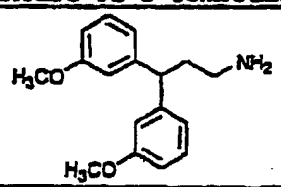
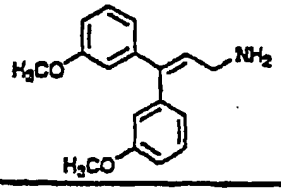
3,3-bis(3-fluorophenyl)-2-ethyl-1-propylamine (Compound 55)		0.035
3,3-bis(3-fluorophenyl)-2-hydroxyethyl-1-propylamine (Compound 54)		0.036
3,3-bis(3-fluorophenyl)-3-ethyl-1-propylamine (Compound 82)		0.106
3,3-bis(3-fluorophenyl)-2,2-diethyl-1-propylamine (Compound 80)		28

[a]: Inhibition of NMDA/glycine-induced increases in intracellular calcium in cultured rat cerebellar granule cells (RCGC's) (see Example 1).

[0341] The next series of SAR experiments investigated the effect of incorporation of a double bond within the propyl chain on HMDA receptor antagonist potency in vitro (Table 7). As can be seen in Table 7, the incorporation of a double bond decreased potency in a consistent manner.

Table 7

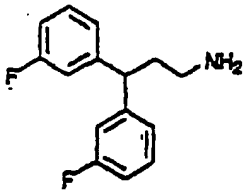
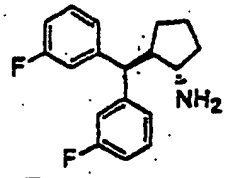
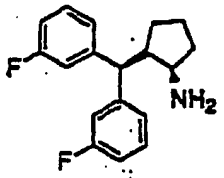
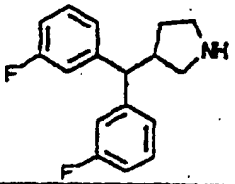
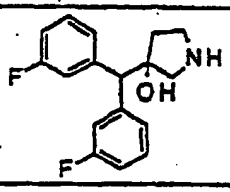
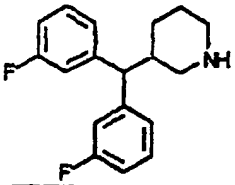
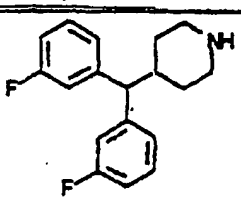
Compound	Structure	IC_{50} (μM) vs. NMDA a
3,3-bis(3-fluorophenyl)-prop-2-ene-1-amine (Compound 139)		1.4
3,3-diphenyl-1-propylamine (Compound 19)		0.435

3,3-diphenyl-prop-2-ene-1-amine (Compound 81)		1.4
3-(3-fluorophenyl)-3-phenyl-prop-2-ene-1-amine (Compound 107)	 (mixture of 2 compounds)	2.67
3,3-bis(3-methoxyphenyl)-1-propylamine (Compound 115)		1.9
3,3-bis(3-methoxyphenyl)-prop-2-ene-1-amine (Compound 116)		4.47

[a]: Inhibition of NMDA/glycine-induced increases in intracellular calcium in cultured rat cerebellar granule cells (RCGC's) (see Example 1).

[0342] The next series of SAR experiments investigated the effect of incorporation of the propylamine chain into a ring structure on NMDA receptor antagonist potency *in vitro* (Table 8).

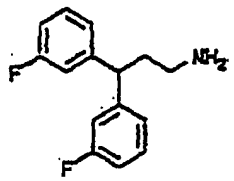
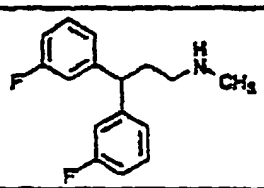
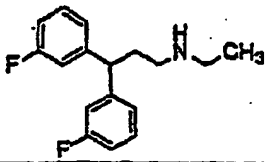
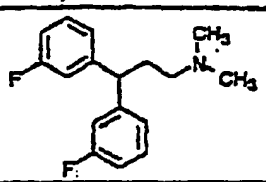
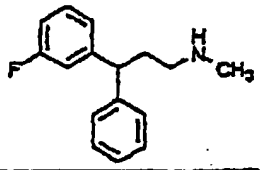
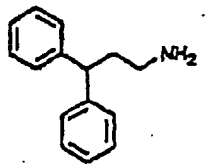
Table 8

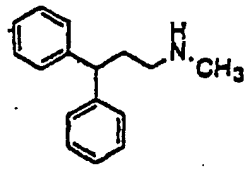
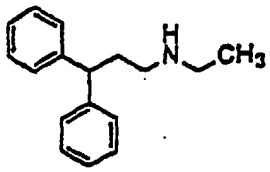
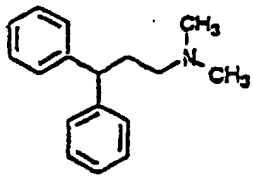
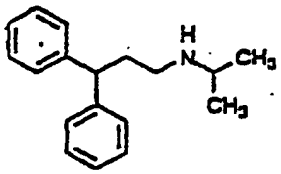
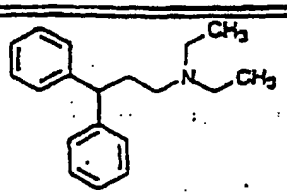
Compound	Structure	IC_{50} (μM) vs. NMDA a
3,3-bis(3-fluorophenyl)-1-propylamine (Compound 20)		0.070
Compound 63		0.093
Compound 64		0.309
Compound 102		1.01
Compound 84		7.9
Compound 111		0.790
Compound 112		28.9

[a]: Inhibition of NMDA/glycine-induced increases in intracellular calcium in cultured rat cerebellar granule cells (RCGC's) (see Example 1).

[0343] The next series of SAR experiments investigated the effect of simple alkyl substitution on the nitrogen on NMDA receptor antagonist potency *in vitro* (Table 9).

Table 9

Compound	Structure	IC_{50} (μM) vs. NMDA [a]
3,3-bis(3-fluorophenyl)-1-propylamine (Compound 20)		0.070
N-methyl-3,3-bis(3-fluorophenyl)-1-propylamine (Compound 60)		0.416
N-ethyl-3,3-bis(3-fluorophenyl)-1-propylamine (Compound 59)		0.272
N,N-dimethyl-3,3-bis(3-fluorophenyl)-1-propylamine (Compound 123)		9.6
N-methyl-3-(3-fluorophenyl)-3-phenyl-1-propylamine (Compound 108)		1.06
3,3-diphenylpropylamine (Compound 19)		0.435

N-methyl-3,3-diphenylpropylamine (Compound 67)		10.95
N-ethyl-3,3-diphenylpropylamine (Compound 68)		2.9
N,N-dimethyl-3,3-diphenylpropylamine (Compound 73)		12.6
N-isopropyl-3,3-diphenylpropylamine (Compound 72)		7.4
N,N-diethyl-3,3-diphenylpropylamine (Compound 74)		27.5

[a]: Inhibition of NMDA/glycine-induced increases in intracellular calcium in cultured rat cerebellar granule cells (RCGC's) (see Example 1).

[0344] Certain simplified arylalkylamine compounds were selected for evaluation of activity in a battery of neurotransmitter receptor binding assays, and for activity against the L-type calcium channel and delayed rectifier potassium channel. The compounds were inactive (less than 50% inhibition at concentrations up to 10 μM) in the following assays: nonselective α2 adrenergic receptor ([^{3}H]RX 821002 binding in rat cortex), H1 histamine receptor ([^{3}H]pyrilamine binding in bovine cerebellum), nonselective sigma receptor ([^{3}H]DTG binding in guinea pig brain), nonselective opiate receptor ([^{3}H]naloxone binding in rat forebrain), monoamine oxidase (MAO) activity, both MAO-A ([^{14}C] serotonin metabolism in rat liver mitochondria) and MAO-B ([^{14}C]phenylethylamine metabolism in rat liver mitochondria).

[0345] As can be seen in Table 10, activity was noted for several compounds at concentrations below 10 μM in the following assays: L-type calcium channel, delayed rectifier potassium channel, central muscarinic cholinergic receptor binding, and monoamine (dopamine, norepinephrine, and serotonin) uptake binding assays. This profile of activity in the central muscarinic cholinergic receptor and monoamine uptake binding assays is not unexpected, given the chemical structures of our simplified arylalkylamines (refer to Table 2 above). With the exceptions, however, of the activity

of Compounds **63** and **64** in the dopamine uptake binding assay, and the activity of Compound **60** in the dopamine and serotonin uptake binding assays, the simplified arylalkylamine compounds were most potent at the NMDA receptor.

Table 10

Compound	IC_{50} (μM) vs. NMDA[a]	L-type calcium channel[b]	Delayed rectifier potassium channel[c]	Central miscarinic cholinergic receptor[d]	Monoamine uptake binding assays[e]
Compound **63**	0.093	1.9	not tested	11% at 0.1B1% at 10	64% at 0.1[f]98% at 10[f]7% at 0.1[g]76% at 10[g]13% at 0.1[h]85% at 10[h]
Compound **64**	0.309	not tested	not tested	11% at 0.183% at 10	50% at 0.1[f]99% at 10[f] 8% at 0.1[g]65% at 10[g]29% at 0.1[h]68% at 10[h]
Compound **58**	0.028	1.6	not tested	1% at 0.148% at 10	0% at 0.1[f]45% at 10[f]1% at 0.1[g]67% at 10[g]27% at 0.1[h]95% at 10[h]
Compound **59**	0.272	not tested	not tested	9% at 0.187% at 10	2% at 0.1[f]78% at 10[f]7% at 0.1[g]51% at 10[g]14% at 0.1[h]86% at 10[h]
Compound **60**	0.416	2.3	not tested	13% at 0.193% at 10	0.914[f]16% at 0.1[g]64% at 10[g] 0.068[h]

[a]:Inhibition of NMDA/glycine-induced increases in intracellular calcium in cultured rat cerebellar granule cells (RCGC's) (see Example 1).
[b]:Inhibition of KCl depolarization-induced increases in intracellular calcium in cultured rat cerebellar granule cells (RCGCs); estimated IC_{50} value in μM.
[c]:Inhibition of delayed rectifier potassium channel in cultured N1E-115 neuroblastoma cells; estimated IC_{50} value in μM.
[d]:Inhibition of the binding of [^{3}H]quinuclidinylbenzilate (QNB) to rat cortical membranes; percent block at indicated concentration in μM.
[e]:Inhibition of the binding of [^{3}H]WIN-35,428 to guinea pig striatal membranes (dopamine uptake binding assay), [^{3}H]desipramine to rat cortical membranes (norepinephrine uptake binding assay), or [^{3}H]citalopram to rat forebrain membranes (serotonin uptake binding assay); percent block at indicated concentration in μM, or IC_{50} when available.
[f]:dopamine uptake binding assay
[g]:norepinephrine uptake binding assay
[h]:serotonin uptake binding assay

[0346] Advantageous properties of the arylalkylamine compounds of the present invention are illustrated by the fact that concentrations which suppress NMDA receptor-mediated synaptic transmission fail to inhibit LTP.

Formulation and Administration

[0347] As demonstrated herein, useful compounds of this invention and their pharmaceutically acceptable salts may be used to treat neurological disorders or diseases. While these compounds will typically be used in therapy for human patients, they may also be used to treat similar or identical diseases in other vertebrates such as other primates, farm animals such as swine, cattle and poultry, and sports animals and pets such as horses, dogs and cats.

[0348] In therapeutic and/or diagnostic applications, the compounds of the invention can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in *Remington's Pharmaceutical Sciences,* Mack Publishing Co., Easton PA.

[0349] Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art, and may

include, by way of example but not limitation, acetate, benzenesulfonate, besylate, benzoate, bicarbonate, bitarcrace, calcium edetate, camsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionace, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/disphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, *Remington's Pharmaceutical Sciences,* Mack Publishing Co., Easton, PA (18th ed, 1990).

[0350] Preferred pharmaceutically acceptable salts include, for example, acetate, benzoate, bromide, carbonate, citrate, gluconate, hydrobromide, hydrochloride, maleate, mesylate, napsylate pamoate (embonate), phosphate, salicylate, succinate, sulfate, or tartrate.

[0351] The useful compounds of this invention may also be in the form of pharmaceutically acceptable complexes. Pharmaceutically acceptable complexes are known to those of ordinary skill in the art and include, by way of example but not limitation, B-chlorotheophyllinate (teoclate).

[0352] The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g. Fingl et al., in The Pharmacological Basis of Therapeutics, 1975, Ch. 1 p. 1).

[0353] It should be noted that the attending physician would know how and when to terminate, interrupt, or adjust administration due to toxicity or organ dysfunction. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical responses were not adequate (precluding toxicity). The magnitude of an administered dose in the management of the disorder of interest will vary with the severity of the condition to be treated and to the route of administration. The severity of the condition may, for example, be evaluated in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[0354] Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed or sustained-release form as is known to those skilled in the art. Techniques for formulation and administration may be found in *Remington's Pharmaceutical Sciences,* Mack Publishing Co., Easton, PA. Suitable routes may include oral, buccal, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections, just to name a few.

[0355] For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0356] Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the invention. With proper choice of carrier and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

[0357] Agents intended to be administered intracellularly may be administered using techniques well known to those of ordinary skill in the art. For example, such agents may be encapsulated into liposomes, then administered as described above. Liposomes are spherical lipid bilayers with aqueous interiors. All molecules present in an aqueous solution at the time of liposome formation are incorporated into the aqueous interior. The liposomal contents are both protected from the external microenvironment and, because liposomes fuse with cell membranes, are efficiently delivered into the cell cytoplasm. Additionally, due to their hydrophobicity, small organic molecules may be directly administered intracellularly.

[0358] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0359] In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipiencs and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

[0360] The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

[0361] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspension. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid ester, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0362] Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

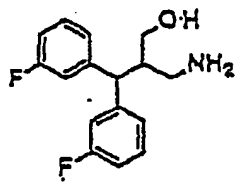
[0363] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG., and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0364] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable, liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGS). In addition, stabilizers may be added.

[0365] Other embodiments are within the following claims.

Claims

1. Use of a compound which is selected from the group consisting of



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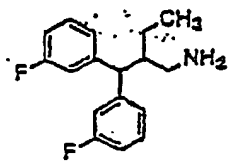

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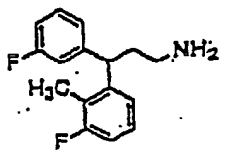

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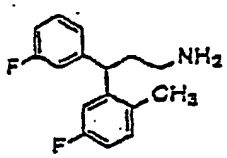

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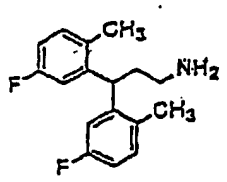

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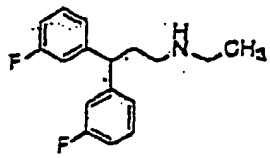

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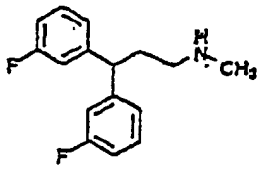

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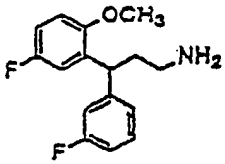

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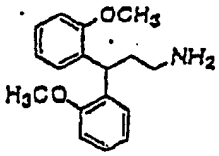

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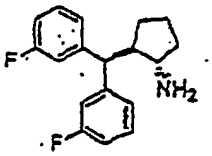

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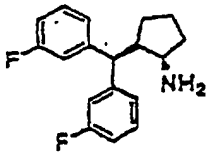

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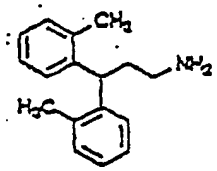

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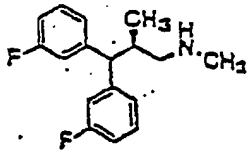

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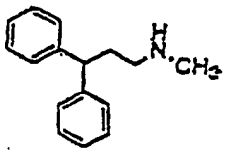

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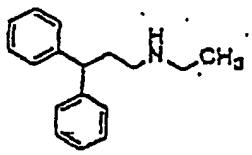

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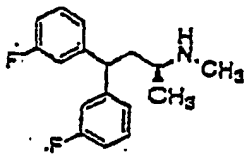

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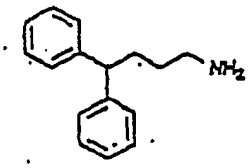

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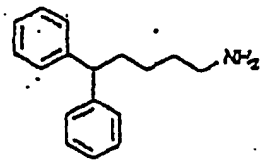

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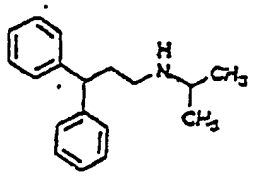

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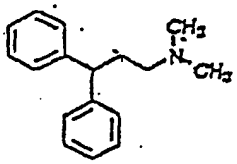

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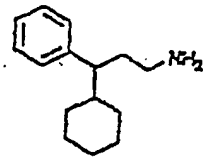

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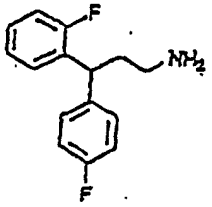

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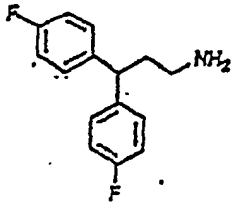

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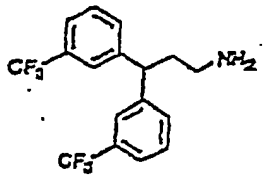

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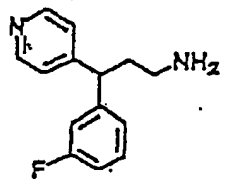

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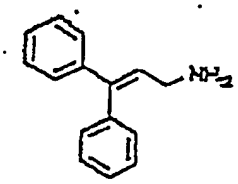

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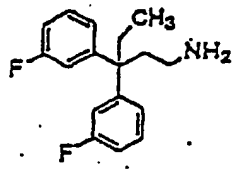

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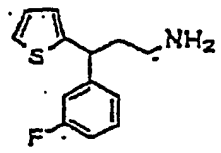

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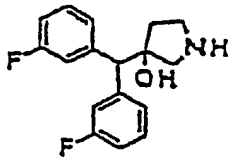

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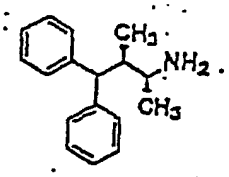
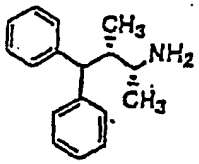
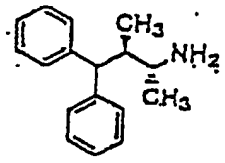
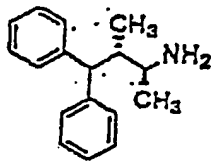


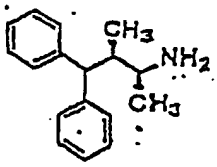


Compound 85 (mixture of 2 compounds)

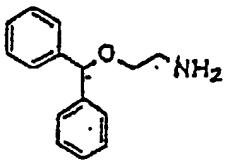




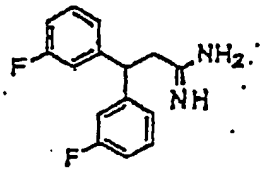
Compound 86 (mixture of 2 compounds)



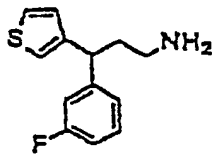
Compound 87



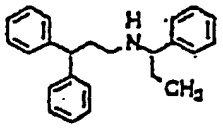
Compound 88.



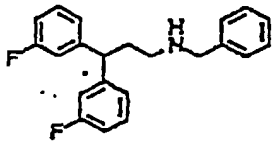
Compound 89



Compound 90



Compound 91



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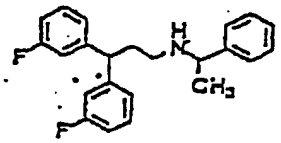

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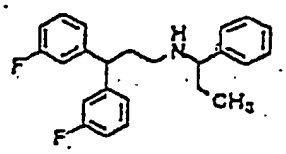

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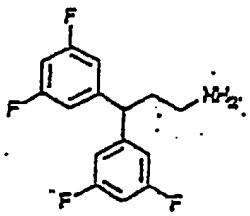

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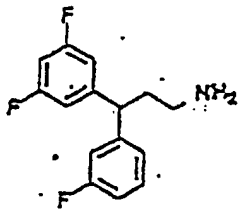

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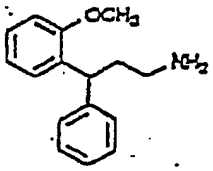

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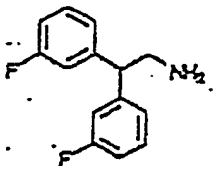

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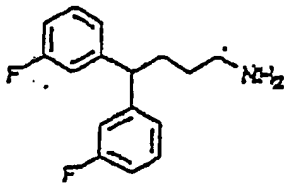

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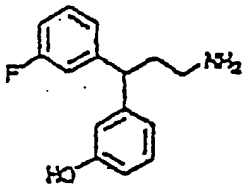

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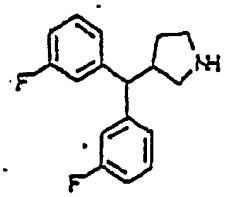

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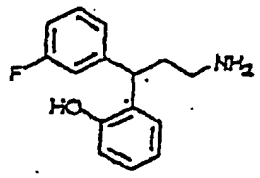
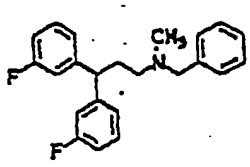
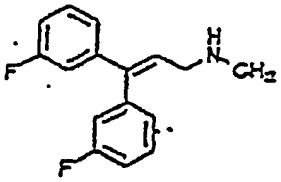


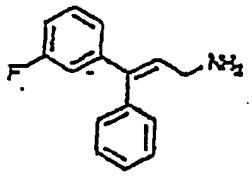
Compound 103

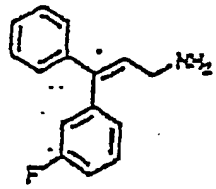


Compound 105

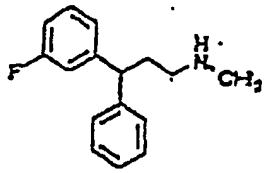


Compound 106

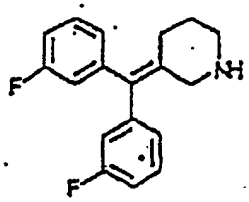




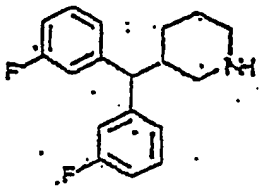
Compound 107
(mixture of 2
compounds)



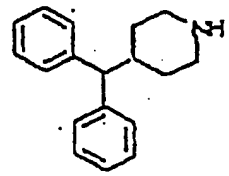
Compound 108



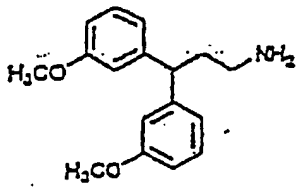
Compound 109



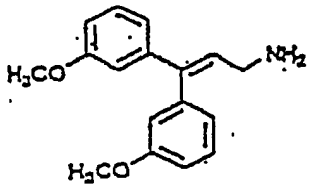
Compound 111



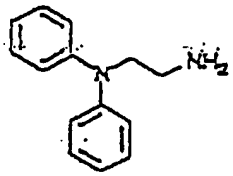
Compound 114



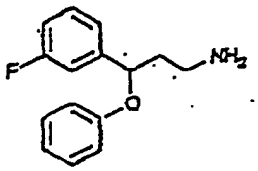
Compound 115



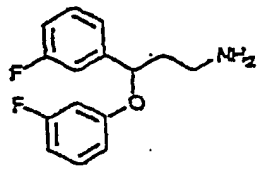
Compound 116



Compound 117



Compound 118



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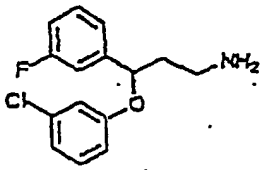
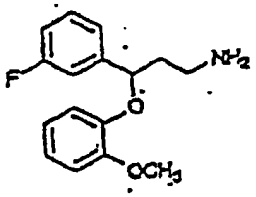
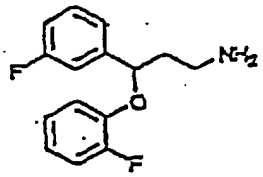


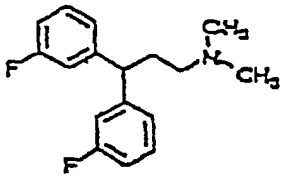
Compound 120



Compound 121



Compound 122



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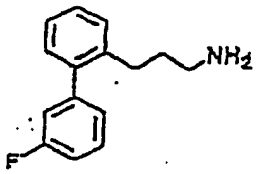
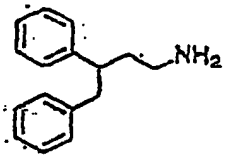


Compound 124



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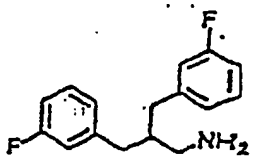
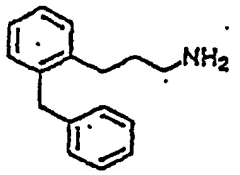
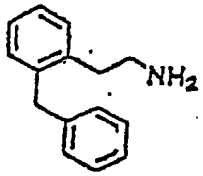


Compound 126



Compound 127



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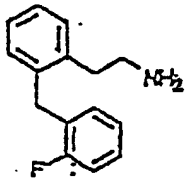

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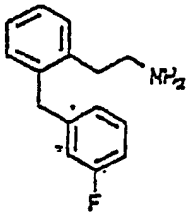
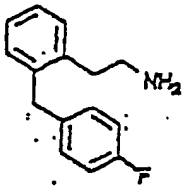


Compound 130



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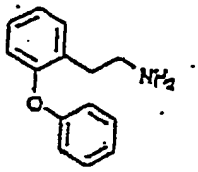
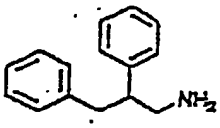
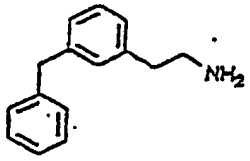


Compound 132



Compound 133



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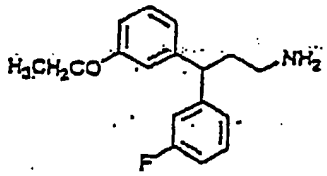
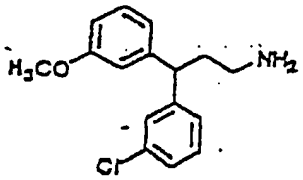
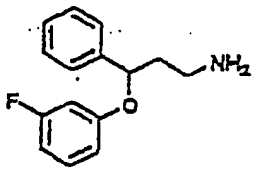


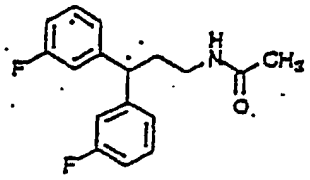
Compound 135



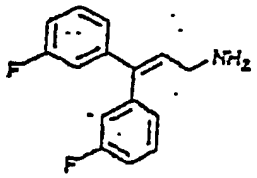
Compound 136



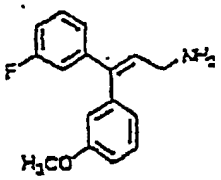
Compound 137



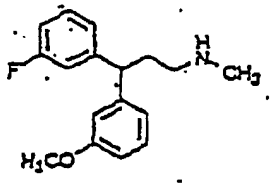
Compound 138



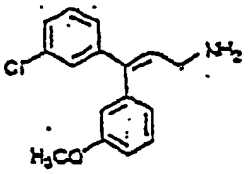
Compound 139



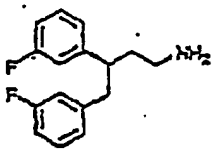
Compound 141



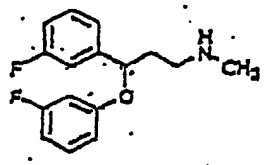
Compound 142



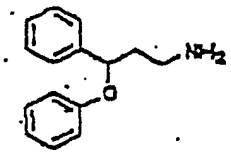
Compound 143



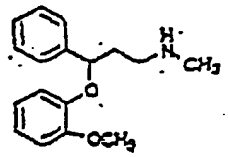
Compound 144



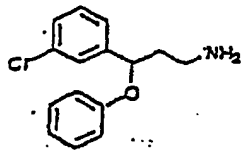
Compound 145



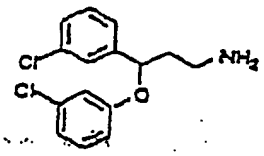
Compound 146



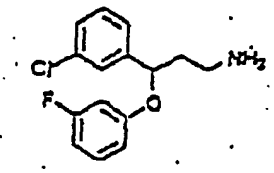
Compound 147



Compound 148



Compound 149



Compound 150

, and pharmaceutically acceptable salts and complexes thereof for the preparation of a pharmaceutical composition for the treatment of a neurological disease or disorder.

2. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 54-66, 68-71, 75, 76, 78, 79, 81-90, 92-98, 100, 101, 103, 105, 106, 108, 109, 111, 114-122, 124-136, 138, 139, 141-144, 148-150, and pharmaceutically acceptable salts and complexes thereof.

3. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 54-66, 69, 70, 75, 76, 81-83, 85-97, 100- 103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135-139, 142, 144-150, and pharmaceutically acceptable salts and complexes thereof.

4. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 54-66, 69, 70, 75, 76, 81-83, 85-90, 92-97, 100, 101, 103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135, 136, 138, 139, 142, 144, 148-150, and pharmaceutically acceptable salts and complexes thereof.

5. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 54-66, 69, 82, 83, 89-97, 103, 111, 118-120, 122, 126, 135-138, 142, 144, 145, 147-150, and pharmaceutically acceptable salts and complexes thereof.

6. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 54-66, 69, 82, 83, 89-90, 92-97, 103, 111, 118-120, 122, 126, 135, 136, 138, 142, 144, 148-150, and pharmaceutically acceptable salts and complexes thereof.

7. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 60, 66, 69, 103, 111, 118-120, 122, 136, 138, 142, 144, 148-150, and pharmaceutically acceptable salts and complexes thereof.

8. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 118-122, 137, 145, 148-150, and pharmaceutically acceptable salts and complexes thereof.

9. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 118-122, 148-150, and pharmaceutically acceptable salts and complexes thereof.

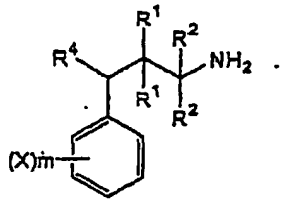
10. The use according to claim 1, wherein the compound is selected from the group consisting of compounds 63 and 64 and pharmaceutically acceptable salts and complexes thereof.

11. The use according to claim 1, wherein the compound is selected from compound 119, and pharmaceutically acceptable salts and complexes thereof.

12. The use according to claim 1, wherein the compound is selected from compound 144, and pharmaceutically acceptable salts and complexes thereof.

13. The use of compound 60, and pharmaceutically acceptable salts and complexes thereof for the preparation of a pharmaceutical composition for the treatment of a neurological disease or disorder.

14. Use of a compound having the formula:

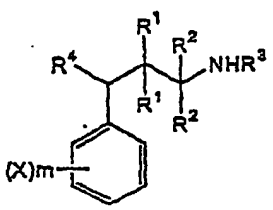


wherein:

X is independently selected from the group consisting of -Br, -Cl, -F, -I,-CF_3, alkyl, -OH, -OCF_3, -O-alkyl, and -O-acyl;
R_1 is independently selected from the group consisting of -H, C_1-C_4 alkyl, and -O-acyl;
R_2 is independently selected from the group consisting of -H, alkyl, and hydroxyalkyl, or both R_2s together are imino;
R_4 is phenoxy which is optionally substituted with -F, -Cl, -Br, -I, -CF_3, alkyl, -OH,- OCF_3-O-alkyl, or -O-acyl; and
m is independently an integer from 0 to 5; and pharmaceutically acceptable salts and complexes thereof provided that said compound is not:
3-(p-isopropoxyphenoxy)-3-phenylpropylamine
3-(2'-methyl-4',5'-dichlorophenoxy)-3-phenylpropylamine
3-(p-t-butylphenoxy)-3-phenylpropylamine
3-(2',4'-dichlorophenoxy)-3-phenyl-2-methyl propylamine
3-(o-ethylphenoxy)-3-phenylpropylamine
3-(o-methoxyphenoxy)-3-phenylpropylamine
3-phenoxy-3-phenylpropylamine

for the preparation of a pharmaceutical composition for the treatment of a neurological disease or disorder.

15. Use of a compound having the formula

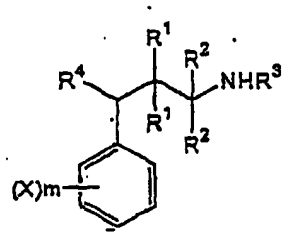


wherein:

X is independently selected from the group consisting of-F, -Cl, -Br, -I, -CF_3 alkyl, -OH, -OCF_3, -O-alkyl, and -O-acyl;
R_1 is independently selected from the group consisting of -H, C_1-C_4 alkyl, and -O-acyl;
R_2 is independently selected from the group consisting of -H, C_1-C_4 alkyl, and hydroxyalkyl, or both R_2s together are imino;
R_3 is selected from the group consisting of methyl and ethyl;
R_4 is phenoxy which is optionally substituted with -F, -Cl, -Br, -I, -CF_3, alkyl, -OH, -OCF_3, -O-alkyl, or -O-acyl; and m is independently an integer from 0 to 5; and pharmaceutically acceptable salts and complexes thereof provided that said compound is not
N-methyl 3-(o-chloro-p-tolyloxy)-3-phenyl-1-methylpropylamine
N-methyl 3-(p-tolyloxy)-3-phenylpropylamine
N-methyl 3-(o-chloro-p-isopropylphenoxy)-3-phenyl-2-methylpropylamine
N-methyl 3-(p-iodophenoxy)-3-phenyl-propylamine
N-methyl 3-(3-n propylphenoxy)-3-phenyl-propylamine
N-methyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine
N-methyl 3-(m-chlorophenoxy)-3-phenylpropylamine
N-methyl 3-(p-fluorophenoxy)-3-phenylpropylamine
N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine
N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine
N-methyl 3-(o-fluorophenoxy)-3-phenylpropylamine
N-methyl 3-(m-fluorophenoxy)-3-phenylpropylamine
N-methyl 3-(p-chlorophenoxy)-3-phenylpropylamine
N-methyl 3-(m-fluorophenoxy)-3-phenylpropylamine
N-methyl 3-phenoxy-3-phenyl-2-methylpropylamine
N-methyl 3-phenoxy-3-phenyl-1-methylpropylamine
N-methyl 3-phenoxy-3-phenylpropylamine
N-methyl 3-(o-trifluoromethylphenoxy)-3-phenylpropylamine
N-methyl 3-(m-methoxyphenoxy)-3-phenylpropylamine
N-methyl 3-(o,p-difluorophenoxy)-3-phenylpropylamine
N-ethyl-3-(o-iodophenoxy)-3-phenylpropylamine
N-methyl-3-(o-chlorophenoxy)-3-phenylpropylamine
N-methyl-3-(o-bromophenoxy)-3-phenylpropylamine

for the preparation of a pharmaceutical composition for the treatment of a neurological disease or disorder.

16. Use of a compound having the formula:



wherein:

(X)m is selected from the group consisting of meta-fluoro, meta-chloro, Ortho-O-C_1-C_4 alkyl, ortho-methyl, ortho-fluoro, ortho-chloro, meta-O-C_1-C_4 alkyl, meta-methyl, ortho-OH, and meta-OH;
R_1 is H;
R_2 is H;
R_3 is selected from the group consisting of methyl and ethyl;
R_4 is phenoxy which is optionally substituted with -F, -Cl, -Br, -I, -CF_3, alkyl, -OH, -OCF_3, -O-alkyl, or -O-acyl; and pharmaceutically acceptable salts and complexes thereof, for the preparation of a pharmaceutical composition for the treatment of a neurological disease or disorder.

17. The use of any one of claims 1 to 16, wherein the neurological disease or disorder comprises stroke, head trauma, spinal cord injury, spinal cord ischemia, ischemia- or hypoxia-induced nerve cell damage, epilepsy, pain, anxiety, neuropsychiatric or cognitive deficits due to ischemia or hypoxia such as those that frequently occur as a consequence of cardiac surgery under cardiopulmonary bypass, Alzheimer's disease, Huntington's disease, Parkinson's disease, or amyotyrophic lateral sclerosis.

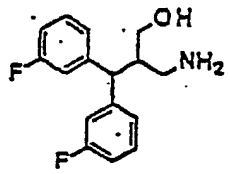
18. The use of claim 17, wherein said stroke is global ischemic.

19. The use of claim 17, wherein said stroke is focal ischemic.

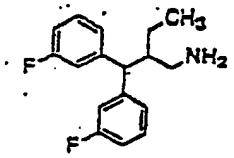
20. The use of claim 17, wherein said stroke is hemorrhagic.

21. The use of claim 17, wherein the neurological disease or disorder comprises Parkinson's disease.

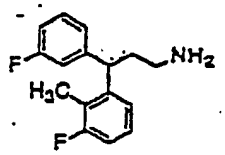
22. A compound selected from the group consisting of



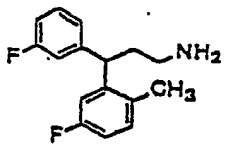
Compound 54



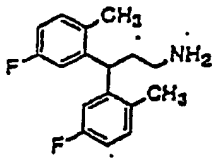
Compound 55



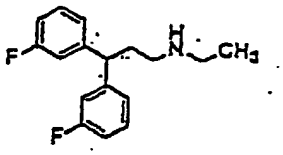
Compound 56



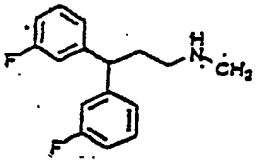
Compound 57



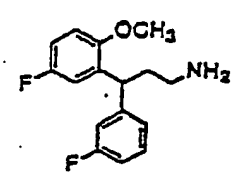
Compound 58



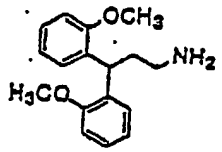
Compound 59



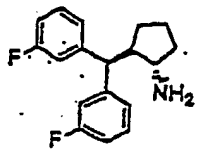
Compound 60



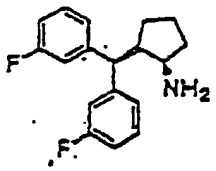
Compound 61



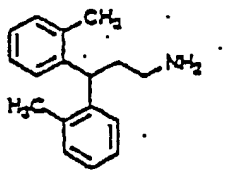
Compound 62



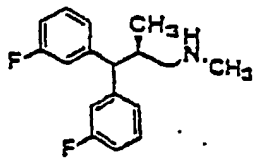
Compound 63



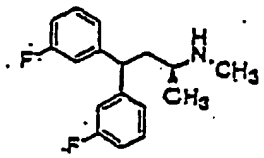
Compound 64



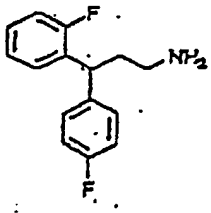
Compound 65



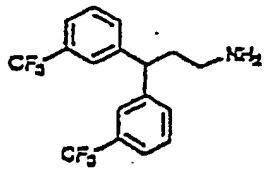
Compound 66



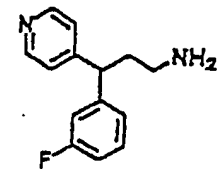
Compound 69



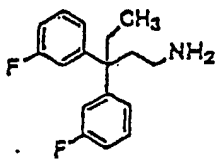
Compound 75



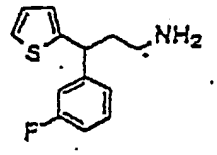
Compound 78



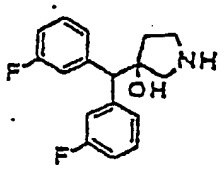
Compound 79



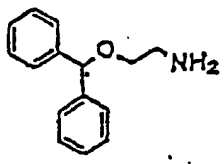
Compound 82



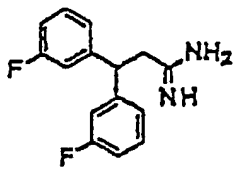
Compound 83



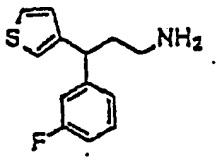
Compound 84



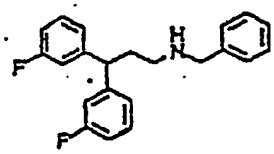
Compound 88



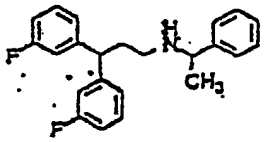
Compound 89



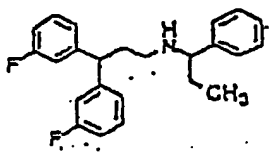
Compound 90



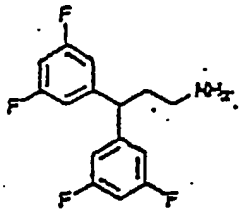
Compound 92



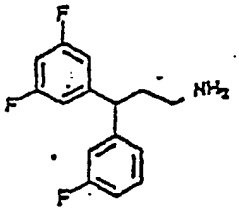
Compound 93



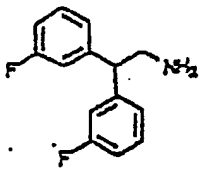
Compound 94



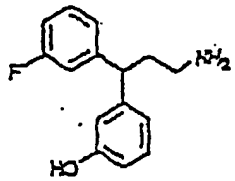
Compound 95



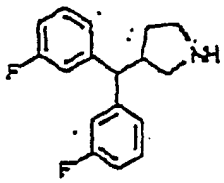
Compound 96



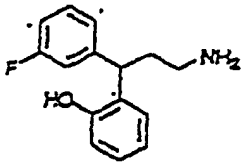
Compound 98



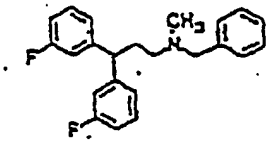
Compound 101



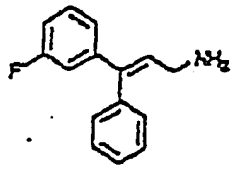
Compound 102

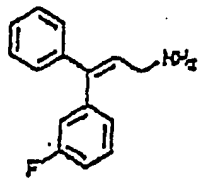


Compound 103

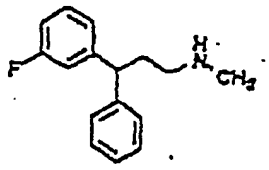


Compound 105

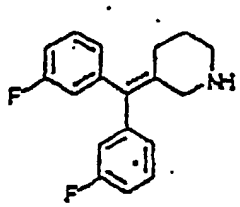




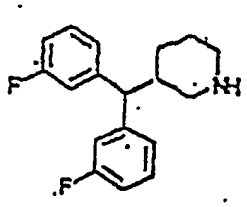
Compound 107
(mixture of 2
compounds)



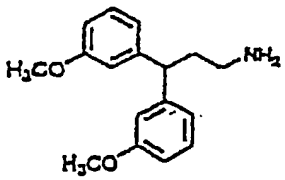
Compound 108



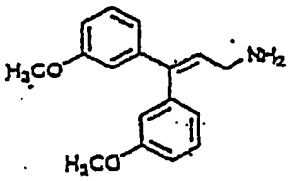
Compound 109



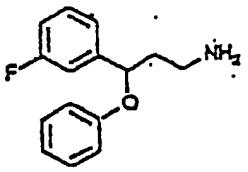
Compound 111



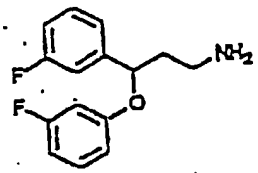
Compound 115



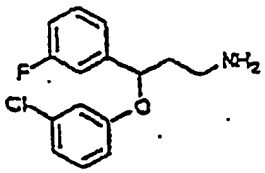
Compound 116



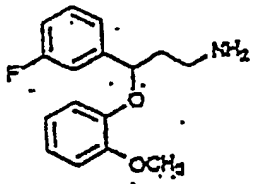
Compound 118



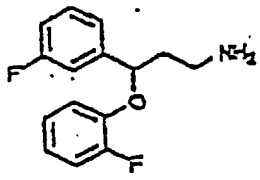
Compound 119



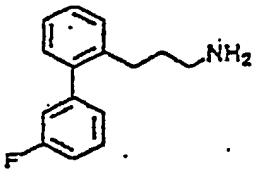
Compound 120



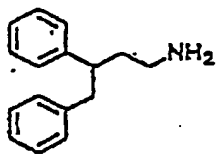
Compound 121



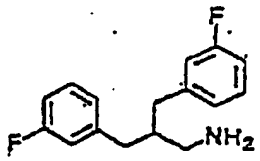
Compound 122



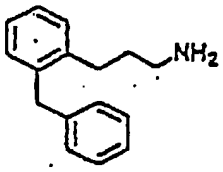
Compound 124



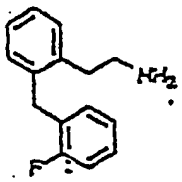
Compound 125



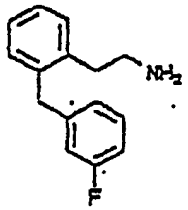
Compound 126



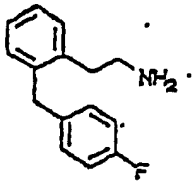
Compound 127



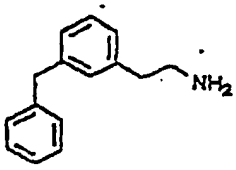
Compound 129



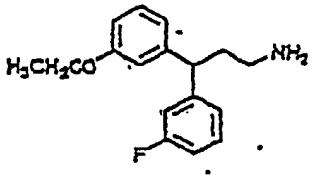
Compound 130



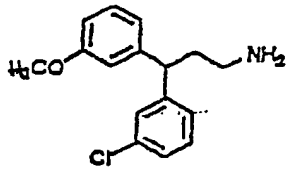
Compound 131



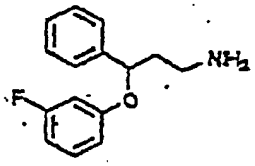
Compound 134



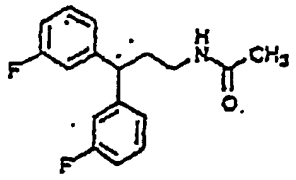
Compound 135



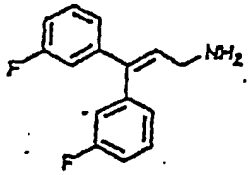
Compound 136



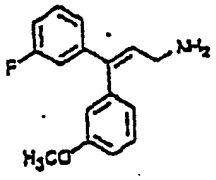
Compound 137



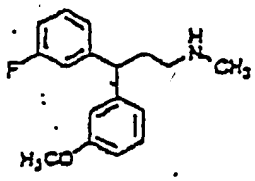
Compound 138



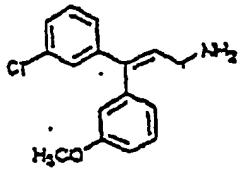
Compound 139



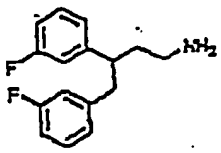
Compound 141



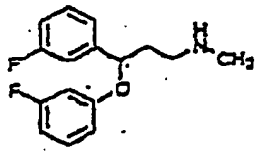
Compound 142



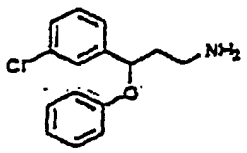
Compound 143



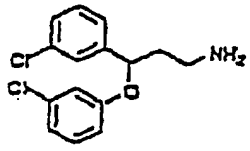
Compound 144



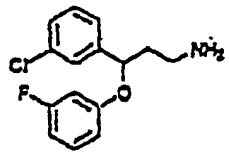
Compound 145



Compound 148



Compound 149



Compound 150

and pharmaceutically acceptable salts thereof.

23. The compound according to claim 22, selected from the group consisting of compounds 54-66, 69, 76, 82, 83,

88-90, 92-96, 101, 102, 103, 105, 108, 109, 111, 115, 118-122, 125-127, 129-131, 135-139, 142, 144, 145, 148-150, or pharmaceutically acceptable salts thereof.

24. The compound according to claim 22, selected from the group consisting of compounds 54-66, 69, 82, 83, 89, 90, 93-96, 103, 111,118-120, 122, 126, 135-138, 142,144,145,148-150, or pharmaceutically acceptable salts thereof.

25. The compound according to claim 22, selected from the group consisting of compounds 60, 66, 69, 103, 111, 118-120, 122, 136-138, 142, 144, 145, 148-150, or pharmaceutically acceptable salts thereof.

26. The compound according to claim 22, selected from the group consisting of compounds 118-122, 137, 145, 148-150, or pharmaceutically acceptable salts thereof.

27. The compound according to claim 22, selected from the group consisting of compounds 118-122,148-150, or pharmaceutically acceptable salts thereof.

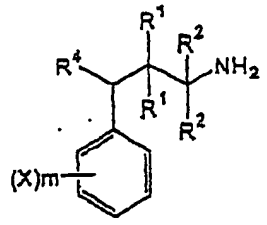
28. The compound according to claim 22, selected from the group consisting of compounds 63 and 64, or pharmaceutically acceptable salts thereof.

29. The compound according to claim 22, which is compound 119, or pharmaceutically acceptable salts thereof.

30. The compound according to claim 22, which is compound 144, or pharmaceutically acceptable salts thereof.

31. Compound 60, or pharmaceutically acceptable salts thereof.

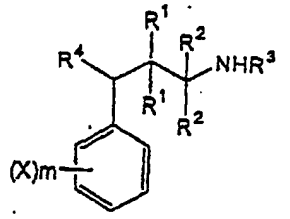
32. A compound of the formula:



wherein:

X is independently selected from the group consisting of -Br, -Cl, -F, -I,-CF_3, alkyl, -OH, -OCF_3, -O-alkyl, and -O-acyl;
R_1 is independently selected from the group consisting of -H, C_1-C_4 alkyl, and -O-acyl;
R_2 is independently selected from the group consisting of -H, alkyl, and hydroxyalkyl, or both R_2s together are imino;
R_4 is phenoxy which is optionally substituted with -F, -Cl, -Br, -I, -CF_3, alkyl, -OH,- OCF_3 -O-alkyl, or -O-acyl; and
m is independently an integer from 1 to 5; and pharmaceutically acceptable salts and complexes thereof:

33. A compound of the formula:

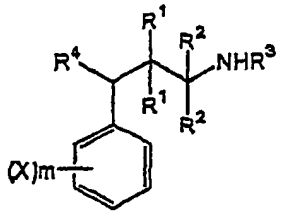


wherein:

X is independently selected from the group consisting of -F, -Cl, -Br, -I, -CF_3 alkyl, -OH, -OCF_3, -O-alkyl, and -O-acyl;
R_1 is independently selected from the group consisting of-H, C_1-C_4 alkyl, and -O-acyl;
R_2 is independently selected from the group consisting of-H, C_1-C_4 alkyl, and hydroxyalkyl, or both R_2s together are imino;
R_3 is selected from the group consisting of methyl and ethyl;
R_4 is phenoxy which is optionally substituted with -F, -Cl, -Br, -I, -CF_3, alkyl, -OH, -OCF_3, -O-alkyl, or -O-acyl;

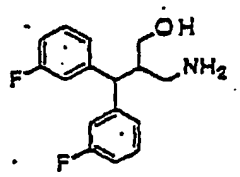
and m is independently an integer from 1 to 5; and pharmaceutically acceptable salts and complexes thereof provided that said compound is not N-methyl 3-(m-trifluoromethylphenoxy)-3-(4-fluorophenyl)propylamine.

34. A compound of the formula:

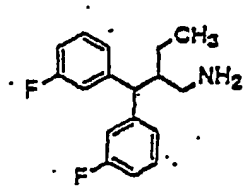


(X)m is selected from the group consisting of meta-fluoro, meta-chloro, ortho-O-C_1-C_4 alkyl, ortho-methyl, ortho-fluoro, ortho-chloro, meta-O- C_1-C_4 alkyl, meta-methyl, ortho-OH, and meta-OH;
R_1 is H;
R_2 is H;
R_3 is selected from the group consisting of methyl and ethyl;
R_4 is phenoxy which is optionally substituted with -F, -Cl, -Br, -I, -CF_3, alkyl, -OH, -OCF_3, -O-alkyl, or -O-acyl;
and pharmaceutically acceptable salts and complexes thereof.

35. A pharmaceutical composition comprising a compound which is selected from the group consisting of



Compound 54



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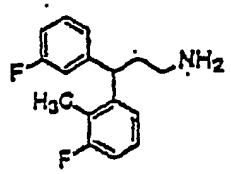
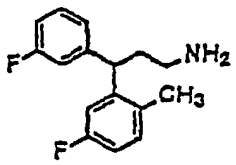


Compound 56



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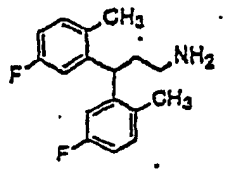

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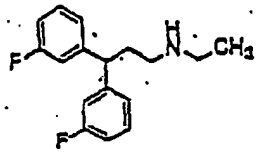

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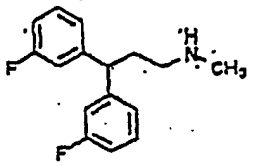

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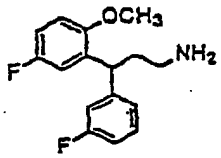
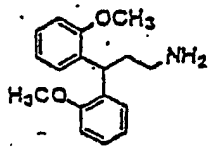


Compound 61



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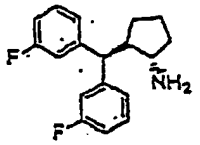
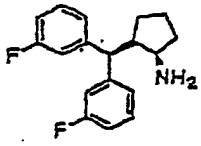


Compound 63



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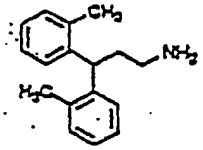

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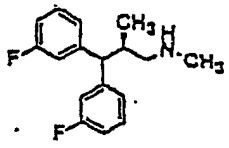
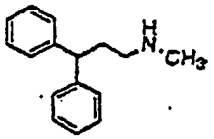


Compound 66



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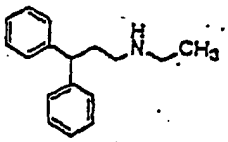

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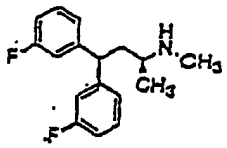

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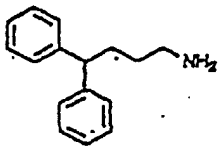
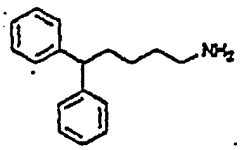


Compound 70



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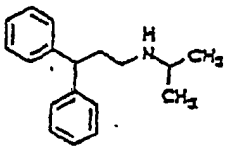

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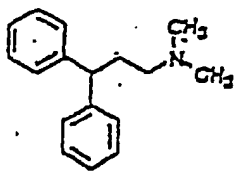

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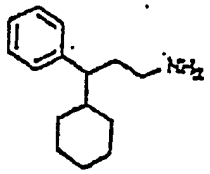

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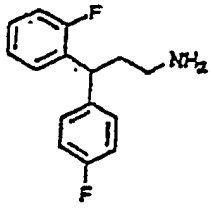

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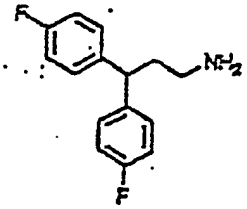

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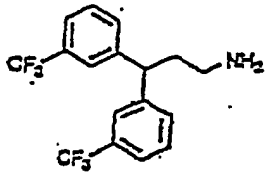

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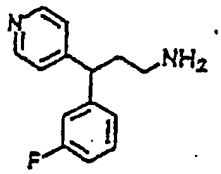

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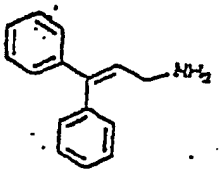
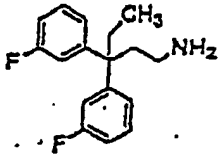
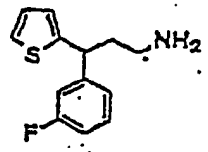


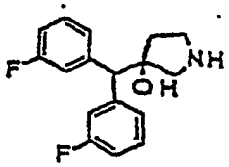
Compound 81



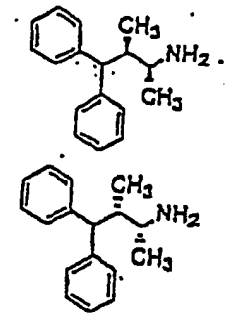
Compound. 82



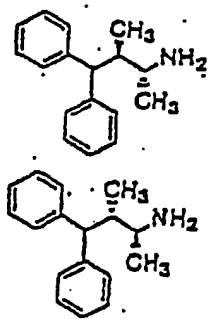
Compound 83



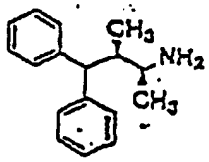
Compound 84



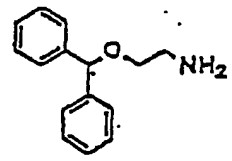
Compound 85
(mixture of 2
compounds)



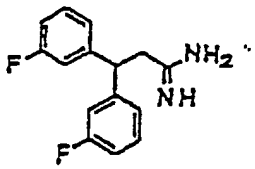
Compound 86
(mixture of 2
compounds)



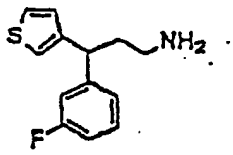
Compound 87



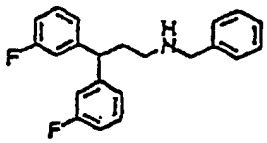
Compound 88



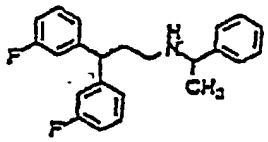
Compound 89



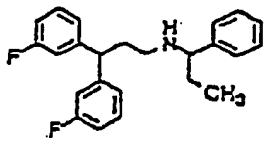
Compound 90



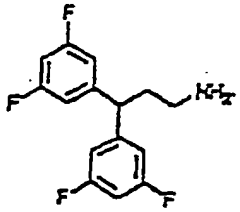
Compound 92



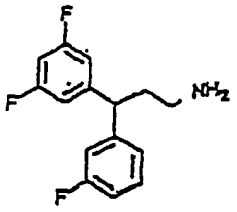
Compound 93



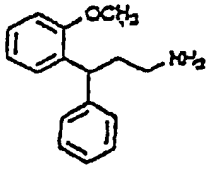
Compound 94



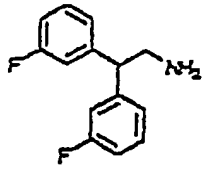
Compound 95



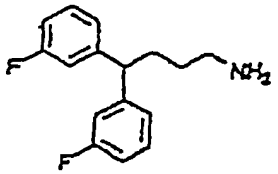
Compound 96



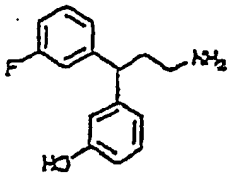
Compound 97



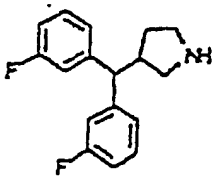
Compound 98



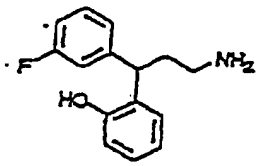
Compound 100



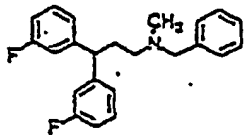
Compound 101



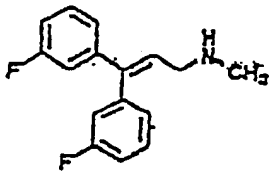
Compound 102



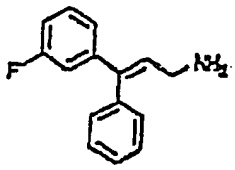
Compound 103

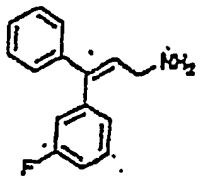


Compound 105

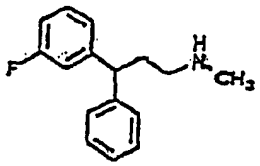


Compound 106

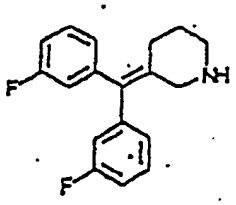




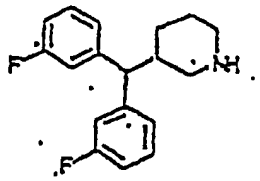
Compound 107
(mixture of 2
compounds)



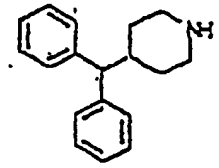
Compound 108



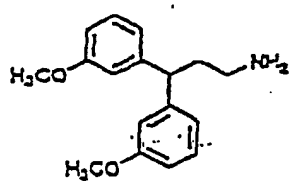
Compound 109



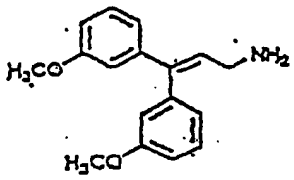
Compound 111



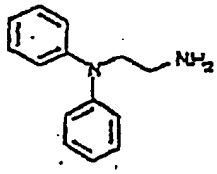
Compound 114



Compound 115



Compound 116



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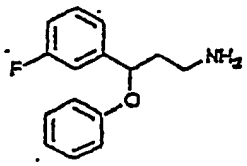
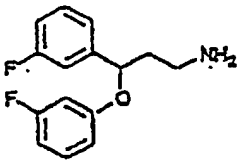
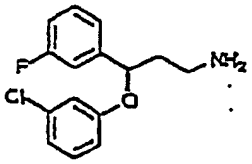


Compound 118



Compound 119



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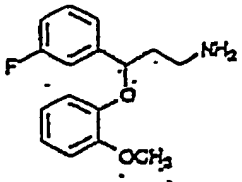

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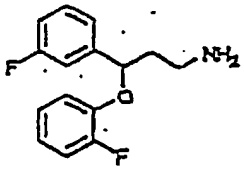

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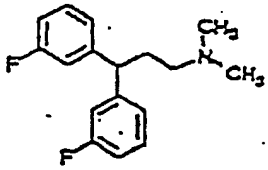

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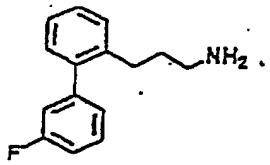

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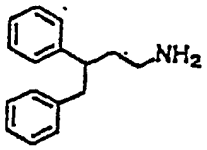

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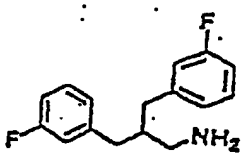

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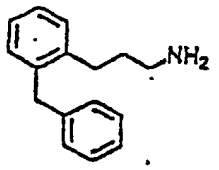

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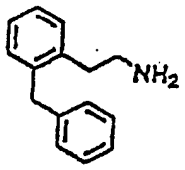

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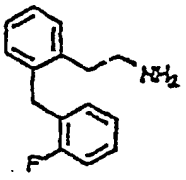

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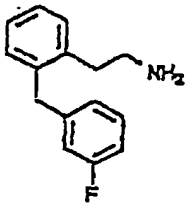

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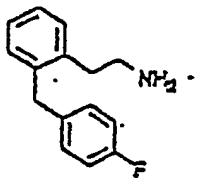

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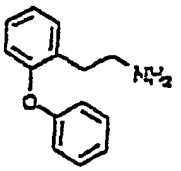

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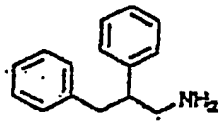

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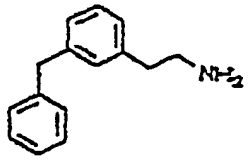

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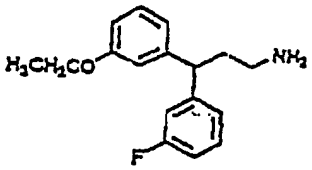

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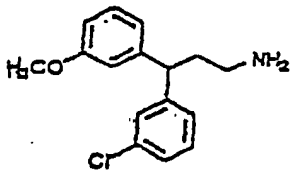

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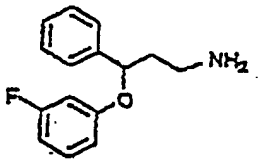

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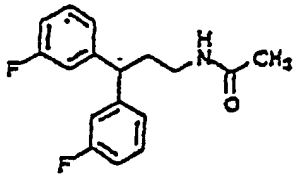

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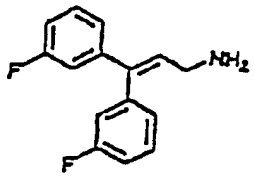

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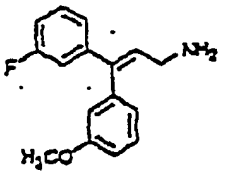

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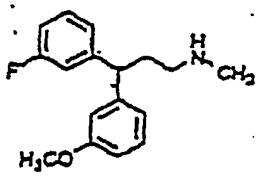

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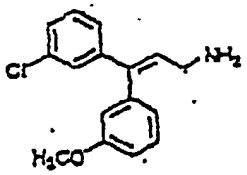

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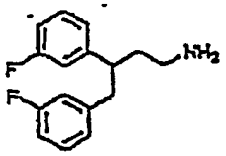

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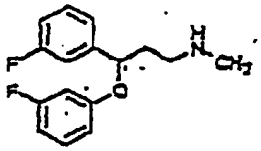

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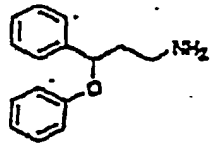

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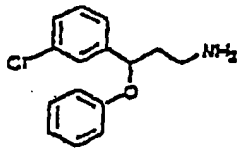
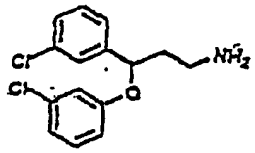
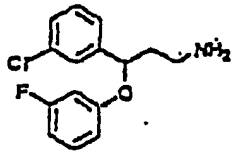


Compound 148



Compound 149



Compound 150

and pharmaceutically acceptable salts thereof in a pharmaceutically acceptable carrier.

36. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 54-71, 73, 76-79, 81-84, 88-90, 92-98, 101-103, 105, 107-109, 111, 115, 117-123, 125-127, 129-136, 138, 139, 142, 144-146, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

37. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 54-66, 69, 70, 75, 76, 81-83, 85-90, 92-97, 100-103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135-139, 142, 144-146, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

38. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 54-66, 69, 70, 76, 81-83, 88-90, 92-97, 101-103, 105, 106, 108, 109, 111, 115, 118-122, 125-127, 129-133, 135, 136, 138, 139, 142, 144-146, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

39. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 54-66, 69, 82, 83, 89, 90, 93-97, 103, 111, 118-120, 122, 126, 135- 138, 142, 144, 145, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

40. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 54-66, 69, 82, 83, 89, 90, 93-97, 103, 111, 118-120, 122, 126, 135, 136, 138, 142, 144, 145, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

41. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 60, 66, 69, 103, 111, 118-120, 122, 136-138, 142, 144, 145, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

42. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 118-122, 137, 145, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

43. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 118-122, 148-150, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

44. The pharmaceutical composition according to claim 35, comprising a compound selected from the group consisting of compounds 63 and 64, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

45. The pharmaceutical composition according to claim 35, comprising a compound selected from compound 119, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

46. The pharmaceutical composition according to claim 35, comprising a compound selected from compound 144, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

47. A pharmaceutical composition comprising a compound selected from compound 60, and pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable carrier.

48. A pharmaceutical composition comprising a compound of claim 32, in a phamiaceutically acceptable carrier.

49. A pharmaceutical composition comprising a compound of claim 33, in a pharmaceutically acceptable carrier.

50. A pharmaceutical composition comprising a compound of claim 34, in a pharmaceutically acceptable carrier.

51. The pharmaceutical composition of any one of claims 35-50 adapted for the treatment of a neurological disease or disorder.

52. The pharmaceutical composition of claim 51, wherein said neurological disease or disorder is selected from the group consisting of stroke, head trauma, spinal cord injury, epilepsy, anxiety, Alzheimer's disease, Huntington's disease, Parkinson's disease, or amyotrophic lateral sclerosis.

53. The pharmaceutical composition of claim 51, wherein said pharmaceutical composition has neuroprotectant activity.

54. The pharmaceutical composition of claim 52, wherein said stroke is global ischemic.

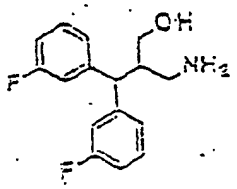
55. The pharmaceutical composition of claim 52, wherein said stroke is focal ischemic.

56. The pharmaceutical composition of claim 52, wherein said stroke is hemorrhagic.

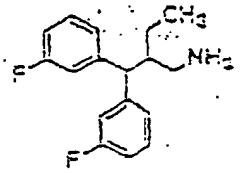
57. The pharmaceutical composition of claim 52, wherein said neurological disease or disorder is Parkinson's disease.

Patentansprüche

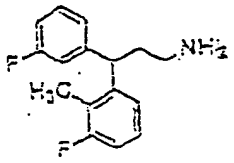
1. Verwendung einer Verbindung, die'aus



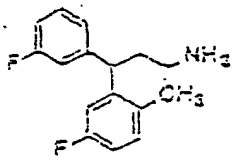
Verbindung 54



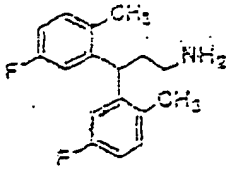
Verbindung 55



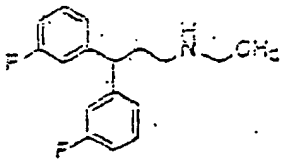
Verbindung 56



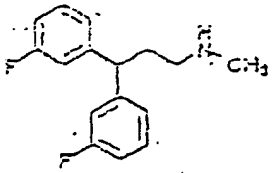
Verbindung 57



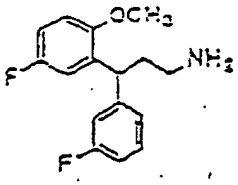
Verbindung 58



Verbindung 59



Verbindung 60



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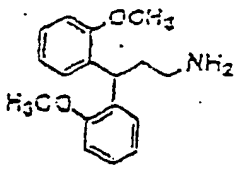

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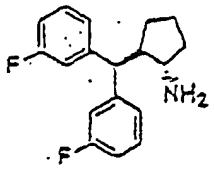

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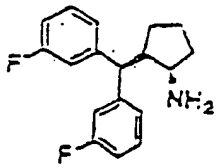

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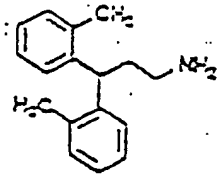

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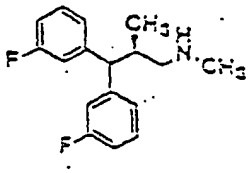
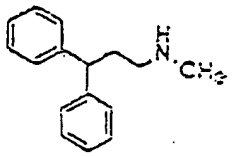
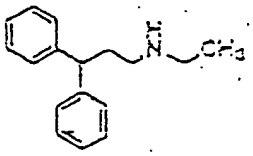


Verbindung 66



Verbindung 67



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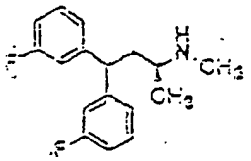
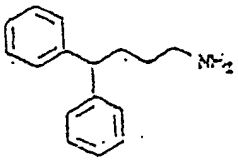
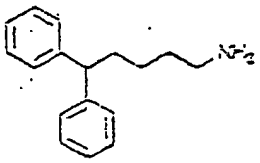


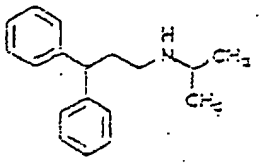
Verbindung 69



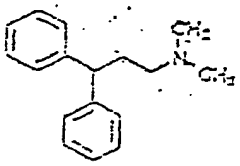
Verbindung 70



Verbindung 71



Verbindung 72



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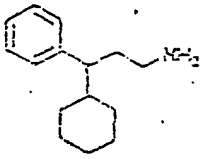

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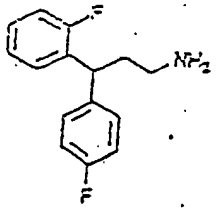
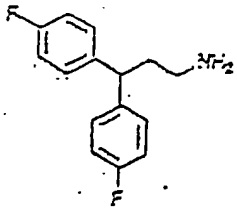


Verbindung 76



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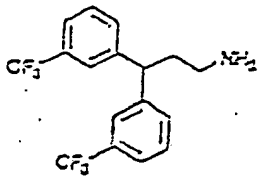

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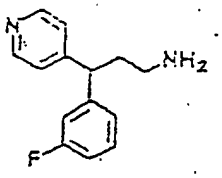

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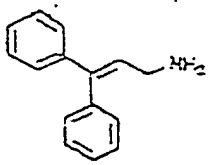
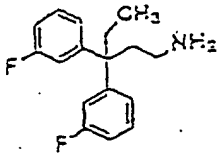
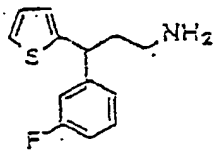


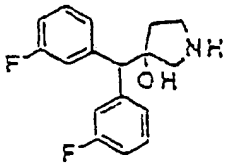
Verbindung 81



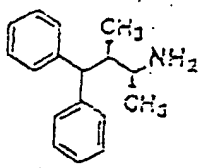
Verbindung 82

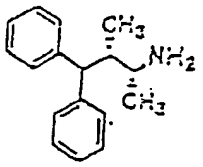


Verbindung 83

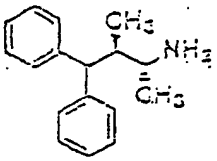


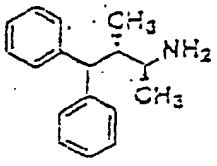
Verbindung 84



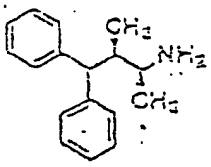


Verbindung 85
(Gemisch aus 2
Verbindungen)

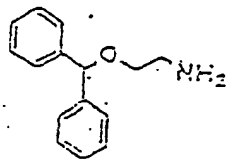




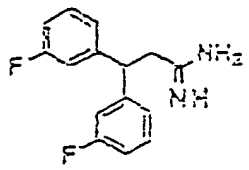
Verbindung 86
(Gemisch aus 2
Verbindungen)



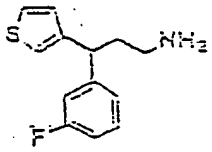
Verbindung 87



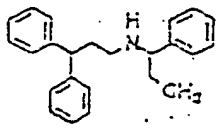
Verbindung 88



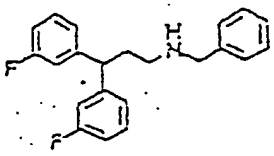
Verbindung 89



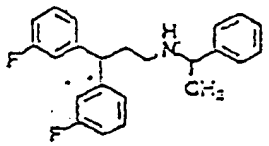
Verbindung 90



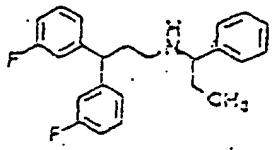
Verbindung 91



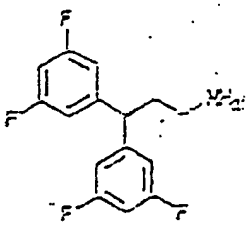
Verbindung 92



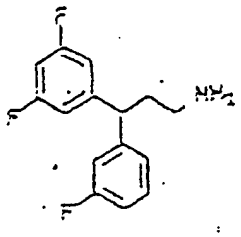
Verbindung 93



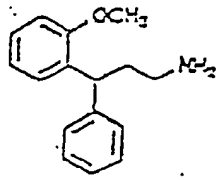
Verbindung 94



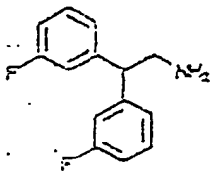
Verbindung 95



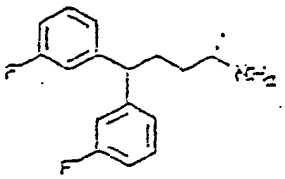
Verbindung 96



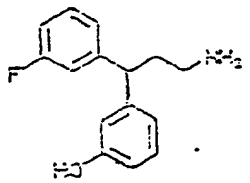
Verbindung 97



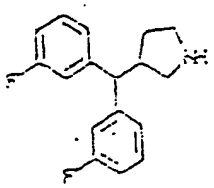
Verbindung 98



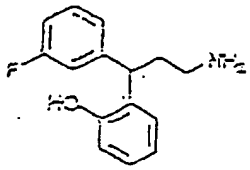
Verbindung 100



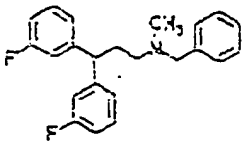
Verbindung 101



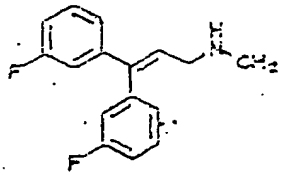
Verbindung 102



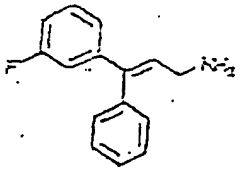
Verbindung 103

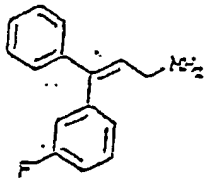


Verbindung 105

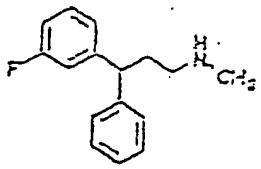


Verbindung 106

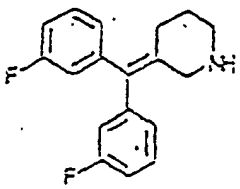




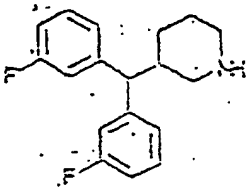
Verbindung 107
(Gemisch aus 2
Verbindungen)



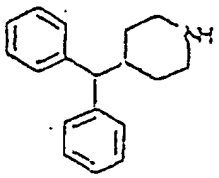
Verbindung 108



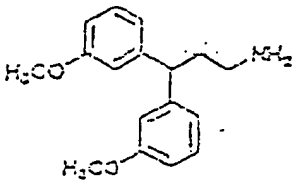
Verbindung 109



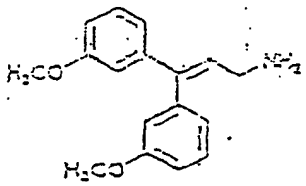
Verbindung 111



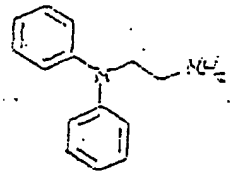
Verbindung 114



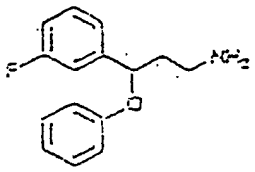
Verbindung 115



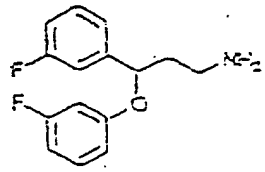
Verbindung 116



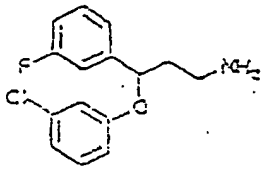
Verbindung 117



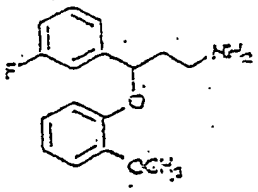
Verbindung 118



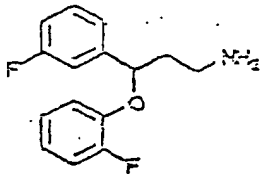
Verbindung 119



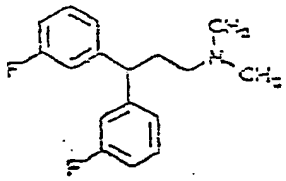
Verbindung 120



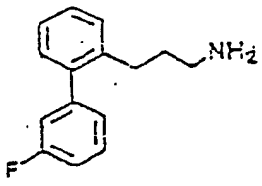
Verbindung 121



Verbindung 122



Verbindung 123



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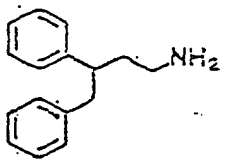
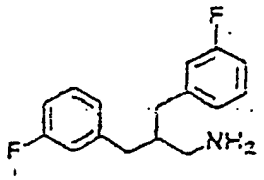
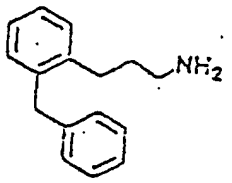


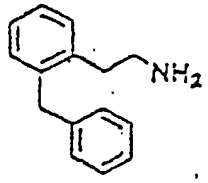
Verbindung 125



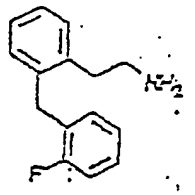
Verbindung 126



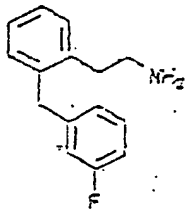
Verbindung 127



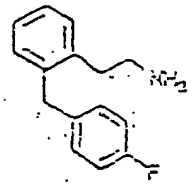
Verbindung 128



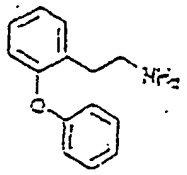
Verbindung 129



Verbindung 130



Verbindung 131



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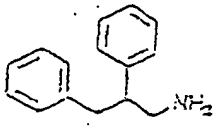

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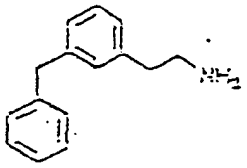
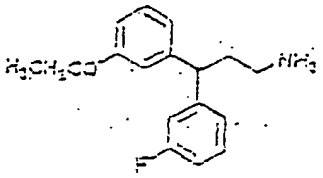


Verbindung 134



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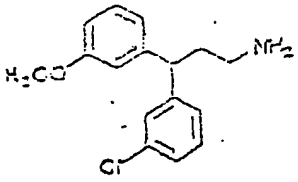
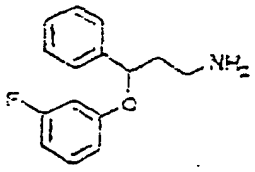
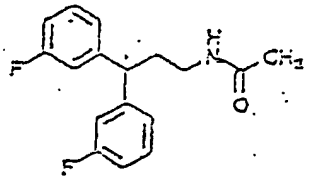


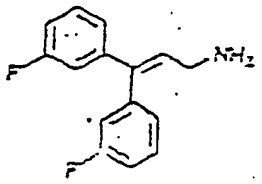
Verbindung 136



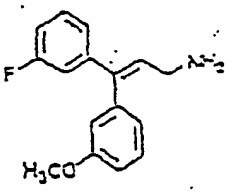
Verbindung 137



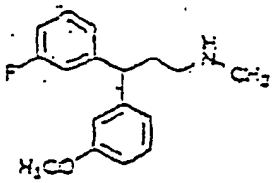
Verbindung 138



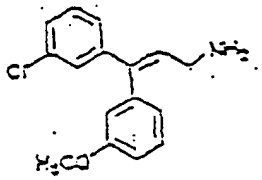
Verbindung 139



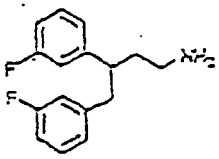
Verbindung 141



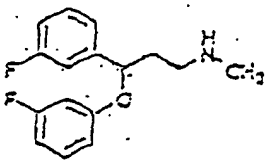
Verbindung 142



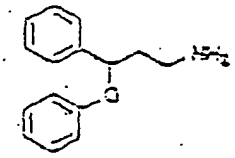
Verbindung 143



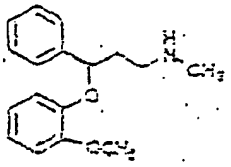
Verbindung 144



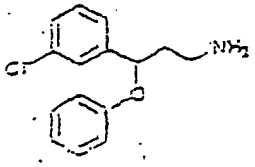
Verbindung 145



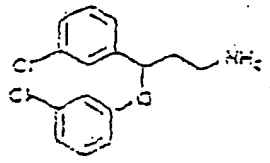
Verbindung 146



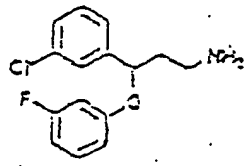
Verbindung 147



Verbindung 148



Verbindung 149



Verbindung 150

und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist, zur Herstellung eines Arzneimittels zur Behandlung von neurologischen Krankheiten oder Störungen.

2. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 54-66, 68-71, 75, 76, 78, 79, 81-90, 92-98, 100, 101, 103, 105, 106, 108, 109, 111, 114-122, 124-136, 138, 139, 141-144, 148-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

3. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 54-66, 69, 70, 75, 76, 81-83, 85-97, 100-103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135-139, 142, 144-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

4. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 54-66, 69, 70, 75, 76, 81-83, 85-90, 92-97, 100, 101, 103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135, 136, 138, 139, 142, 144, 148-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

5. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 54-66, 69, 82, 83, 89-97, 103, 111, 118-120, 122, 126, 135-138, 142, 144, 145, 147-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

6. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 54-66, 69, 82, 83, 89, 90, 92-97, 103, 111, 118-120, 122, 126, 135, 136, 138, 142, 144, 148-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

7. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 60, 66, 69, 103, 111, 118-120, 122, 136, 138, 142, 144, 148-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

8. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 118-122, 137, 145, 148-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

9. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 118-122, 148-150 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

10. Verwendung gemäß Anspruch 1, wobei die Verbindung aus den Verbindungen 63 und 64 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

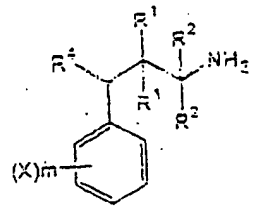
11. Verwendung gemäß Anspruch 1, wobei die Verbindung aus der Verbindung 119 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

12. Verwendung gemäß Anspruch 1, wobei die Verbindung aus der Verbindung 144 und pharmazeutisch verträglichen Salzen und Komplexen davon ausgewählt ist.

13. Verwendung von Verbindung 60 und pharmazeutisch verträglichen Salzen und Komplexen davon zur Herstellung

eines Arzneimittels zur Behandlung von neurologischen Krankheiten oder Störungen.

14. Verwendung einer Verbindung der Formel:



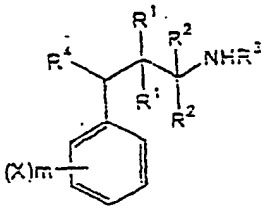
wobei:

X unabhängig aus -Br, -Cl, -F, -I, $-CF_3$, einem Alkylrest, -OH, $-OCF_3$, einem -O-Alkyl- und -O-Acylrest ausgewählt ist;
R_1 unabhängig aus -H, einem C_{1-4}-Alkyl- und -O-Acylrest ausgewählt ist;
R_2 unabhängig aus -H, einem Alkyl- und Hydroxyalkylrest ausgewählt ist oder beide Reste R_2 zusammen eine Iminogruppe sind;
R_4 ein Phenoxyrest ist, der gegebenenfalls mit -F, -Cl, -Br, -I, $-CF_3$, Alkyl,-OH, $-OCF_3$, -O-Alkyl oder -O-Acyl substituiert ist; und
m unabhängig eine ganze Zahl von 0 bis 5 ist; und pharmazeutisch verträglicher Salze und Komplexe davon mit der Maßgabe, dass die Verbindung nicht:

3-(p-Isopropoxyphenoxy)-3-phenylpropylamin
3-(2'-Methyl-4',5'-dichlorphenoxy)-3-phenylpropylamin
3-(p-t-Butylphenoxy)-3-phenylpropylamin
3-(2',4'-Dichlorphenoxy)-3-phenyl-2-methylpropylamin
3-(o-Ethylphenoxy)-3-phenylpropylamin
3-(o-Methoxyphenoxy)-3-phenylpropylamin
3-Phenoxy-3-phenylpropylamin ist,

zur Herstellung eines Arzneimittels zur Behandlung von neurologischen Krankheiten oder Störungen.

15. Verwendung einer Verbindung der Formel:



wobei:

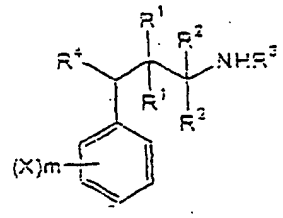
X unabhängig aus -F, -Cl, -Br, -I, $-CF_3$, einem Alkylrest, -OH, $-OCF_3$, einem -O-Alkyl- und -O-Acylrest ausgewählt ist;
R_1 unabhängig aus -H, einem C_{1-4}-Alkyl- und -O-Acylrest ausgewählt ist;
R_2 unabhängig aus -H, einem C_{1-4}-Alkyl- und Hydroxyalkylrest ausgewählt ist oder beide Reste R_2 zusammen eine Iminogruppe sind;
R_3 aus einer Methyl- und Ethylgruppe ausgewählt ist;
R_4 ein Phenoxyrest ist, der gegebenenfalls mit -F, -Cl, -Br, -I, $-CF_3$, Alkyl,-OH, $-OCF_3$, -O-Alkyl oder -O-Acyl

substituiert ist; und
m unabhängig eine ganze Zahl von 0 bis 5 ist; und pharmazeutisch verträglicher Salze und Komplexe davon, mit der Maßgabe, dass die Verbindung nicht:

N-Methyl-3-(o-chlor-p-tolyloxy)-3-phenyl-1-methylpropylamin
N-Methyl-3-(p-tolyloxy)-3-phenylpropylamin
N-Methyl-3-(o-chlor-p-isopropylphenoxy)-3-phenyl-2-methylpropylamin
N-Methyl-3-(p-iodphenoxy)-3-phenylpropylamin
N-Methyl-3-(3-n-propylphenoxy)-3-phenylpropylamin
N-Methyl-3-(p-trifluormethylphenoxy)-3-phenylpropylamin
N-Methyl-3-(m-chlorphenoxy)-3-phenylpropylamin
N-Methyl-3-(p-fluorphenoxy)-3-phenylpropylamin
N-Methyl-3-(p-methoxyphenoxy)-3-phenylpropylamin
N-Methyl-3-(o-methoxyphenoxy)-3-phenylpropylamin
N-Methyl-3-(o-fluorphenoxy)-3-phenylpropylamin
N-Methyl-3-(o-tolyloxy)-3-phenylpropylamin
N-Methyl-3-(p-chlorphenoxy)-3-phenylpropylamin
N-Methyl-3-(m-fluorphenoxy)-3-phenylpropylamin
N-Methyl-3-phenoxy-3-phenyl-2-methylpropylamin
N-Methyl-3-phenoxy-3-phenyl-1-methylpropylamin
N-Methyl-3-phenoxy-3-phenylpropylamin
N-Methyl-3-(o-trifluormethylphenoxy)-3-phenylpropylamin
N-Methyl-3-(m-methoxyphenoxy)-3-phenylpropylamin
N-Methyl-3-(o,p-difluorphenoxy)-3-phenylpropylamin
N-Ethyl-3-(o-iodphenoxy)-3-phenylpropylamin
N-Methyl-3-(o-chlorphenoxy)-3-phenylpropylamin
N-Methyl-3-(o-bromphenoxy)-3-phenylpropylamin ist,

zur Herstellung eines Arzneimittels zur Behandlung von neurologischen Krankheiten oder Störungen.

16. Verwendung einer Verbindung der Formel:



wobei:

(X)m aus einem meta-Fluor-, meta-Chloratom, ortho-O-C_{1-4}-Alkylrest, einer ortho-Methylgruppe, einem ortho-Fluor-, ortho-Chloratom, meta-O-C_{1-4}Alkylrest, einer meta-Methylgruppe, ortho-OH und meta-OH ausgewählt ist;
R_1 H ist;
R_2 H ist;
R_3 aus einer Methyl- und Ethylgruppe ausgewählt ist;
R_4 ein Phenoxyrest ist, der gegebenenfalls mit -F, -Cl, -Br, -I, -CF_3, Alkyl,-OH, -OCF_3, -O-Alkyl oder -O-Acyl substituiert ist; und
pharmazeutisch verträglicher Salze und Komplexe davon zur Herstellung eines Arzneimittels zur Behandlung von neurologischen Krankheiten oder Störungen.

17. Verwendung gemäß einem der Ansprüche 1 bis 16, wobei die neurologische Krankheit oder Störung Schlaganfall, Schädeltrauma, Rückenmarksverletzung, Rückenmarksischämie, eine durch Ischämie oder Hypoxie bedingte Schädigung von Nervenzellen, Epilepsie, Schmerz, Ängstlichkeit, von Ischämie oder Hypoxie ausgelöste neuro-

psychiatrische oder kognitive Defizite, wie diejenigen, die häufig als eine Konsequenz einer Herzchirurgie mit einem kardiopulmonalen Bypass auftreten, Alzheimer-Krankheit, Chorea Huntington, Parkinson-Krankheit oder amyotrophische Lateralsklerose umfasst.

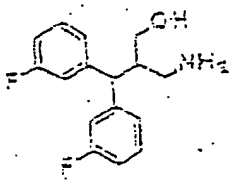
18. Verwendung gemäß Anspruch 17, wobei der Schlaganfall totalischämisch auftritt.

19. Verwendung gemäß Anspruch 17, wobei der Schlaganfall als fokale Ischämie auftritt.

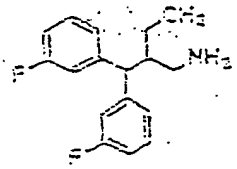
20. Verwendung gemäß Anspruch 17, wobei der Schlaganfall in hemorrhagischer Form auftritt.

21. Verwendung gemäß Anspruch 17, wobei die neurologische Krankheit oder Störung Parkinson-Krankheit umfasst.

22. Verbindung, ausgewählt aus



Verbindung 54



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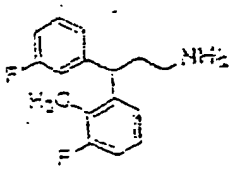
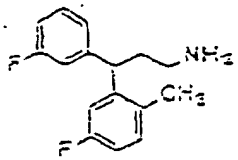
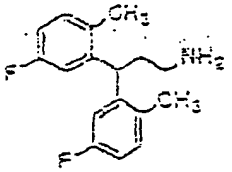


Verbindung 56



Verbindung 57



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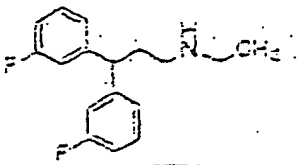

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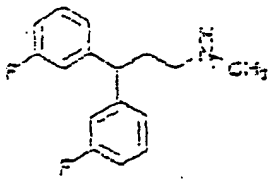

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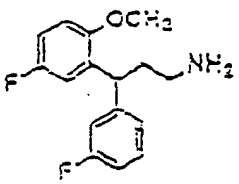

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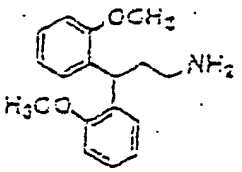
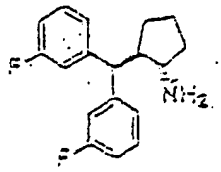


Verbindung 62



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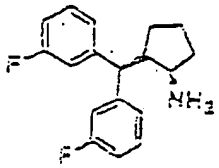

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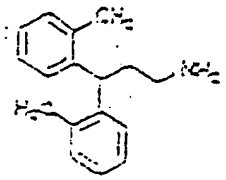

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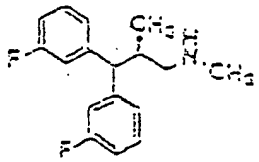

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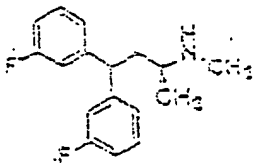

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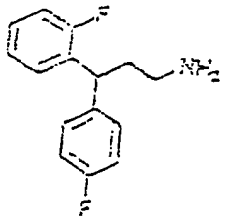

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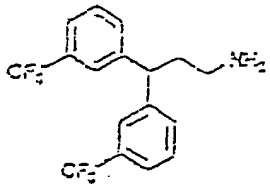

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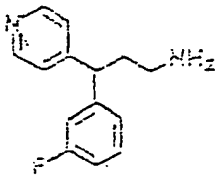

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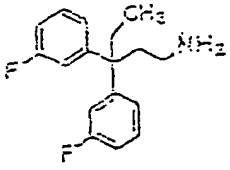

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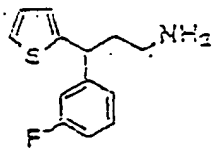

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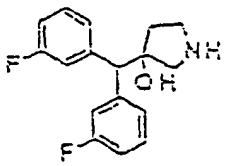

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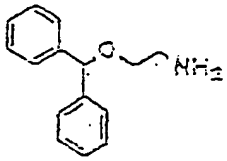

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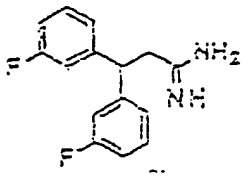

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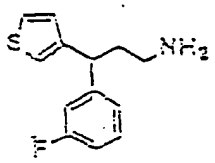

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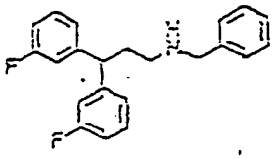

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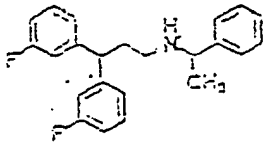

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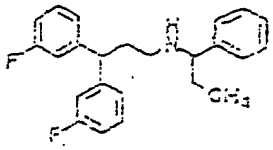

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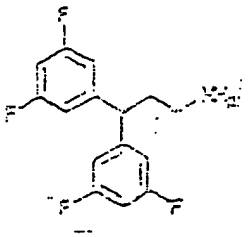
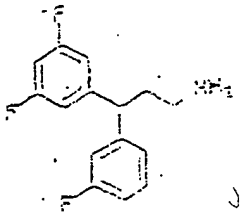


Verbindung 95



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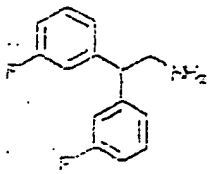

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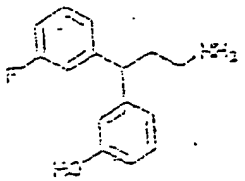

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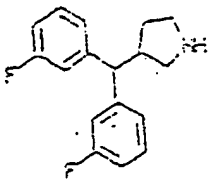

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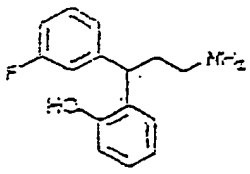
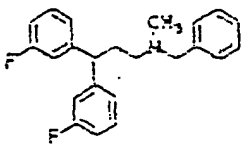


Verbindung 103



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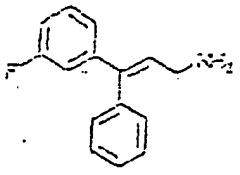
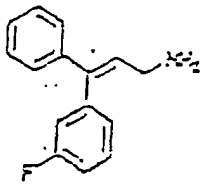
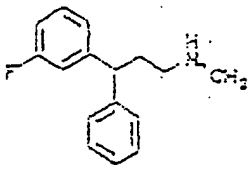
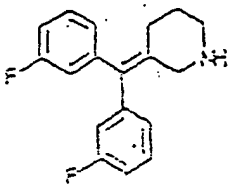




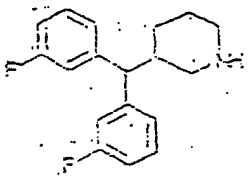
Verbindung 107
(Gemisch aus 2
Verbindungen)



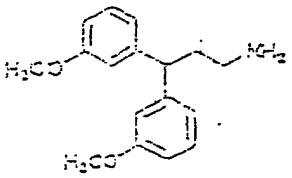
Verbindung 108



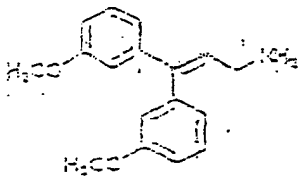
Verbindung 109



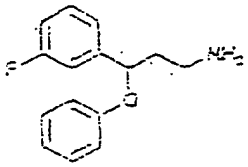
Verbindung 111



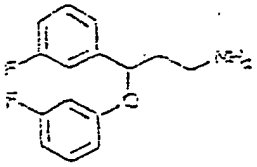
Verbindung 115



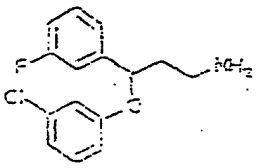
Verbindung 116



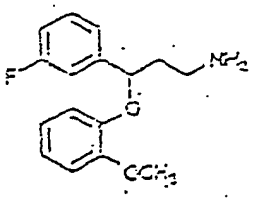
Verbindung 118



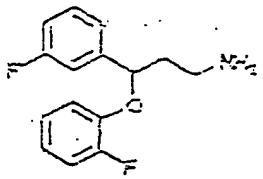
Verbindung 119



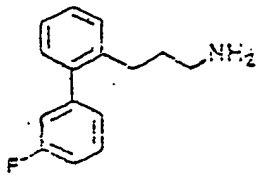
Verbindung 120



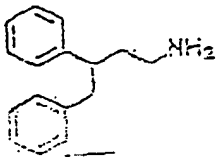
Verbindung 121



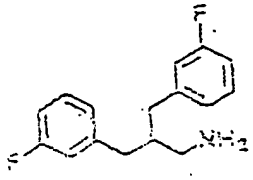
Verbindung 122



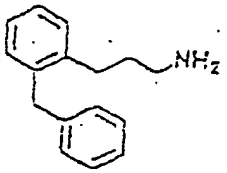
Verbindung 124



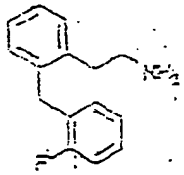
Verbindung 125



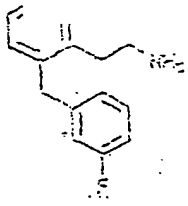
Verbindung 126



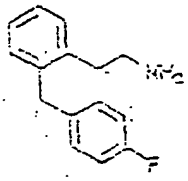
Verbindung 127



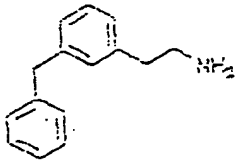
Verbindung 129



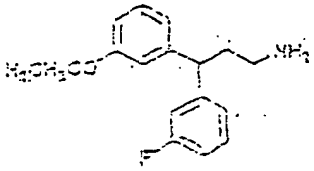
Verbindung 130



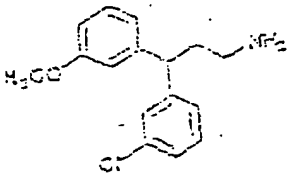
Verbindung 131



Verbindung 134



Verbindung 135



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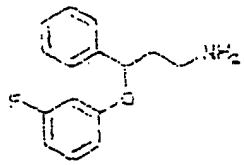
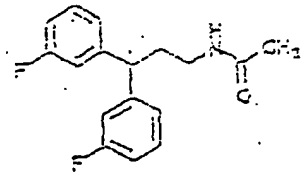
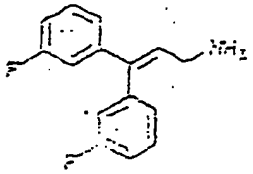


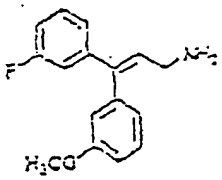
Verbindung 137



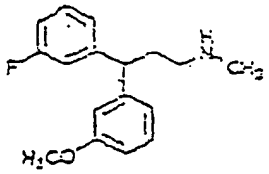
Verbindung 138



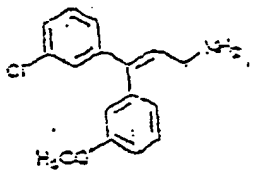
Verbindung 139



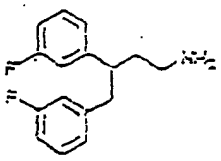
Verbindung 141



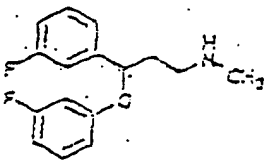
Verbindung 142



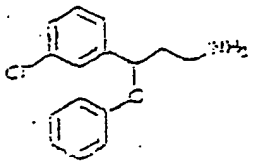
Verbindung 143



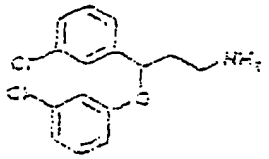
Verbindung 144



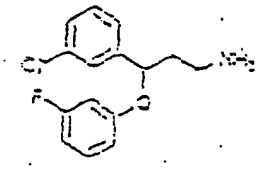
Verbindung 145



Verbindung 148



Verbindung 149



Verbindung 150

und pharmazeutisch verträglichen Salzen davon.

23. Verbindung gemäß Anspruch 22, die aus den Verbindungen 54-66, 69, 76, 82, 83, 88-90, 92-96, 101, 102, 103, 105, 108, 109, 111, 115, 118-122, 125-127, 129-131,135-139, 142, 144, 145, 148-150 oder pharmazeutisch verträglichen Salzen davon ausgewählt ist.

24. Verbindung gemäß Anspruch 22, die aus den Verbindungen 54-66, 69, 82, 83, 89, 90, 93-96, 103, 111, 118-120, 122, 126, 135-138, 142, 144, 145, 148-150 oder. pharmazeutisch verträglichen Salzen davon ausgewählt ist.

25. Verbindung gemäß Anspruch 22, die aus den Verbindungen 60, 66, 69, 103, 111, 118-120, 122, 136-138, 142, 144, 145, 148-150 oder pharmazeutisch verträglichen Salzen davon ausgewählt ist.

26. Verbindung gemäß Anspruch 22, die aus den Verbindungen 118-122, 137, 145, 148-150 oder pharmazeutisch verträglichen Salzen davon ausgewählt ist.

27. Verbindung gemäß Anspruch 22, die aus den Verbindungen 118-122, 148-150 oder pharmazeutisch verträglichen Salzen davon ausgewählt ist.

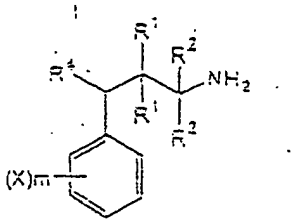
28. Verbindung gemäß Anspruch 22, die aus den Verbindungen 63 und 64 oder pharmazeutisch verträglichen Salzen davon ausgewählt ist.

29. Verbindung gemäß Anspruch 22, die aus der Verbindung 119 oder pharmazeutisch verträglichen Salzen davon ausgewählt ist.

30. Verbindung gemäß Anspruch 22, die aus der Verbindung 144 oder pharmazeutisch verträglichen Salzen davon ausgewählt ist.

31. Verbindung 60 oder pharmazeutisch verträgliche Salze davon.

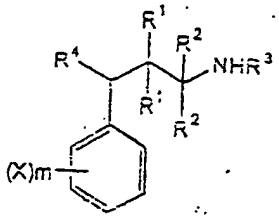
32. Verbindung der Formel:



wobei:

X unabhängig aus -Br, -Cl, -F, -I, $-CF_3$, einem Alkylrest, -OH, $-OCF_3$, einem -O-Alkyl- und -O-Acylrest ausgewählt ist;
R_1 unabhängig aus -H, einem C_{1-4}-Alkyl- und -O-Acylrest ausgewählt ist;
R_2 unabhängig aus -H, einem Alkyl- und Hydroxyalkylrest ausgewählt ist oder beide Reste R_2 zusammen eine Iminogruppe sind;
R_4 ein Phenoxyrest ist, der gegebenenfalls mit -F,-Cl, -Br, -I, $-CF_3$, Alkyl,-OH, $-OCF_3$, -O-Alkyl oder -O-Acyl substituiert ist; und
m unabhängig eine ganze Zahl von 1 bis 5 ist; und pharmazeutisch verträgliche Salze und Komplexe davon.

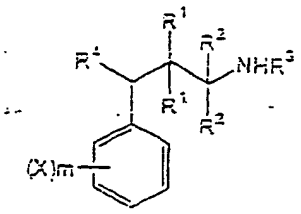
33. Verbindung der Formel:



wobei:

X unabhängig aus -F, -Cl, -Br, -I, $-CF_3$, einem Alkylrest, -OH, $-OCF_3$, einem-O-Alkyl- und -O-Acylrest ausgewählt ist;
R_1 unabhängig aus -H, einem C_{1-4}-Alkyl- und -O-Acylrest ausgewählt ist;
R_2 unabhängig aus -H, einem C_{1-4}-Alkyl- und Hydroxyalkylrest ausgewählt ist oder beide Reste R_2 zusammen eine Iminogruppe sind;
R_3 aus einer Methyl- und Ethylgruppe ausgewählt ist;
R_4 ein Phenoxyrest ist, der gegebenenfalls mit -F, -Cl, -Br, -I, $-CF_3$, Alkyl,-OH, $-OCF_3$, -O-Alkyl oder -O-Acyl substituiert ist; und
m unabhängig eine ganze Zahl von 1 bis 5 ist; und pharmazeutisch verträgliche Salze und Komplexe davon mit der Maßgabe, dass die Verbindung nicht N-Methyl-3-(m-trifluormethylphenoxy)-3-(4-fluorphenyl)propylamin ist.

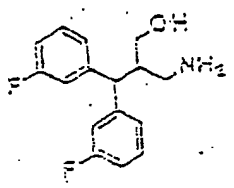
34. Verbindung der Formel:



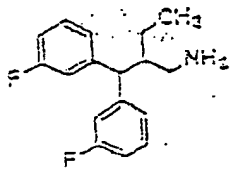
wobei:

(X)m aus einem meta-Fluor-, meta-Chloratom, ortho-O-C_{1-4}-Alkylrest, einer ortho-Methylgruppe, einem ortho-Fluor-, ortho-Chloratom, meta-O-C_{1-4}-Alkylrest, einer meta-Methylgruppe, ortho-OH und meta-OH ausgewählt ist;
R_1 H ist;
R_2 H ist;
R_3 aus einer Methyl- und Ethylgruppe ausgewählt ist;
R_4 ein Phenoxyrest ist, der gegebenenfalls mit -F, -Cl, -Br, -I, $-CF_3$, einem Alkyl, -OH. $-OCF_3$, -O-Alkyl oder -O-Acyl substituiert ist; und
pharmazeutisch verträgliche Salze und Komplexe davon.

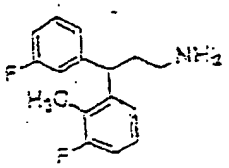
35. Arzneimittel, umfassend eine Verbindung, welche aus



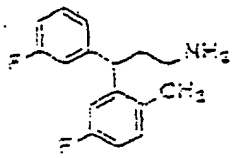
Verbindung 54



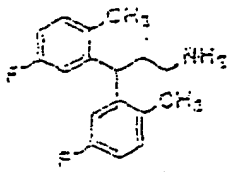
Verbindung 55



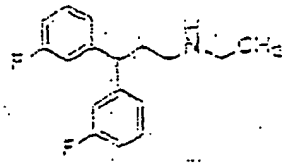
Verbindung 56



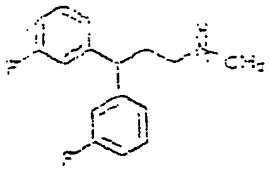
Verbindung 57



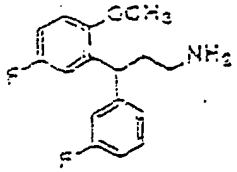
Verbindung 58



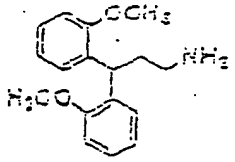
Verbindung 59



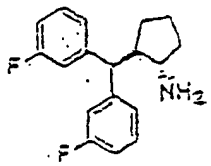
Verbindung 60



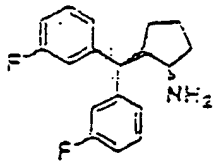
Verbindung 61



Verbindung 62



Verbindung 63



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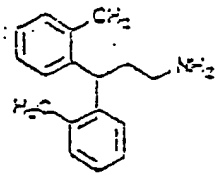

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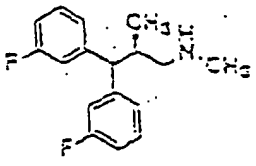

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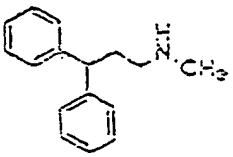
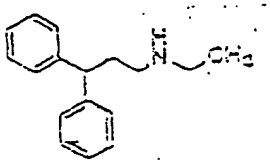


Verbindung 67



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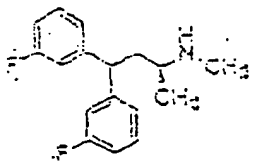

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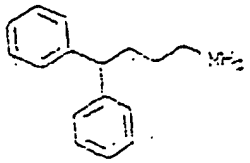

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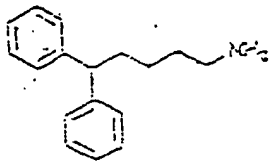

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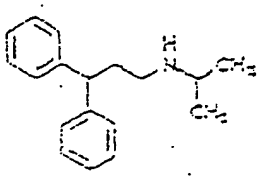

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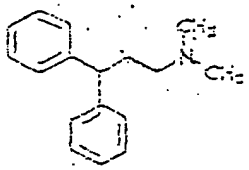

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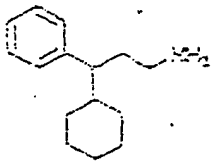

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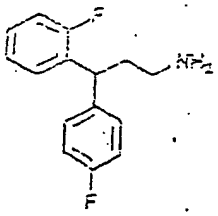

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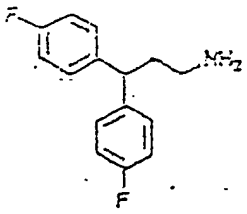

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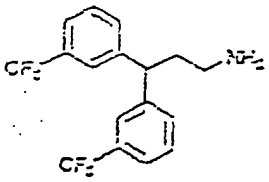

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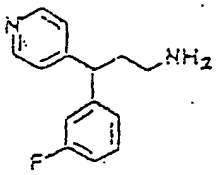

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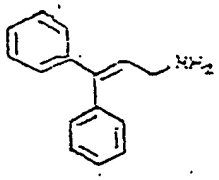

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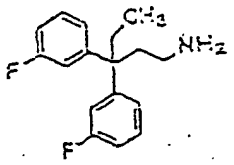
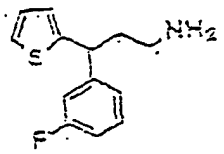
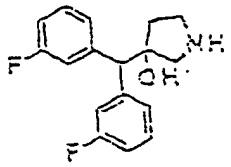


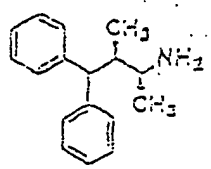
Verbindung 82

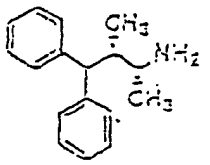


Verbindung 83

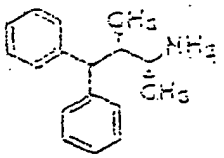


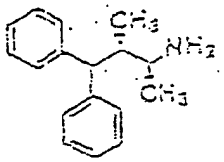
Verbindung 84



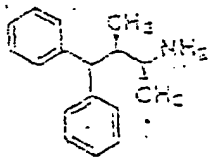


Verbindung 85
(Gemisch aus 2
Verbindungen)

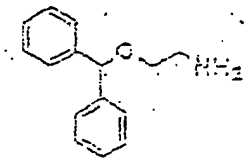




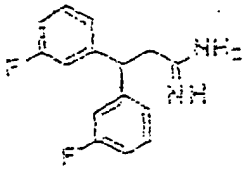
Verbindung 86
(Gemisch aus 2
Verbindungen)



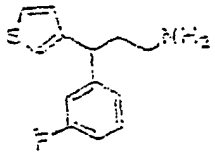
Verbindung 87



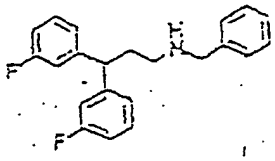
Verbindung 88



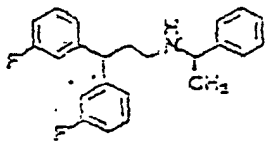
Verbindung 89



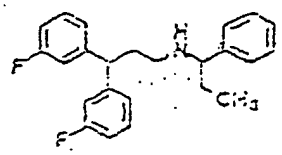
Verbindung 90



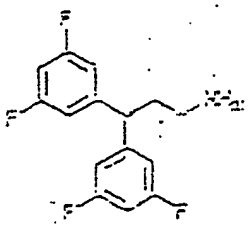
Verbindung 92



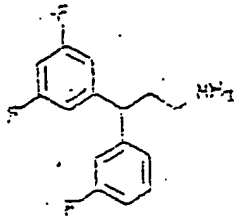
Verbindung 93



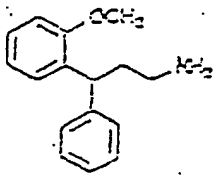
Verbindung 94



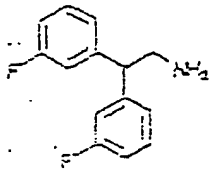
Verbindung 95



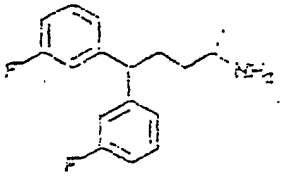
Verbindung 96



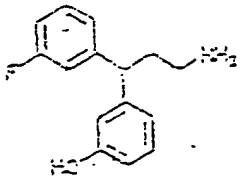
Verbindung 97



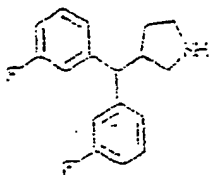
Verbindung 98



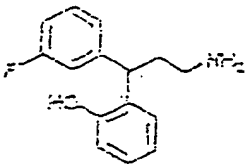
Verbindung 100



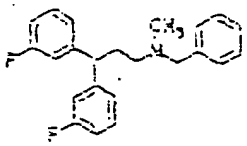
Verbindung 101



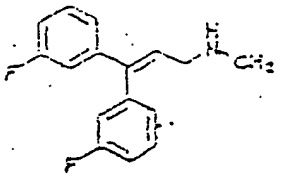
Verbindung 102



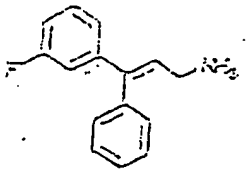
Verbindung 103

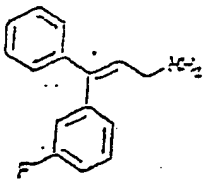


Verbindung 105

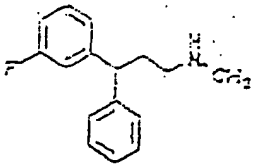


Verbindung 106

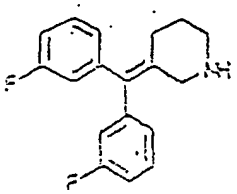




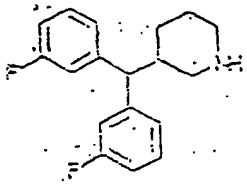
Verbindung 107
(Gemisch aus 2
Verbindungen)



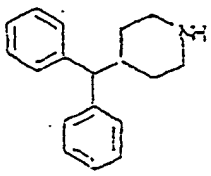
Verbindung 108



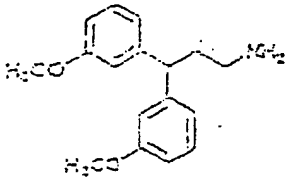
Verbindung 109



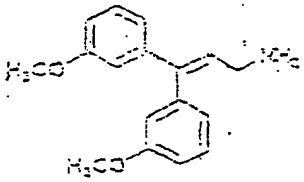
Verbindung 111



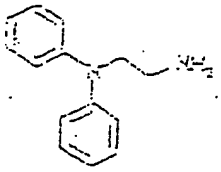
Verbindung 114



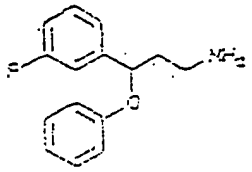
Verbindung 115



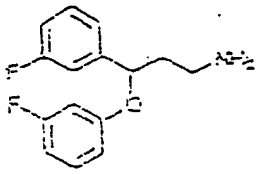
Verbindung 116



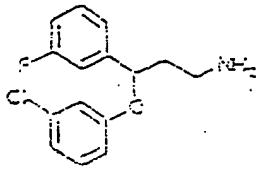
Verbindung 117



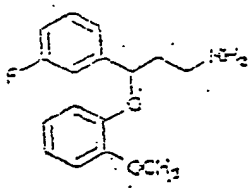
Verbindung 118



Verbindung 119



Verbindung 120



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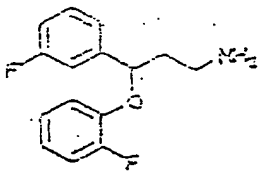

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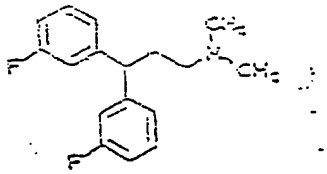

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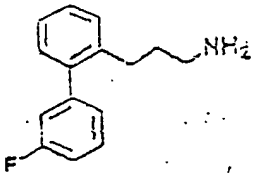
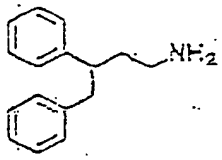


Verbindung 124



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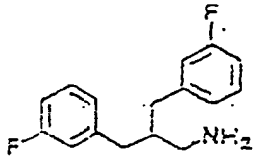

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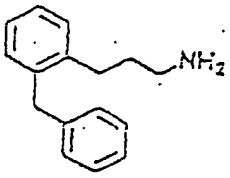

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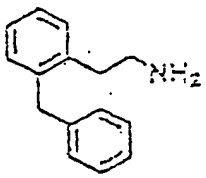
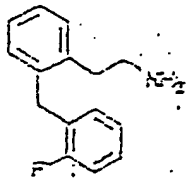
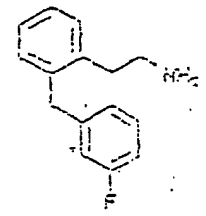


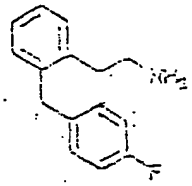
Verbindung 128



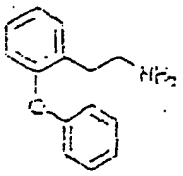
Verbindung 129



Verbindung 130



Verbindung 131



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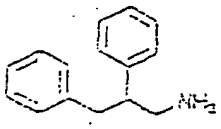

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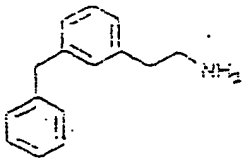

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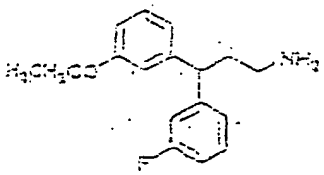

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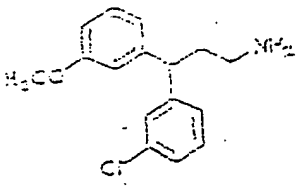

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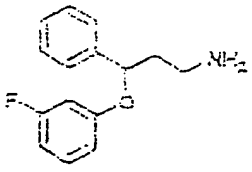
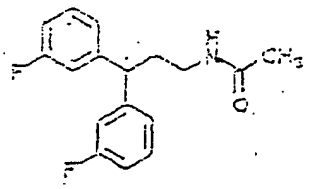
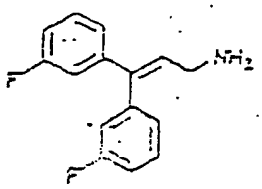


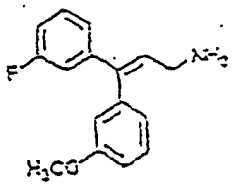
Verbindung 137



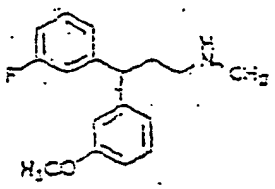
Verbindung 138



Verbindung 139



Verbindung 141



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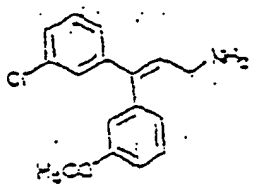

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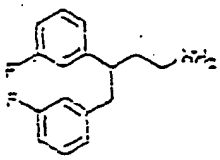

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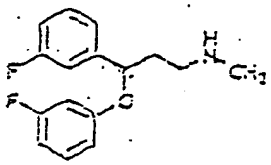

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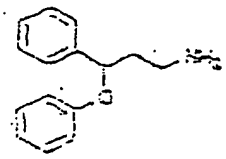
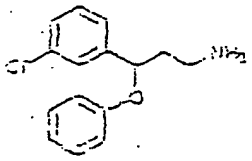
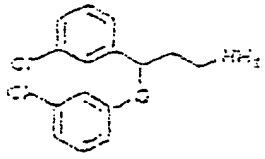


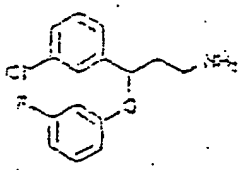
Verbindung 146



Verbindung 148



Verbindung 149



Verbindung 150

und pharmazeutisch verträglichen Salzen davon ausgewählt ist in einem pharmazeutisch verträglichen Träger.

36. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 54-71, 73, 76-79, 81-84, 88-90, 92-98, 101-103, 105, 107-109, 111, 115, 117-123, 125-127, 129-136, 138, 139, 142, 144-146, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

37. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 54-66, 69, 70, 75, 76, 81-83, 85-90, 92-97, 100-103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135-139, 142, 144-146, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

38. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 54-66, 69, 70, 76, 81-83, 88-90, 92-97, 101-103, 105, 106, 108, 109, 111, 115, 118-122, 125-127, 129-133, 135, 136, 138, 139, 142, 144-146, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

39. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 54-66, 69, 82, 83, 89, 90, 93-97, 103, 111, 118-120, 122, 126, 135-138, 142, 144, 145, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

40. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 54-66, 69, 82, 83, 89, 90, 93-97, 103, 111, 118-120, 122, 126, 135, 136, 138, 142, 144, 145, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

41. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 60, 66, 69, 103, 111, 118-120, 122, 136-138, 142, 144, 145, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

42. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 118-122, 137, 145, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

43. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 118-122, 148-150 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

44. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus den Verbindungen 63 und 64 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

45. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus der Verbindung 119 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

46. Arzneimittel gemäß Anspruch 35, umfassend eine Verbindung, die aus der Verbindung 144 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

47. Arzneimittel umfassend eine Verbindung, die aus der Verbindung 60 und pharmazeutisch verträglichen Salzen davon ausgewählt ist, in einem pharmazeutisch verträglichen Träger.

48. Arzneimittel umfassend eine Verbindung gemäß Anspruch 32 in einem pharmazeutisch verträglichen Träger.

49. Arzneimittel umfassend eine Verbindung gemäß Anspruch 33 in einem pharmazeutisch verträglichen Träger.

50. Arzneimittel umfassend eine Verbindung gemäß Anspruch 34 in einem pharmazeutisch verträglichen Träger.

51. Arzneimittel gemäß einem der Ansprüche 35-50, das an die Behandlung von neurologischen Krankheiten und Störungen angepasst ist.

52. Arzneimittel gemäß Anspruch 51, wobei die neurologische Krankheit oder Störung aus Schlaganfall, Schädeltrauma, Rückenmarksverletzung, Epilepsie, Ängstlichkeit, Alzheimer-Krankheit, Chorea Huntington, Parkinson-Krankheit oder amyotrophische Lateralsklerose ausgewählt ist.

53. Arzneimittel gemäß Anspruch 51, wobei das Arzneimittel neuroprotektive Wirkung aufweist.

54. Arzneimittel gemäß Anspruch 52, wobei der Schlaganfall als Totalischämie auftritt.

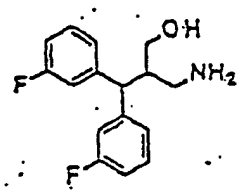
55. Arzneimittel gemäß Anspruch 52, wobei der Schlaganfall als fokale Ischämie auftritt.

56. Arzneimittel gemäß Anspruch 52, wobei der Schlaganfall in hemorrhagischer Form auftritt.

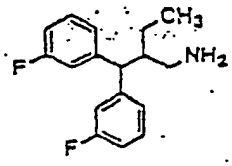
57. Arzneimittel gemäß Anspruch 52, wobei die neurologische Krankheit oder Störung Parkinson-Krankheit ist.

Revendications

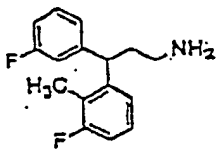
1. Utilisation d'un composé qui est choisi dans le groupe consistant en :



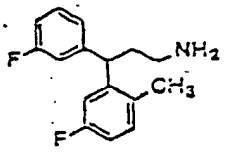
Composé 54



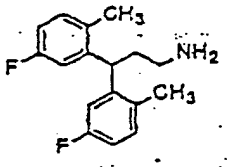
Composé 55



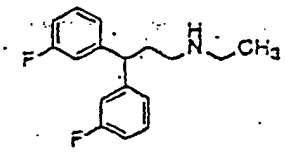
Composé 56



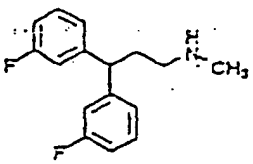
Composé 57



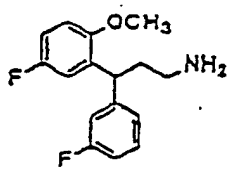
Composé 58



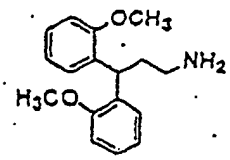
Composé 59



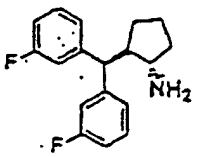
Composé 60



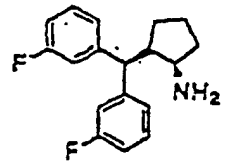
Composé 61



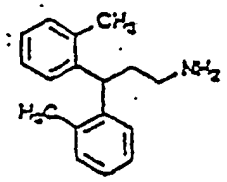
Composé 62



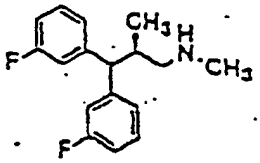
Composé 63



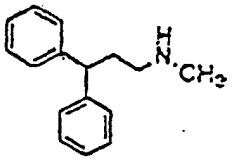
Composé 64



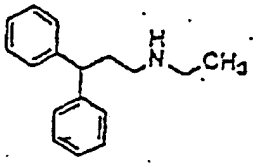
Composé 65



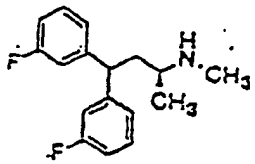
Composé 66



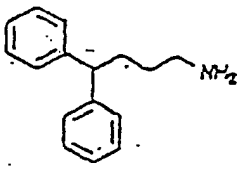
Composé 67



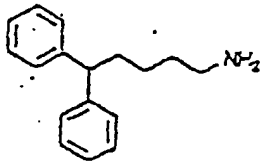
Composé 68



Composé 69



Composé 70



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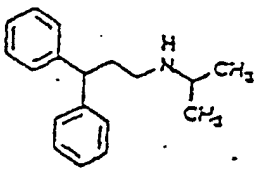

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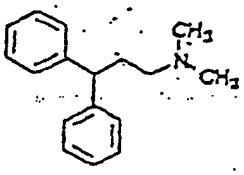

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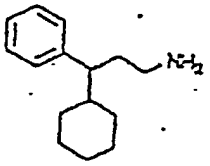
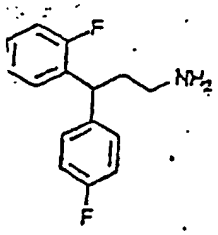
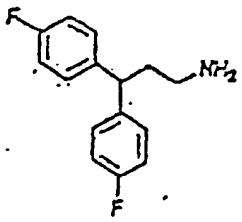


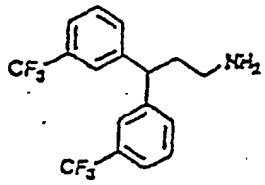
Composé 75



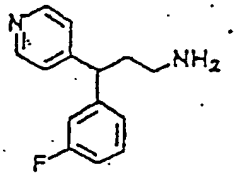
Composé 76



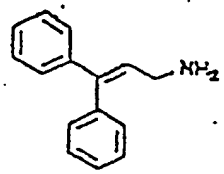
Composé 77



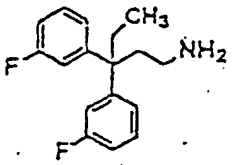
Composé 78



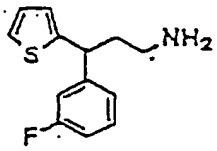
Composé 79



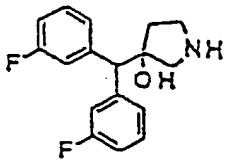
Composé 81



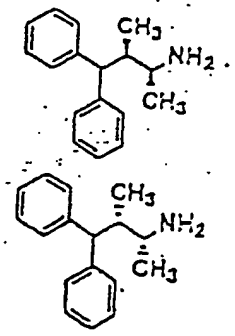
Composé 82



Composé 83

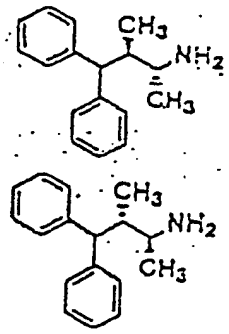


Composé 84



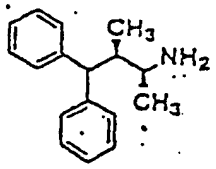
Composé 85

(Mélange de 2 composés)

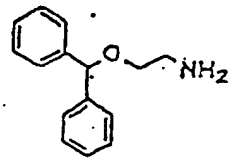


Composé 86

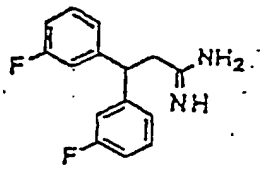
(Mélange de 2 composés)



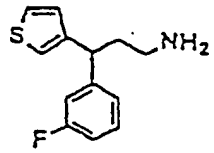
Composé 87



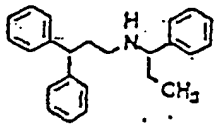
Composé 88



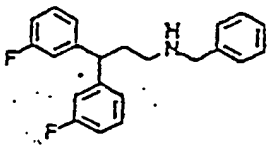
Composé 89



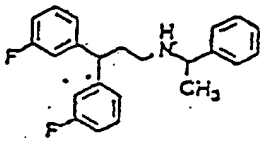
Composé 90



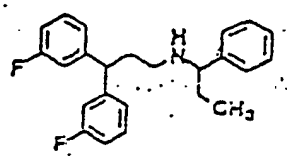
Composé 91



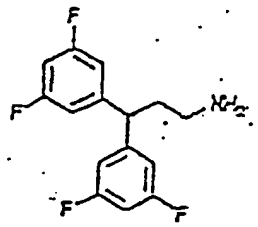
Composé 92



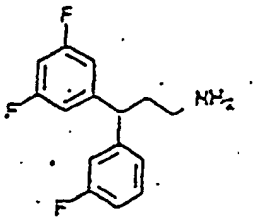
Composé 93



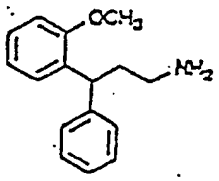
Composé 94



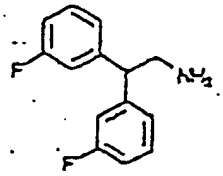
Composé 95



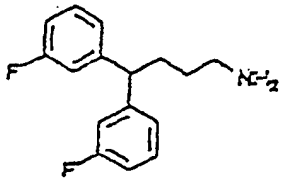
Composé 96



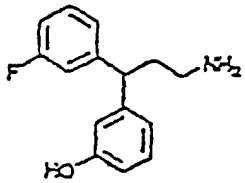
Composé 97



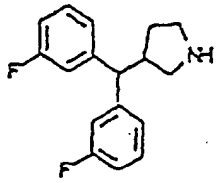
Composé 98



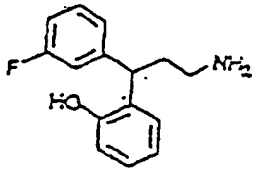
Composé 100



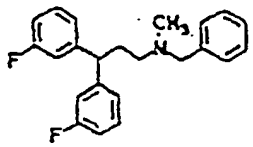
Composé 101



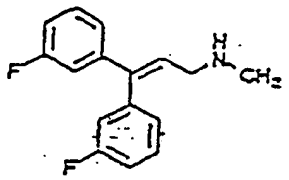
Composé 102



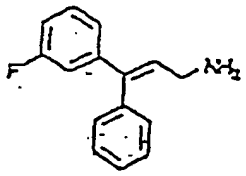
Composé 103

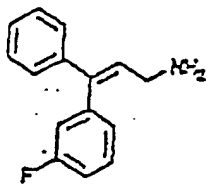


Composé 105



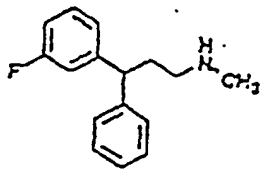
Composé 106



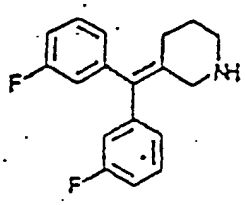


Composé 107

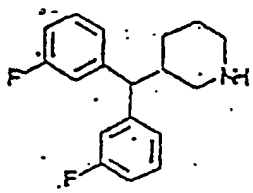
(Mélange de 2 composés)



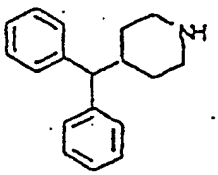
Composé 108



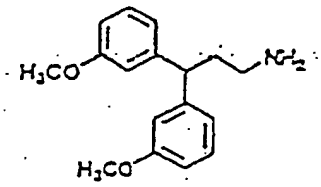
Composé 109



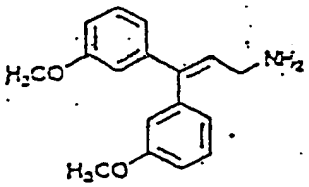
Composé 111



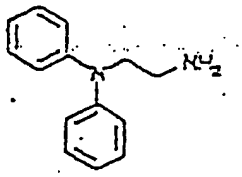
Composé 114



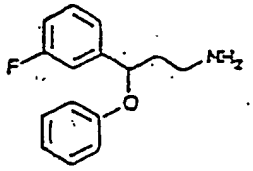
Composé 115



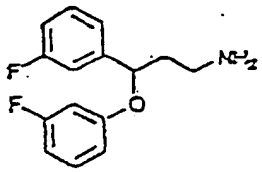
Composé 116



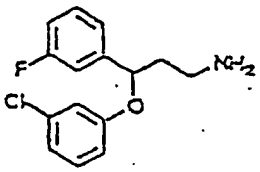
Composé 117



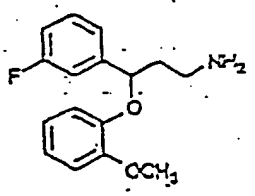
Composé 118



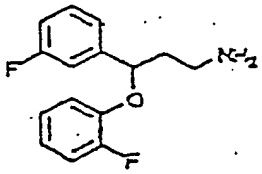
Composé 119



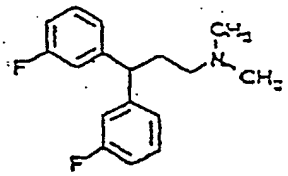
Composé 120



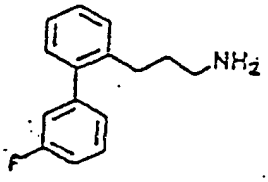
Composé 121



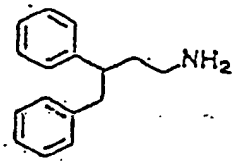
Composé 122



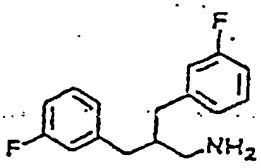
Composé 123



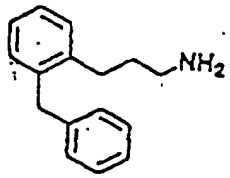
Composé 124



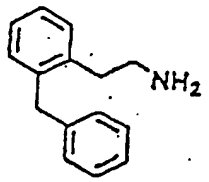
Composé 125



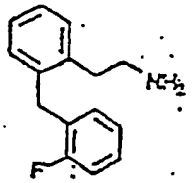
Composé 126



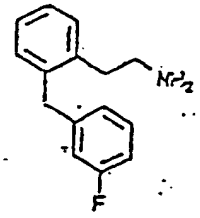
Composé 127



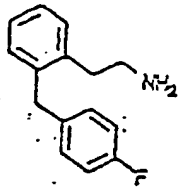
Composé 128



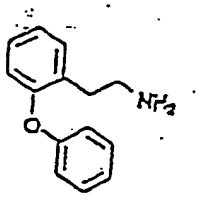
Composé 129



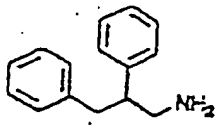
Composé 130



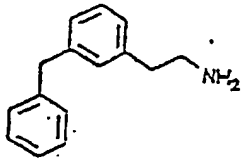
Composé 131



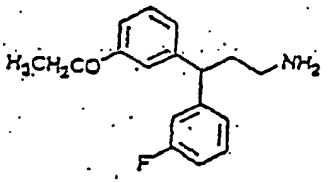
Composé 132



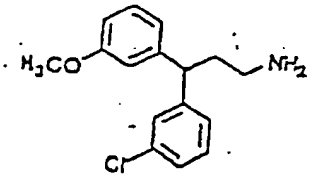
Composé 133



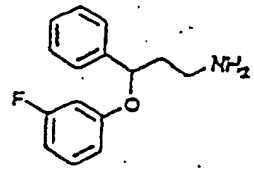
Composé 134



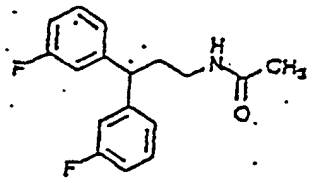
Composé 135



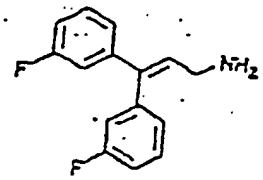
Composé 136



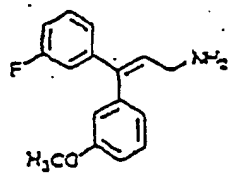
Composé 137



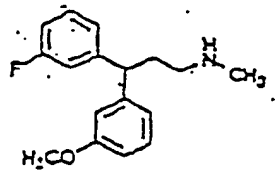
Composé 138



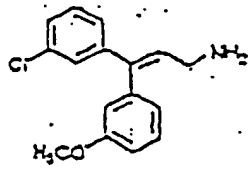
Composé 139



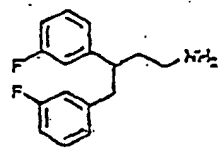
Composé 141



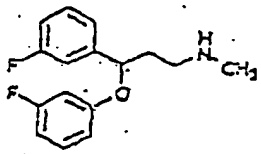
Composé 142



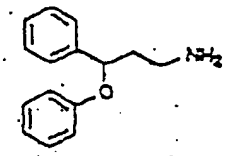
Composé 143



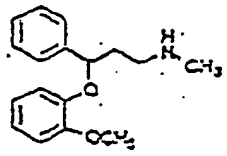
Composé 144



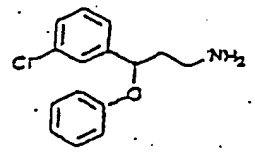
Composé 145



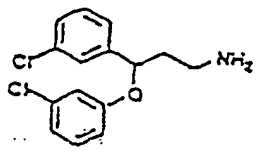
Composé 146



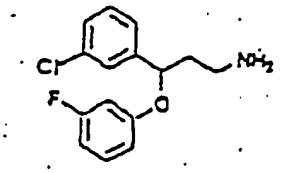
Composé 147



Composé 148



Composé 149



Composé 150

et leurs sels et complexes pharmaceutiquement acceptables pour la préparation d'une composition pharmaceutique pour le traitement d'une maladie ou d'un désordre neurologique.

2. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 54-66, 68-71, 75, 76, 78, 79, 81-90, 92-98, 100, 101, 103, 105, 106, 108, 109, 111, 114-122, 124-136, 138, 139, 141-144, 148-150, et leurs sels et complexes pharmaceutiquement acceptables.

3. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 54-66, 69, 70, 75, 76, 81-83, 85-97, 100-103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135-139, 142, 144-150, et leurs sels et complexes pharmaceutiquement acceptables.

4. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 54-66, 69, 70, 75, 76, 81-83, 85-90, 92-97, 100, 101, 103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135, 136, 138, 139, 142, 144, 148-150, et leurs sels et complexes pharmaceutiquement acceptables.

5. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 54-66, 69, 82, 83, 89-97, 103, 111, 118-120, 122, 126, 135-138, 142, 144, 145, 147-150, et leurs sels et complexes pharmaceutiquement acceptables.

6. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 54-66, 69, 82, 83, 89-90, 92-97, 103, 111, 118-120, 122, 126, 135, 136, 138, 142, 144, 148-150, et leurs sels et complexes pharmaceutiquement acceptables.

7. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 60, 66, 69, 103, 111, 118-120, 122, 136, 138, 142, 144, 148-150, et leurs sels et complexes pharmaceutiquement acceptables.

8. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 118-122, 137, 145, 148-150, et leurs sels et complexes pharmaceutiquement acceptables.

9. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 118-122, 148-150, et leurs sels et complexes pharmaceutiquement acceptables.

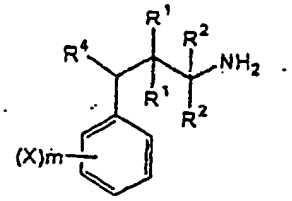
10. Utilisation selon la revendication 1, dans laquelle le composé est choisi dans le groupe consistant en les composés 63 et 64 et leurs sels et complexes pharmaceutiquement acceptables.

11. Utilisation selon la revendication 1, dans laquelle le composé est choisi parmi le composé 119 et ses sels et complexes pharmaceutiquement acceptables.

12. Utilisation selon la revendication 1, dans laquelle le composé est choisi parmi le composé 144 et ses sels et complexes pharmaceutiquement acceptables.

13. Utilisation du composé 60 et de ses sels et complexes pharmaceutiquement acceptables pour la préparation d'une composition pharmaceutique pour le traitement d'une maladie ou d'un désordre neurologique.

14. Utilisation d'un composé de formule :



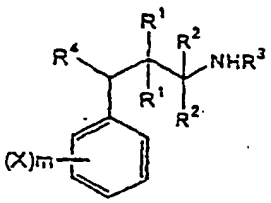
dans laquelle :

X est choisi indépendamment dans le groupe consistant en -Br, -Cl, -F, -I, $-CF_3$, alkyle, -OH, $-OCF_3$, -O-alkyle et -O-acyle ;
R_1 est choisi indépendamment dans le groupe consistant en -H, C_1-C_4 alkyle, et -Oacyle ;
R_2 est choisi indépendamment dans le groupe consistant en -H, alkyle et hydroxyalkyle, ou les deux R_2 ensemble sont imino ;
R_4 est phénoxy éventuellement substitué par -F, -Cl, -Br, -I, $-CF_3$, alkyle, -OH,$-O-CF_3$, -O-alkyle et -O-acyle ; et m est indépendamment un nombre entier de 0 à 5 ; et ses sels et complexes pharmaceutiquement acceptables sous réserve que le dit composé n'est pas :

3-(p-isopropoxyphénoxy)-3-phénylpropylamine
3-(2'-methyl-4',5'-dichlorophénoxy)-3-phénylpropylamine
3-(p-tert-butylphénoxy)-3-phénylpropylamine
3-(2',4'-dichlorophénoxy)-3-phényl-2-méthylpropylamine
3-(o-éthylphénoxy)-3-phénylpropylamine
3-(o-méthoxyphénoxy)-3-phénylpropylamine
3-phénoxy-3-phénylpropylamine

pour la préparation d'une composition pharmaceutique pour le traitement d'une maladie ou d'un désordre neurologique.

15. Utilisation d'un composé de formule :



dans laquelle :

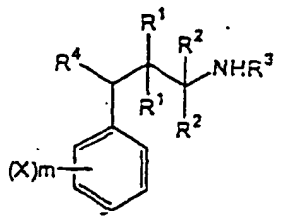
X est choisi indépendamment dans le groupe consistant en -F, -Cl, -Br, -I, $-CF_3$, alkyle, -OH, $-OCF_3$, -O-alkyle et -O-acyle ;
R_1 est choisi indépendamment dans le groupe consistant en -H, C_1-C_4 alkyle, et-O-acyle ;
R_2 est choisi indépendamment dans le groupe consistant en -H, C_1-C_4 alkyle et hydroxyalkyle, ou les deux R_2 ensemble sont imino ;
R_3 est choisi dans le groupe consistant en méthyle et éthyle ;
R_4 est phénoxy éventuellement substitué par -F, -Cl, -Br, -I, $-CF_3$, alkyle, -OH,$-OCF_3$, -O-alkyle et -O-acyle ; et m est indépendamment un nombre entier de 0 à 5 ; et leurs sels et complexes pharmaceutiquement acceptables sous réserve que le dit composé n'est pas :

N-méthyl 3-(o-chloro-p-tolyloxy)-3-phényl-1-méthylpropylamine
N-méthyl 3-(p-tolyloxy)-3-phénylpropylamine

N-méthyl 3-(o-chloro-p-isopropylphénoxy)-3-phényl-2-méthylpropylamine
N-méthyl 3-(p-iodophénoxy)-3-phényl-propylamine
N-méthyl 3-(3-n propylphénoxy)-3-phénylpropylamine
N-méthyl 3-(p-trifluorométhylphénoxy)-3-phénylpropylamine
N-méthyl 3-(m-chlorophénoxy)-3-phénylpropylamine
N-méthyl 3-(p-fluorophénoxy)-3-phénylpropylamine
N-méthyl 3-(p-méthoxyphénoxy)-3-phénylpropylamine
N-méthyl 3-(o-méthoxyphénoxy)-3-phénylpropylamine
N-méthyl 3-(o-fluorophénoxy)-3-phénylpropylamine
N-méthyl 3-(o-tolyloxy)-3-phénylpropylamine
N-méthyl 3-(p-chlorophénoxy)-3-phénylpropylamine
N-méthyl 3-(m-fluorophénoxy)-3-phénylpropylamine
N-méthyl 3-phénoxy-3 -phényl-2-méthylpropylamine
N-méthyl 3-phénoxy-3-phényl-1-méthylpropylamine
N-méthyl 3-phénoxy-3-phénylpropylamine
N-méthyl 3-(o-trifluorométhylphénoxy)-3-phénylpropylamine
N-méthyl 3-(m-méthoxyphénoxy)-3-phénylpropylamine
N-méthyl 3-(o,p-difluorophénoxy)-3-phénylpropylamine
N-éthyl 3-(o-iodophénoxy)-3-phénylpropylamine
N-méthyl 3-(o-chlorophénoxy)-3-phénylpropylamine
N-méthyl 3-(o-bromophénoxy)-3-phénylpropylamine

pour la préparation d'une composition pharmaceutique pour le traitement d'une maladie ou d'un désordre neurologique.

16. Utilisation d'un composé de formule :



dans laquelle :

(X)m est choisi dans le groupe consistant en méta-fluoro, méta-chloro, ortho-O-C_1-C_4 alkyle, ortho-méthyle, ortho-fluoro, ortho-chloro, méta-O-C_1-C_4 alkyle, métaméthyle, ortho-OH et méta-OH ;
R_1 est H;
R_2 est H;
R_3 est choisi dans le groupe consistant en méthyle et éthyle ;
R_4 est phénoxy éventuellement substitué par -F, -Cl, -Br, -I, -CF_3, alkyle, -OH,-OCF_3, -O-alkyle et -O-acyle ;

et ses sels et complexes pharmaceutiquement acceptables pour la préparation d'une composition pharmaceutique pour le traitement d'une maladie ou d'un désordre neurologique.

17. Utilisation selon l'une quelconque des revendications 1 à 6, dans laquelle la maladie ou le désordre comprend un accident vasculaire cérébral, un traumatisme crânien, une lésion de la moelle épinière, une ischémie de la moelle épinière, un dommage neuronal induit par une ischémie ou une hypoxie, l'épilepsie, la douleur, l'anxiété, des déficits neuropsychiatriques ou cognitifs dus à une ischémie ou une hypoxie tels que ceux survenant fréquemment en tant que conséquence d'une opération chirurgicale cardiaque sous dérivation cardio-pulmonaire, la maladie d'Alzheimer, la maladie de Huntington, la maladie de Parkinson, ou la sclérose amyotrophique latérale.

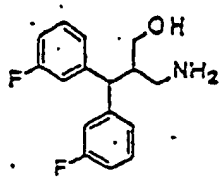
18. Utilisation selon la revendication 17, dans laquelle l'accident vasculaire cérébral est de nature ischémique global.

19. Utilisation selon la revendication 17, dans laquelle l'accident vasculaire cérébral est de nature ischémique focal.

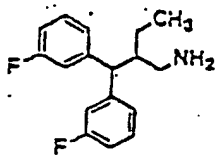
20. Utilisation selon la revendication 17, dans laquelle l'accident vasculaire cérébral est de nature hémmoragique.

21. Utilisation selon la revendication 17, dans laquelle la maladie ou le désordre neurologique comprend la maladie de Parkinson.

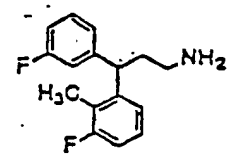
22. Composé choisi dans le groupe consistant en :



Composé 54



Composé 55



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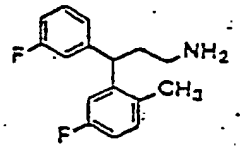

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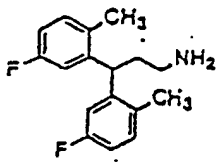
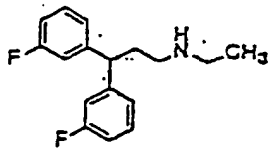


Composé 58



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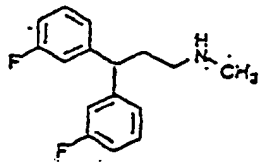

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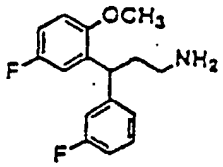

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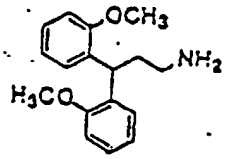
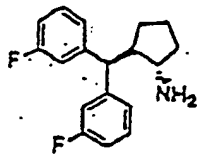
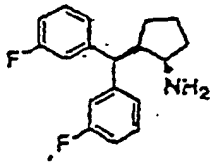


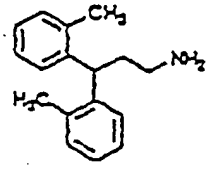
Composé 62



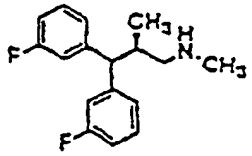
Composé 63



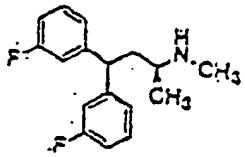
Composé 64



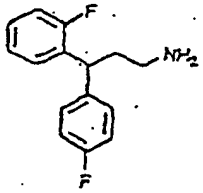
Composé 65



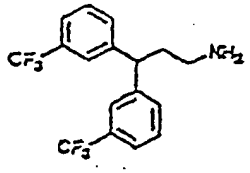
Composé 66



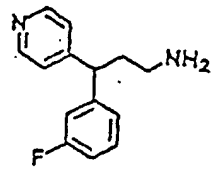
Composé 65



Composé 76



Composé 78



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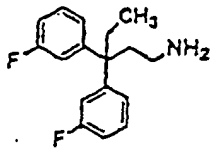
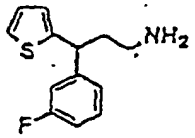
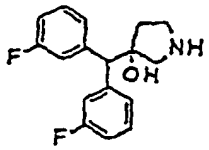


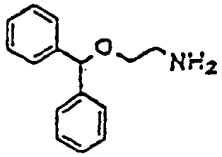
Composé 82



Composé 83



Composé 84



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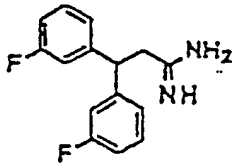
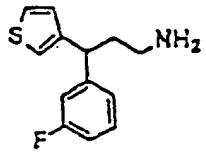


Composé 89



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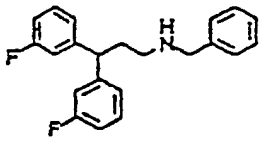
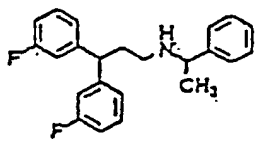
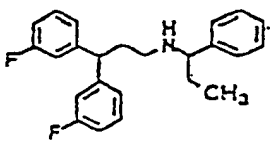


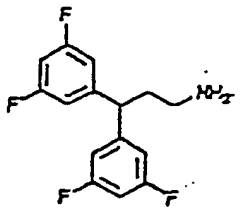
Composé 52



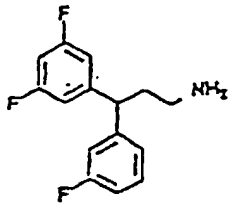
Composé 93



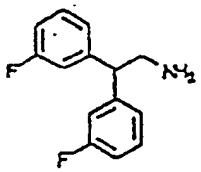
Composé 94



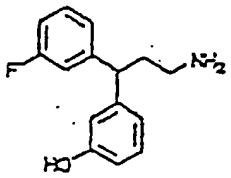
Composé 95



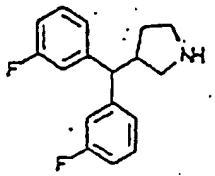
Composé 96



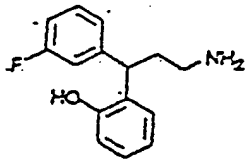
Composé 98



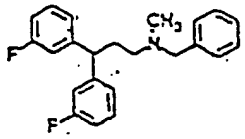
Composé 101



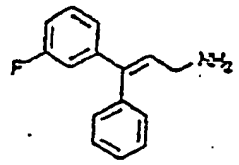
Composé 102

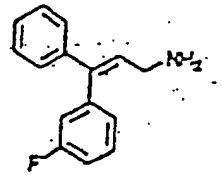


Composé 103



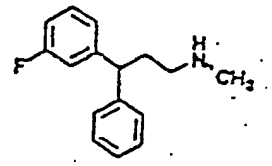
Composé 105



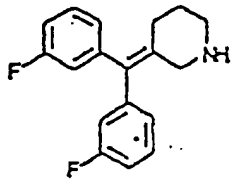


Composé 107

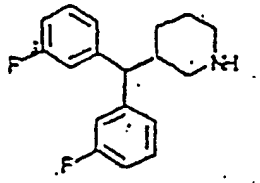
(Mélange de 2 composés)



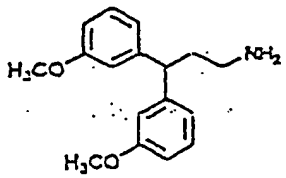
Composé 108



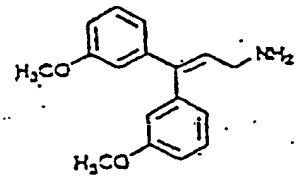
Composé 109



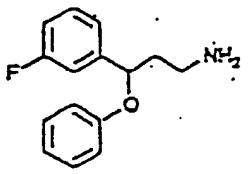
Composé 111



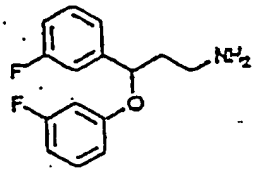
Composé 115



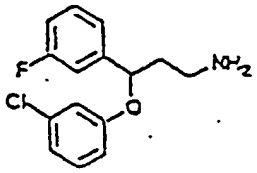
Composé 116



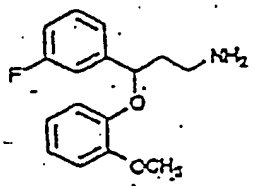
Composé 118



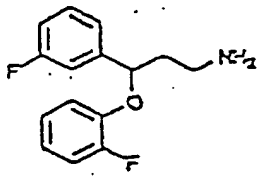
Composé 119



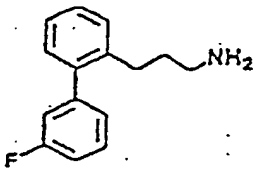
Composé 120



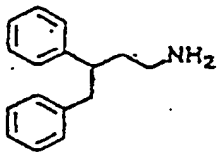
Composé 121



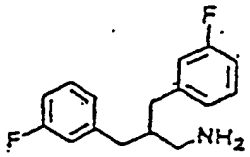
Composé 122



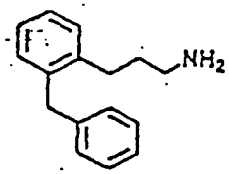
Composé 124



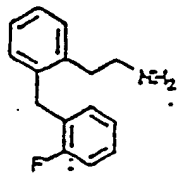
Composé 125



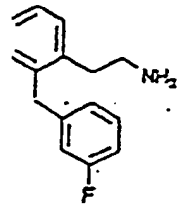
Composé 126



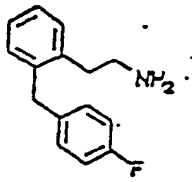
Composé 127



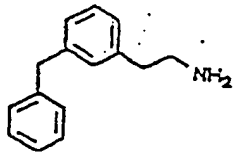
Composé 129



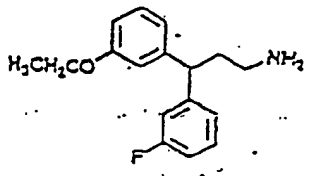
Composé 130



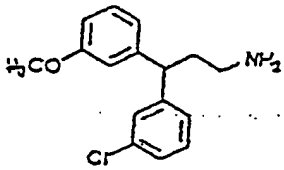
Composé 131



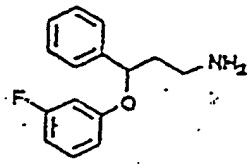
Composé 134



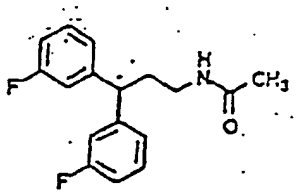
Composé 135



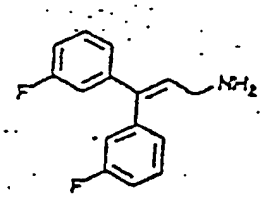
Composé 136



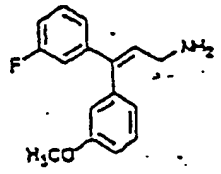
Composé 137



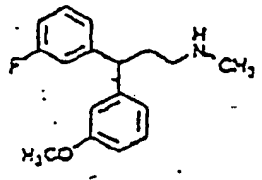
Composé 138



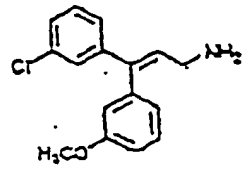
Composé 139



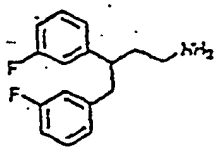
Composé 141



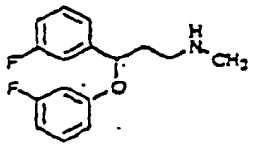
Composé 142



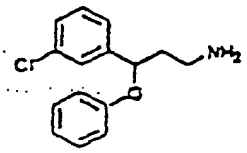
Composé 143



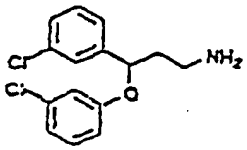
Composé 144



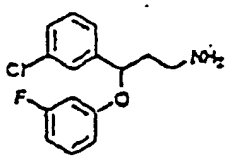
Composé 145



Composé 148



Composé 149



Composé 150

et leurs sels pharmaceutiquement acceptables.

23. Composé selon la revendication 22 choisi dans le groupe consistant en les composés 54-66, 69, 76, 82, 83, 88-90, 92-96, 101, 102, 103, 105, 108, 109, 111, 115, 118-122, 125-127, 129-131, 135-139, 142, 144, 145, 148-150, ou leurs sels pharmaceutiquement acceptables.

24. Composé selon la revendication 22 choisi dans le groupe consistant en les composés 54-66, 69, 82, 83, 89, 90, 93-96, 103, 111, 118-120, 122, 126, 135-138, 142, 144, 145, 148-150, ou ses sels pharmaceutiquement acceptables.

25. Composé selon la revendication 22 choisi dans le groupe consistant en les composés 60-66, 69, 70, 103, 111, 118-120, 122, 136-138, 142, 144, 145, 148-150, ou ses sels pharmaceutiquement acceptables.

26. Composé selon la revendication 22 choisi dans le groupe consistant en les composés, 118-122, 137, 145, 148-150, ou ses sels pharmaceutiquement acceptables.

27. Composé selon la revendication 22 choisi dans le groupe consistant en les composés 118-122, 148-150, ou ses sels pharmaceutiquement acceptables.

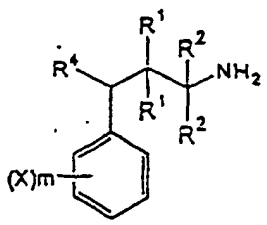
28. Composé selon la revendication 22 choisi dans le groupe consistant en les composés 63 et 64 ou ses sels pharmaceutiquement acceptables.

29. Composé selon la revendication 22 choisi parmi le composé 119 ou ses sels pharmaceutiquement acceptables.

30. Composé selon la revendication 22 choisi parmi le composé 144 ou ses sels pharmaceutiquement acceptables.

31. Composé 60 ou ses sels pharmaceutiquement acceptables.

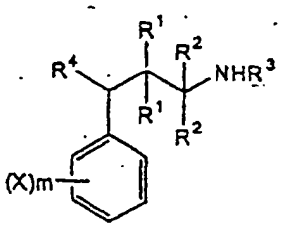
32. Composé de formule :



dans laquelle :

X est choisi indépendamment dans le groupe consistant en -Br, -Cl, -F, -I, $-CF_3$, alkyle, -OH, $-OCF_3$, -O-alkyle et -O-acyle ;
R_1 est choisi indépendamment dans le groupe consistant en -H, C_1-C_4 alkyle, et-O-acyle ;
R_2 est choisi indépendamment dans le groupe consistant en -H, alkyle et hydroxyalkyle, ou les deux R_2 ensemble sont imino ;
R_4 est phénoxy éventuellement substitué par -F, -Cl, -Br, -I, $-CF_3$, alkyle, -OH,$-OCF_3$, -O-alkyle et -O-acyle ; et m est indépendamment un nombre entier de 1 à 5 ; et ses sels et complexes pharmaceutiquement acceptables

33. Composé de formule :

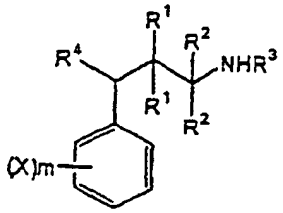


dans laquelle :

X est choisi indépendamment dans le groupe consistant en -F, -Cl, -Br,-I, $-CF_3$, alkyle, -OH, $-OCF_3$, -O-alkyle et -O-acyle ;
R_1 est choisi indépendamment dans le groupe consistant en -H, C_1-C_4 alkyle, et-O-acyle ;
R_2 est choisi indépendamment dans le groupe consistant en -H, C_1-C_4 alkyle et hydroxyalkyle, ou les deux R_2 ensemble sont imino ;
R_3 est choisi dans le groupe consistant en méthyle et éthyle ;

R_4 est phénoxy éventuellement substitué par -F, -Cl, -Br, -I, -CF_3, alkyle, -OH,-OCF_3, -O-alkyle ou-O-acyle ; et m est indépendamment un nombre entier de 1 à 5 ; et ses sels et complexes pharmaceutiquement acceptables sous réserve que le dit composé n'est pas N-méthyl 3-(m-trifluorométhylphénoxy)-3-(4-fluorophényl)propylamine.

34. Composé de formule :

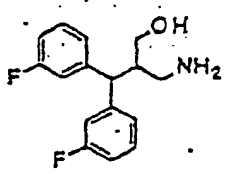


dans laquelle :

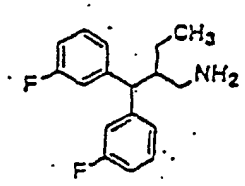
(X)m est choisi dans le groupe consistant en méta-fluoro, méta-chloro, ortho-O-C_1-C_4 alkyle, ortho-méthyle, ortho-fluoro, ortho-chloro, méta-O- C_1-C_4 alkyle, métaméthyle, ortho-OH et méta-OH ;
R_1 est H;
R_2 est H;
R_3 est choisi dans le groupe consistant en méthyle et éthyle ;
R_4 est phénoxy éventuellement substitué par -F, -Cl, -Br, -I, -CF_3, alkyle, -OH,-OCF_3, -O-alkyle ou-O-acyle ;

et ses sels et complexes pharmaceutiquement acceptables.

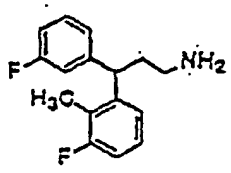
35. Composition pharmaceutique comprenant un composé choisi dans le groupe consistant en



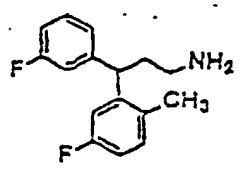
Composé 54



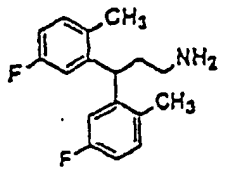
Composé 55



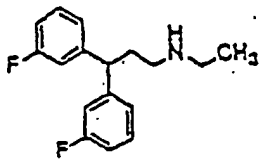
Composé 56



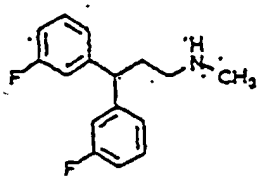
Composé 57



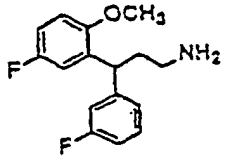
Composé 58



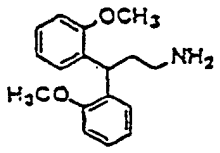
Composé 59



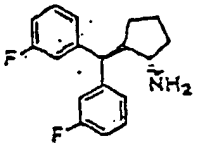
Composé 60



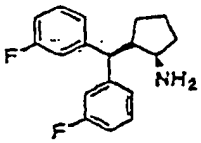
Composé 61



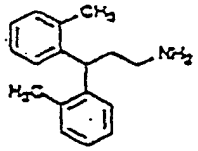
Composé 62



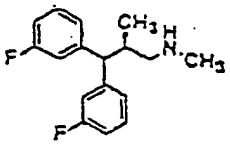
Composé 63



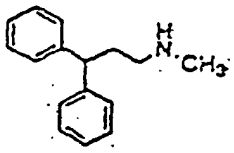
Composé 64



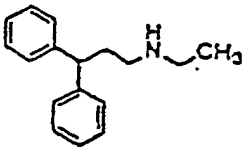
Composé 65



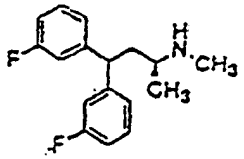
Composé 66



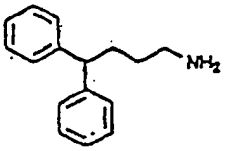
Composé 67



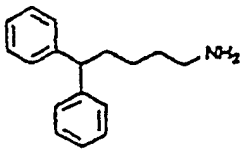
Composé 68



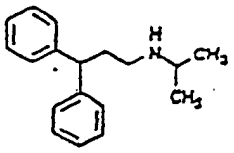
Composé 69



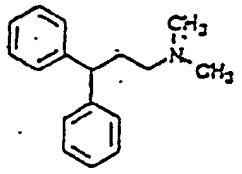
Composé 70



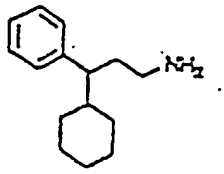
Composé 71



Composé 72



Composé 73



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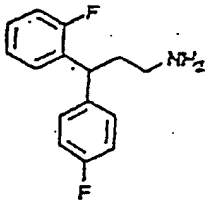

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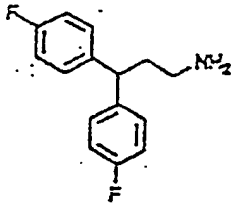
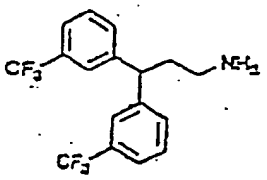
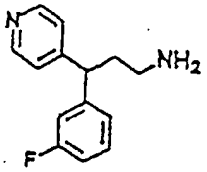


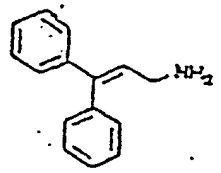
Composé 77



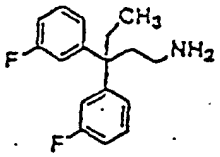
Composé 78



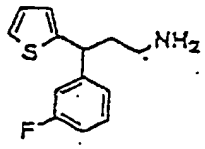
Composé 79



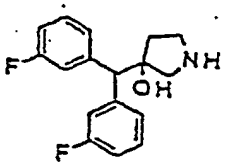
Composé 81



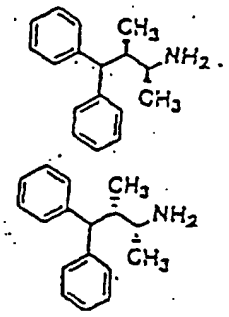
Composé 82



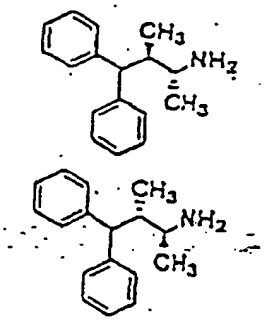
Composé 83



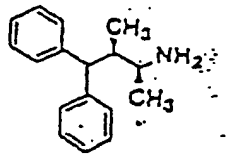
Composé 84



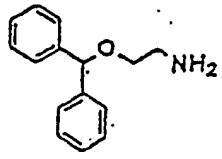
Composé 85
(Mélange de 2 composés)



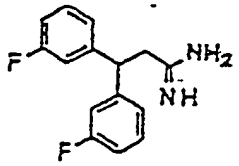
Composé 86
(Mélange de 2 composés)



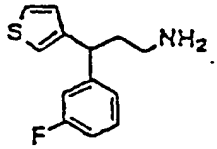
Composé 87



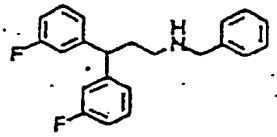
Composé 88



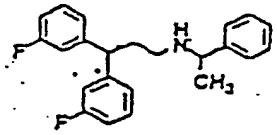
Composé 89



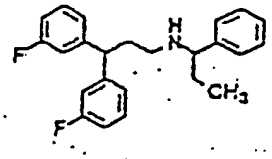
Composé 90



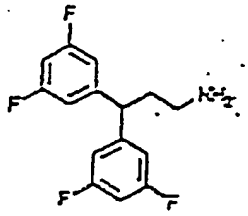
Composé 92



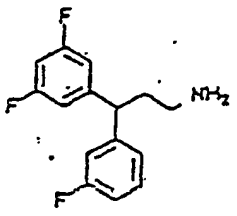
Composé 93



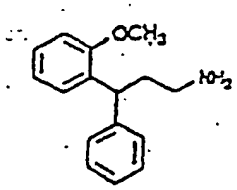
Composé 94



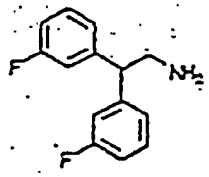
Composé 95



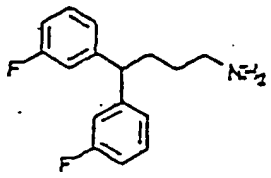
Composé 96



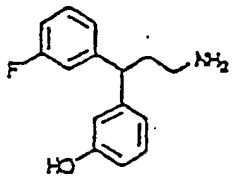
Composé 97



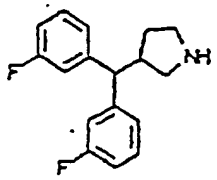
Composé 98



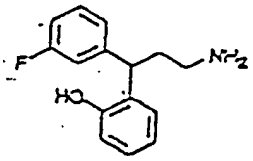
Composé 100



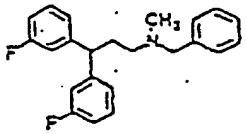
Composé 101



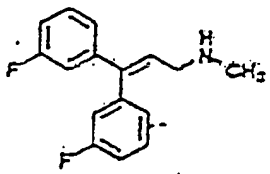
Composé 102



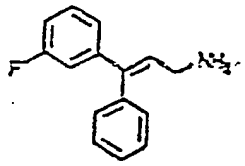
Composé 103

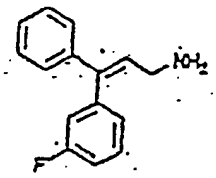


Composé 105



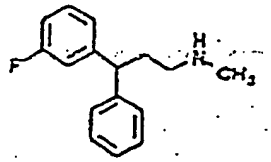
Composé 106



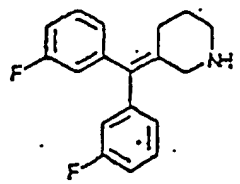


Composé 107

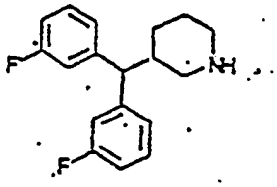
(Mélangé de 2 composés).



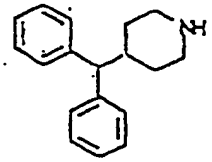
Composé 108



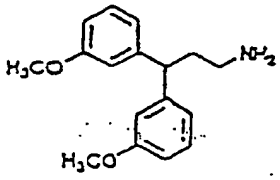
Composé 109



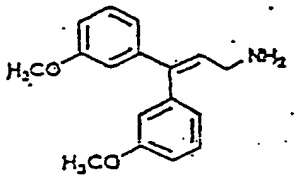
Composé 111



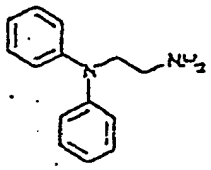
Composé 114



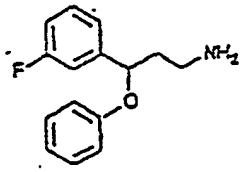
Composé 115



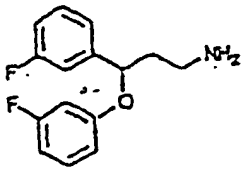
Composé 116



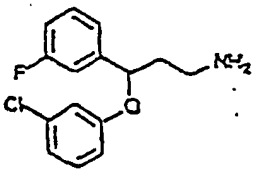
Composé 117



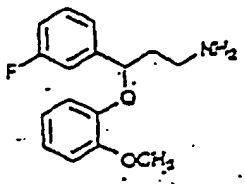
Composé 118



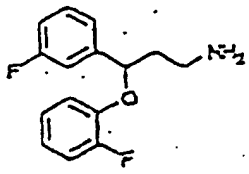
Composé 119



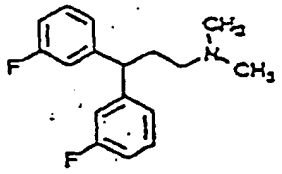
Composé 120



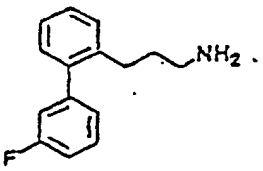
Composé 121



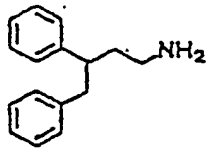
Composé 122



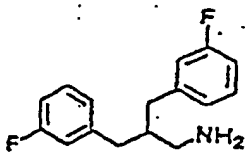
Composé 123



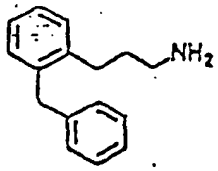
Composé 124



Composé 125



Composé 126



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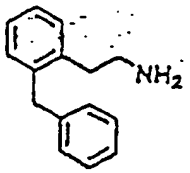

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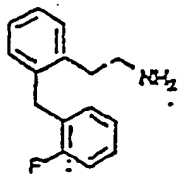

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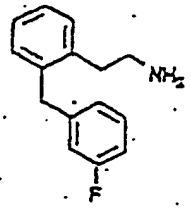

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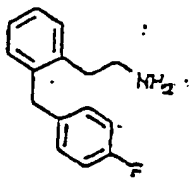

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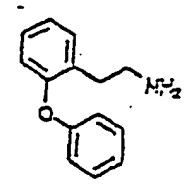

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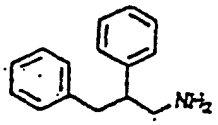

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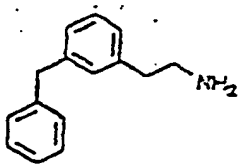

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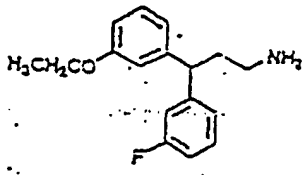

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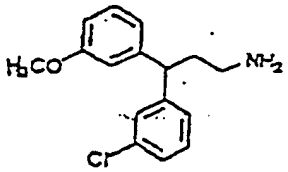

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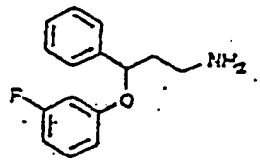

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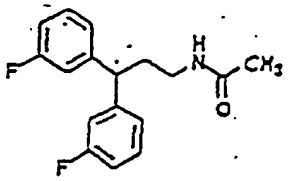

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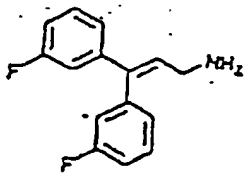

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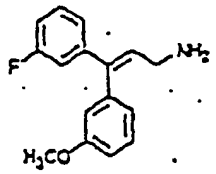

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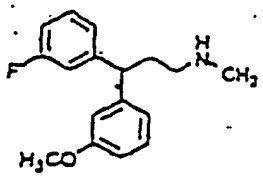

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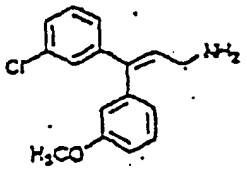

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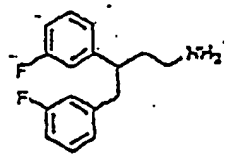

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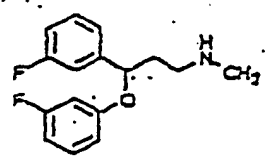

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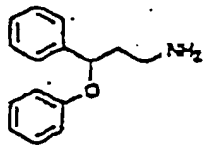

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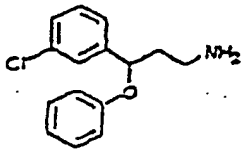

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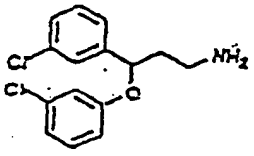

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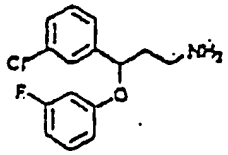

Composé 150

et leurs sels pharmaceutiquement acceptables dans un véhicule pharmaceutiquement acceptable.

36. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 54-71, 73, 76-79, 81-84, 88-90, 92-98, 101-103, 105, 107-109, 111, 115, 117-123, 125-127, 129-136, 138, 139, 142, 144-146, 148-150, et leurs sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

37. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 54-66, 69, 70, 75, 76, 81-83, 85-90, 92-97, 100-103, 105, 106, 108, 109, 111, 115, 118-122, 125-133, 135-139, 142, 144-146, 148-150, et leurs sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

38. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 54-66, 69, 70, 76, 81-83, 88-90, 92-97, 101-103, 105, 106, 108, 109, 111, 115, 118-122, 125-127, 129-133, 135, 136, 138, 139, 142, 144-146, 148-150, et leurs sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

39. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 54-66, 69, 82, 83, 89, 90, 93-97; 103, 111, 118-120, 122, 126, 135-138, 142, 144, 145, 148-150, et leurs sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

40. Composition pharmaceutique selon la revendication -35 comprenant un composé choisi dans le groupe consistant en les composés 54-66, 69, 82, 83, 89, 90, 93-97, 103, 111, 118-120, 122, 126, 135, 136, 138, 142, 144, 145, 148-150, et leurs sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

41. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 60, 66, 69, 103, 111, 118-120, 122, 136-138, 142, 144, 145, 148-150, et leurs sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

42. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 118-122, 137, 145, 148-150, et leurs sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

43. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 118-122, 148-150, et ses sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

44. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi dans le groupe consistant en les composés 63 et 64 et ses sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

45. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi parmi le composé 119 et ses sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

46. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi parmi le composé 144 et ses sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

47. Composition pharmaceutique selon la revendication 35 comprenant un composé choisi parmi le composé 60 et ses sels pharmaceutiquement acceptables, dans un véhicule pharmaceutiquement acceptable.

48. Composition pharmaceutique comprenant un composé selon la revendication 32, dans un véhicule pharmaceutiquement acceptable.

49. Composition pharmaceutique comprenant un composé selon la revendication 33, dans un véhicule pharmaceutiquement acceptable.

50. Composition pharmaceutique comprenant un composé selon la revendication 34, dans un véhicule pharmaceutiquement acceptable.

51. Composition pharmaceutique selon l'une quelconque des revendication 35-50, adaptée au traitement d'une maladie ou d'un désordre neurologique.

52. Composition pharmaceutique selon la revendication 51, dans laquelle la maladie ou le désordre est choisi dans le groupe consistant en un accident vasculaire cérébral, un traumatisme crânien, une lésion de la moelle épinière, l'épilepsie, l'anxiété, la maladie d'Alzheimer, la maladie de Huntington, la maladie de Parkinson, ou la sclérose amyotrophique latérale.

53. Composition pharmaceutique selon la revendication 51, dans laquelle la composition pharmaceutique a une activité neuro-protectrice.

54. Composition pharmaceutique selon la revendication 52, dans laquelle l'accident vasculaire cérébral est de nature ischémique globale.

55. Composition pharmaceutique selon la revendication 52, dans laquelle l'accident vasculaire cérébral est de nature ischémique focale.

56. Composition pharmaceutique selon la revendication 52, dans laquelle l'accident vasculaire cérébral est de nature hémorragique.

57. Composition pharmaceutique selon la revendication 52, dans laquelle la maladie ou le désordre neurologique est la maladie de Parkinson.

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(54) Antiretroviral compositions with improved bioavailability

(57) The present invention is concerned with novel pharmaceutical compositions of loviride which can be administered to a patient suffering from a retroviral infection, whereby such dosage forms have a high drug content and can be administered at any time of the day independently of the food taken in by said patient. These novel compositions comprise particles obtainable by melt-extruding a mixture comprising loviride and an appropriate water-soluble polymer and subsequently milling said melt-extruded mixture.

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Description

The present invention is concerned with novel pharmaceutical compositions of loviride which can be administered to a patient suffering from a retroviral infection, whereby such dosage forms have a high drug content and can be administered at any time of the day independently of the food taken in by said patient. These novel compositions comprise particles obtainable by melt-extruding a mixture comprising loviride and an appropriate water-soluble polymer and subsequently milling said melt-extruded mixture.

The development of pharmaceutical compositions having good bioavailability of loviride, a compound that is practically insoluble in aqueous media, remains one of the main challenges of pharmaceutical development of this compound.

The term "practically insoluble" or "insoluble" is to be understood as defined in the United States Pharmacopeia, i.e. a "very slightly soluble" compound requiring from 1000 to 10,000 parts of solvent for 1 part of solute; a "practically insoluble" or "insoluble" compound requiring more than 10,000 parts of solvent for 1 part of solute. The solvent referred to herein is water.

Loviride or (±)-α-[(2-acetyl-5-methylphenyl)amino]-2,6-dichlorobenzeneacetamide, is an antiretroviral non-nucleoside reverse transcriptase inhibitor developed for oral, parenteral and topical administration to patients suffering from HIV infection and is disclosed in WO-92/00952 (23.01.1992). Loviride is currently undergoing extensive phase II evaluations as monotherapy and in combinations with other anti-HIV compounds. As its half-life is short, loviride is administered three times a day (t.i.d.). Suitable oral doses are 100 mg t.i.d., 200 mg t.i.d. or even 300 mg t.i.d. The oral formulation can be a capsule comprising drug-coated beads. Since not more than 100 mg of the active ingredient can be formulated into one capsule, patients are expected to ingest from 3 to 9 capsules a day. Clearly, a dosage form having a higher drag content, e.g. 200 mg or even 300 mg would mark a significant step forward.

The term "loviride" as used hereinafter is to be interpreted broadly and comprises the free base form and the pharmaceutically acceptable addition salts of loviride, or of one of its enantiomers, or of a mixture of its two enantiomers. The preferred loviride compound is the racemic mixture of the enantiomers in the free base form ; to all practical purposes this compound is insoluble. Its solubility at room temperature in water at a pH of 6.5 is less than 0.1 mg/100ml. The acid addition forms may be obtained by reaction of the base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-butenedioic, (E)-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.

In order to achieve the desired antiretroviral effect, it is essential that therapeutically effective plasma levels of loviride can be maintained. As loviride is practically insoluble, effective formulations should be designed in such a manner that the drug is readily bioavailable. In other words, the main problem with the administration of loviride in therapeutically effective amounts is concerned with ensuring that a sufficient amount of loviride remains in a bioavailable physical form (solution, microcrystal) sufficiently long to allow it to get into the circulation, and does not convert into a form that is not readily bioavailable, in particular crystalline loviride (which is formed for example when loviride precipitates in an aqueous medium). To that purpose loviride in capsules is preferably ingested during or at the end of a meal. This, however, limits the ease with which the patients can comply with their prescribed therapy ; for example, some patients are not able to eat normally or swallow medicaments easily (let alone three times a day) because of illness, nausea or because of opportunistic infections of the esophagus. It would therefore be highly desirable to have pharmaceutical dosage forms which have a high drug content and can be administered to a patient at any time of the day independently of food taken in. i.e. dosage forms which can be administered to patients in a fasted state.

The present invention provides pharmaceutical compositions of loviride and a water-soluble polymer which can be administered to a patient suffering from a retroviral infection, whereby such dosage forms can be administered at any time of the day independently of the food taken in by said patient. The bioavailability of the drug from these dosage forms in fasted and in fed patients is comparable. The dosage forms can be prepared easily, for example by conventional tabletting techniques. The dosage forms comprise a therapeutically effective amount of novel particles as described in detail hereunder.

Said novel particles consist of a solid dispersion comprising

(a) loviride, or one of its enantiomers, or a mixture of its two enantiomers; and
(b) one or more pharmaceutically acceptable water-soluble polymers.

The term "a solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed more or less evenly throughout the other component or

components. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase (as defined in thermodynamics), such a solid dispersion will be called "a solid solution" hereinafter. Solid solutions are preferred physical systems because the components therein are usually readily bioavailable to the organisms to which they are administered. This advantage can probably be explained by the ease with which said solid solutions can form liquid solutions when contacted with a liquid medium such as gastric juice. The ease of dissolution may be attributed at least in part to the fact that the energy required for dissolution of the components from a solid solution is less than that required for the dissolution of components from a crystalline solid phase.

The term "a solid dispersion" also comprises dispersions which are less homogenous throughout than solid solutions. Such dispersions are not chemically and physically uniform throughout or comprise more than one phase. For example, the term "a solid dispersion" also relates to particles having domains or small regions wherein amorphous or microcrystalline (a), or amorphous or microcrystalline (b), or both, are dispersed more or less evenly in another phase comprising (b), or (a), or a solid solution comprising (a) and (b). Said domains are regions within the particles distinctively marked by some physical feature, small in size compared to the size of the particle as a whole, and evenly and randomly distributed throughout the particle. Microcrystalline (a) typically has a domain size of up to about 25 μm, preferably up to 20 μm.

The particles according to the present invention can be prepared by first preparing a solid dispersion of the components, and then optionally grinding or milling that dispersion. Various techniques exist for preparing solid dispersions including melt-extrusion, spray-drying and solution-evaporation.

The melt-extrusion process comprises the following steps :

a) mixing the components (a) and (b),
b) optionally blending additives with the thus obtained mixture,
c) heating the thus obtained blend until one obtains a homogenous melt,
d) forcing the thus obtained melt through one or more nozzles; and
e) cooling the melt till it solidifies.

The terms "melt" and "melting" should be interpreted broadly. For our purposes, these terms not only mean the alteration from a solid state to a liquid state, but can also refer to a transition to a glassy state or a rubbery state, and in which it is possible for one component of the mixture to get embedded more or less evenly into the other. In particular cases, one component will melt and the other component(s) will dissolve in the melt thus forming a solution, which upon cooling may form a solid solution having advantageous dissolution properties.

One of the most important parameters of melt extrusion is the temperature at which the melt-extruder is operating. It was found that the operating temperature can easily range between about 120°C and about 300°C. At temperatures lower than 120°C, loviride will not dissolve sufficiently in most water-soluble polymers and the extrudate will not have the required bioavailability. In addition, the process is difficult because of the high viscosity of the mixture. At temperatures of more than 300°C the water-soluble polymer may decompose to an unacceptable level. It may be noted that there is no need to fear decomposition of loviride at temperatures up to 300°C, since this active ingredient is thermally very stable.

The throughput rate is also of importance because even at relatively low temperatures the water-soluble polymer may start to decompose when it remains too long in contact with the heating element.

It will be appreciated that the person skilled in the art will be able to optimize the parameters of the melt extrusion process within the above given ranges. The working temperatures will also be determined by the kind of extruder or the kind of configuration within the extruder that is used. Most of the energy needed to melt, mix and dissolve the components in the extruder can be provided by the heating elements. However, the friction of the material within the extruder may also provide a substantial amount of energy to the mixture and aid in the formation of a homogenous melt of the components.

Spray-drying of a solution of the components also yields a solid dispersion of said components and may be a useful alternative to the melt-extrusion process, particularly in those cases where the water-soluble polymer is not sufficiently stable to withstand the extrusion conditions and where residual solvent can effectively be removed from the solid dispersion. Yet another possibility consists of preparing a solution of the components, pouring said solution onto a large surface, and evaporating the solvent therefrom.

The solid dispersion product is milled or ground to particles having a particle size of less than 600 μm, preferably less than 400 μm and most preferably less than 125 μm. The particle size proves to be an important factor determining the speed with which tablets having sufficient hardness can be manufactured on a large scale. The particle size distribution is such that more than 70% of the particles (measured by weight) have a diameter ranging from about 50 μm to about 500 μm, in particular from about 50 μm to about 200 μm and most in particular from about 50 μm to about 125 μm. Particles of the dimensions mentioned herein can be obtained by sieving them through nominal standard test

sieves as described in the CRC Handbook, 64th ed., page F-114. Nominal standard sieves are characterized by the mesh/hole width (μm), DIN 4188 (mm), ASTM E 11-70 (No), Tyler® (mesh) or BS 410 (mesh) standard values. Throughout this description and the claims, particle sizes are designated by reference to the mesh/hole width in μm and to the corresponding Sieve No in the ASTM E11-70 standard.

Preferred are particles wherein the loviride is in a non-crystalline phase as these have an intrinsically faster dissolution rate than those wherein part or all of the loviride is in a microcrystalline form.

Preferably, the solid dispersion is in the form of a solid solution comprising (a) and (b). Alternatively, it may be in the form of a dispersion wherein microcrystalline (a) is dispersed more or less evenly in a solid solution comprising (a) and (b).

The water-soluble polymer in the particles according to the present invention is a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution. For example, the water-soluble polymer can be selected from the group comprising

- alkylcelluloses such as methylcellulose,
- hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
- hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
- carboxyalkylcelluloses such as carboxymethylcellulose,
- alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
- carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
- carboxyalkylcellulose esters,
- starches,
- pectines such as sodium carboxymethylamylopectine,
- chitine derivates such as chitosan,
- polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,
- polyacrylic acids and the salts thereof,
- polymethacrylic acids and the salts thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate,
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

Non-enumerated polymers which are pharmaceutically acceptable and have appropriate physico-chemical properties as defined hereinbefore are equally suited for preparing particles according to the present invention.

Preferred water-soluble polymers are hydroxypropyl methylcelluloses or HPMC. Said HPMC contains sufficient hydroxypropyl and methoxy groups to render it water-soluble. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water-soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxypropyl molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule. Hydroxypropyl methylcellulose is the United States Adopted Name for hypromellose (see Martindale, The Extra Pharmacopoeia, 29th edition, page 1435). In the four digit number "2910", the first two digits represent the approximate percentage of methoxyl groups and the third and fourth digits the approximate percentage composition of hydroxypropoxyl groups. 5 mPa.s is a value indicative of the apparent viscosity of a 2 % aqueous solution at 20°C.

The molecular weight of the HPMC normally affects both the release profile of the milled extrudate as well as its physical properties. A desired release profile can thus be designed by choosing an HPMC of an appropriate molecular weight ; for immediate release of the active ingredient from the particles, a low molecular weight polymer is preferred. High molecular weight HPMC is more likely to yield a sustained release pharmaceutical dosage form. The molecular weight of a water-soluble cellulose ether is generally expressed in terms of the apparent viscosity at 20°C of an aqueous solution containing two percent by weight of said polymer. Suitable HPMC include those having a viscosity from about 1 to about 100 mPa.s, in particular form about 3 to about 15 mPa.s, preferably about 5 mPa.s The most preferred type of HPMC having a viscosity of 5 mPa.s., is the commercially available HPMC 2910 5 mPa.s, because this yields particles from which superior oral dosage forms of loviride can be prepared as will be discussed hereunder and in the experimental part.

The weight-by-weight ratio of (a) : (b) is in the range of 1 : 1 to 1 : 8, preferably 1 : 1 to 1 : 5. In the case of (loviride) : (HPMC 2910 5 mPa.s), said ratio may range from about 1 : 1 to about 1 : 2, and optimally is about 1 : 1.5 (or 2 : 3). The weight by weight ratio of loviride to other water-soluble polymers may be determined by a person skilled in the art

by straightforward experimentation. The lower limit is determined by practical considerations. Indeed, given the therapeutically effective amount of loviride (from about 100 mg to about 300 mg, preferably about 200 mg per administration), the lower limit of the ratio is determined by the maximum amount of mixture that can be processed into one dosage form of practical size. When the relative amount of water-soluble polymer is too high, the absolute amount of mixture needed to reach the therapeutic level will be too high to be processed into one capsule or tablet. Tablets, for example, have a maximum weight of about 1 g, and the extrudate can account for maximally about 90 % (w/w) thereof. Consequently, the lower limit of the amount of loviride over hydroxypropyl methyl cellulose will be about 1 : 8 (100 mg loviride + 800 mg water-soluble polymer).

On the other hand, if the ratio is too high, this means the amount of loviride is relatively high compared to the amount of water-soluble polymer, then there is the risk that the loviride will not dissolve sufficiently in the water-soluble polymer, and thus the required bioavailability will not be obtained. The degree to which a compound has dissolved into a water-soluble polymer can often be checked visually : if the extrudate is clear then it is very likely that the compound will have dissolved completely in the water-soluble polymer. The 1 : 1 upper limit is determined by the fact that above said ratio it was observed that the extrudate resulting from extruding loviride with HPMC 2910 5 mPa.s is not "clear", presumably due to the fact that not all of the loviride has dissolved in the HPMC. It will be appreciated that the upper limit of 1 : 1 may be underestimated for particular water-soluble polymers. Since this can be established easily but for the experimentation time involved, solid dispersions wherein the ratio (a) : (b) is larger than 1 : 1 are also meant to be comprised within the scope of the present invention.

Preferred particles are those obtainable by melt-extrusion of the components and grinding, and optionally sieving. More in particular, the present invention concerns particles consisting of a solid dispersion comprising two parts by weight of loviride and three parts by weight of hydroxypropyl methylcellulose HPMC 2910 5 mPa.s, obtainable by blending said components, extruding the blend at a temperature in the range of 120°C - 300°C, grinding the extrudate, and optionally sieving the thus obtained particles.

The particle as described hereinabove may further comprise one or more pharmaceutically acceptable excipients such as, for example, plasticizers, flavors, colorants, preservatives and the like. Said excipients should not be heat-sensitive, in other words, they should not show any degradation or decomposition at the working temperature of the melt-extruder.

In the current loviride : HPMC 2910 5 mPa.s formulations, the amount of plasticizer is preferably small, in the order of 0 % to 15 % (w/w), preferably less than 5 % (w/w). With other water-soluble polymers though, plasticizers may be employed in much different, often higher amounts because plasticizers as mentioned hereinbelow lower the temperature at which a melt of (a), (b) and plasticizer is formed, and this lowering of the melting point is advantagous where the polymer has limited thermal stability. Suitable plasticizers are pharmaceutically acceptable and include low molecular weight polyalcohols such as ethylene glycol, propylene glycol, 1,2 butylene glycol, 2,3-butylene glycol, styrene glycol; polyethylene glycols such as diethylene glycol, triethylene glycol, tetraethylene glycol; other polyethylene glycols having a molecular weight lower than 1,000 g/mol; polypropylene glycols having a molcular weight lower than 200 g/mol; glycol ethers such as monopropylene glycol monoisopropyl ether; propylene glycol monoethyl ether; diethylene glycol monoethyl ether; ester type plasticizers such as sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, allyl glycollate; and amines such as monoethanolamine, diethanolamine, triethanolamine, monoisopropanolamine; triethylenetetramine, 2-amino-2-methyl-1,3-propanediol and the like. Of these, the low molecular weight polyethylene glycols, ethylene glycol, low molecular weight polypropylene glycols and especially propylene glycol are preferred.

Once the extrudate is obtained, it is milled and sieved and used as a "normal" ingredient to make pharmaceutical dosage forms.

The particles of the present invention can be formulated into pharmaceutical dosage forms comprising a therapeutically effective amount of particles. Although, at first instance, pharmaceutical dosage forms for oral administration such as tablets and capsules are envisaged, the particles of the present invention can also be used to prepare pharmaceutical dosage forms e.g. for rectal administration. Preferred dosage forms are those adapted for oral administration shaped as a tablet. They can be produced by conventional tabletting techniques with conventional ingredients or excipients and with conventional tabletting machines. In addition, they can be produced at substantially lower cost than coated cores. As mentioned above, an effective antiretroviral daily dose of loviride ranges from about 100 mg t.i.d. to about 300 mg t.i.d., and preferably is about 200 mg t.i.d. When one considers that the weight-by-weight ratio of (a) : (b) is maximally about 1 : 1, then it follows that one dosage form will weigh at least 400 mg. In order to facilitate the swallowing of such a dosage form by a patient, it is advantageous to give the dosage form, in particular tablets, an appropriate shape. Tablets that can be swallowed comfortably are therefore preferably elongated rather than round in shape. Especially preferred are biconvex oblate tablets. As discussed hereunder in more detail, a film coat on the tablet further contributes to the ease with which it can be swallowed.

Tablets that give an immediate release of loviride upon oral ingestion and that have good bioavailability are designed in such a manner that the tablets disintegrate rapidly in the stomach (immediate release) and that the particles which are liberated thereby are kept away from one another so that they do not coalesce and do not produce high local

concentrations of loviride with the concommittant danger that the drug precipitates (bioavailability). The desired effect can be obtained by distributing said particles homogeneously throughout a mixture of a disintegrant and a diluent.

Suitable disintegrants are those that have a large coefficient of expansion. Examples thereof are hydrophilic, insoluble or poorly water-soluble crosslinked polymers such as crospovidone (crosslinked polyvinylpyrrolidone) and croscarmellose. The amount of disintegrant in immediate release tablets according to the present invention conveniently may range from about 3 to about 15 % (w/w) and preferably is about 7 to 9 % (w/w). This amount tends to be larger than usual in order to ensure that the particles are spread over a large volume of the stomach contents upon ingestion. Because disintegrants by their nature yield sustained release formulations when employed in bulk, it is advantageous to dilute them with an inert substance called a diluent or filler.

A variety of materials may be used as diluents or fillers. Examples are spray-dried or anhydrous lactose, sucrose, dextrose, mannitol, sorbitol, starch, cellulose (e.g. micro-crystalline cellulose Avicel™), dihydrated or anhydrous dibasic calcium phosphate, and others known in the art, and mixtures thereof. Preferred is a commercial spray-dried mixture of lactose monohydrate (75 %) with microcrystalline cellulose (25 %) which is commercially available as Microcelac™.

The tablet may include a variety of one or more other conventional excipients such as binders, buffering agents, lubricants, glidants, thickening agents, sweetening agents, flavors, and colors. Some excipients can serve multiple purposes.

Lubricants and glidants can be employed in the manufacture of certain dosage forms, and will usually be employed when producing tablets. Examples of lubricants and glidants are hydrogenated vegetable oils, e.g hydrogenated Cottonseed oil, magnesium stearate, stearic acid, sodium lauryl sulfate, magnesium lauryl sulfate, colloidal silica, talc, mixtures thereof, and others known in the art. Interesting lubricants and glidants are magnesium stearate, and mixtures of magnesium stearate with colloidal silica. A preferred lubricant is hydrogenated vegetable oil type I, most preferably hydrogenated, deodorized Cottonseed oil (commercially available from Karlshamns as Akofine NF™ (formerly called Sterotex™)). Lubricants and glidants generally comprise 0.2 to 7.0 % of the total tablet weight.

Other excipients such as coloring agents and pigments may also be added to the tablets of the present invention. Coloring agents and pigments include titanium dioxide and dyes suitable for food. A coloring agent is an optional ingredient in the tablet of the present invention, but when used the coloring agent can be present in an amount up to 3.5 % based on the total tablet weight.

Flavors are optional in the composition and may be chosen from synthetic flavor oils and flavoring aromatics or natural oils, extracts from plants leaves, flowers, fruits and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, bay oil, anise oil, eucalyptus, thyme oil. Also useful as flavors are vanilla, citrus oil, including lemon , orange, grape, lime and grapefruit, and fruit essences, including apple, banana, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth, The amount of flavor may depend on a number of factors including the organoleptic effect desired. Generally the flavor will be present in an amount from about 0 % to about 3 % (w/w).

As known in the art, tablet blends may be dry-granulated or wet-granulated before tabletting. The tabletting process itself is otherwise standard and readily practised by forming a tablet from desired blend or mixture of ingredients into the appropriate shape using a conventional tablet press.

Tablets of the present invention may further be film-coated to improve taste, to provide ease of swallowing and an elegant appearance. Many polymeric film-coating materials are known in the art. A preferred film-coating material is hydroxypropyl methylcellulose HPMC, especially HPMC 2910 5 mPa.s. Other suitable film-forming polymers also may be used herein, including, hydroxypropylcellulose, and acrylatemethacrylate copolymers. Besides a film-forming polymer, the film coat may further comprise a plasticizer (e.g. propylene glycol) and optionally a pigment (e.g. titanium dioxide). The film-coating suspension also may contain tale as an anti-adhesive. In immediate release tablets according to the invention, the film coat is small and in terms of weight accounts for about 3 % (w/w) of the total tablet weight.

Preferred dosage forms are those wherein the weight of the particles is at least 40 % of the total weight of the total dosage form, that of the diluent ranges from 20 to 40 %, and that of the disintegrant ranges from 3 to 10 %, the remainder being accounted for by one or more of the excipients described hereinabove. As an example of an oral dosage form comprising 200 mg of loviride, the following formula may be given :

loviride (200 mg)
HPMC 2910 5 mPa.s (300 mg)
spray-dried lactose monohydrate : microcrystalline cellulose (75 : 25) (282.4 mg)
crospolyvidone (78.4 mg)
talc (25.8 mg)
hydrogenated vegetable oil Type I (8.6 mg)
colloidal anhydrous silica (2.6 mg)
magnesium stearate (2.2 mg), yielding
a tablet core (900 mg), and

HPMC 2910 5 mPa.s (16 mg)
propyleneglycol (4 mg)
talc (3.2 mg)
titanium dioxide (4.8 mg), yielding
a film-coat (28 mg).

Preferred dosage forms according to the present invention are those from which at least 85 % of the available loviride dissolves within 60 minutes when a dosage form equivalent to 200 mg loviride is tested as set forth in USP test ⟨711⟩ in a USP-2 dissolution apparatus under conditions at least as stringent as the following : 900 ml water comprising 0.5 % sodium lauryl sulfate, 37°C with paddles turning at 100 rpm. Tablets complying with the preceding definition can be said to have Q > 85 % (60'). Preferably, tablets according to the present invention will dissolve faster and have Q > 85 % (30').

The present invention further concerns a process of preparing particles as described hereinbefore, characterized by blending the components, extruding said blend at a temperature in the range of 120 - 300 °C, grinding the extrudate, and optionally sieving the particles.

The invention also concerns solid dispersions obtained by melt-extrusion of

(a) loviride, or one of its enantiomers, or a mixture of its two enantiomers, and
(b) one or more pharmaceutically acceptable water-soluble polymers.

It is another object of the invention to provide a process of preparing a pharmaceutical dosage form as described hereinbefore, characterized by blending a therapeutically effective amount of particles as described hereinbefore, with pharmaceutically acceptable excipients and compressing said blend into tablets.

The invention also relates to particles as described hereinbefore, for use in preparing a pharmaceutical dosage form for oral administration to a patient suffering from a retroviral infection, wherein said dosage form can be administered at any time of the day independently of the food taken in by said patient.

The present invention also concerns the use of particles as described hereinbefore, for the preparation of a pharmaceutical dosage form for oral administration to a patient suffering from a retroviral infection, wherein said dosage form can be administered at any time of the day independently of the food taken in by said patient.

The invention also relates to a pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form of loviride as described hereinbefore, and associated with said package written matter non-limited as to whether the dosage form can be taken with or without food.

It has been observed that the tablets of the present invention showed a remarkably lower food-effect than loviride capsules. This means that the difference between taking the medication after a meal or in fasted state is significantly less when the tablet of the present invention is administered than when loviride capsules are administered. This is of course a huge advantage because the medication can be taken in at any time during the day and is no longer dependent upon the intake of a meal. Moreover, patients, who are feeling nauseous or who are not able to eat can still take the tablets of the present invention.

Example 1

a) melt extrusion process

A 40/60 (w/w) mixture of loviride (0.5 kg) and HPMC 2910 5 mPa.s (0.75 kg) were both sieved and mixed in a planetary mixer until the mixture was homogenous.

The mixture was fed into a twin screw melt extruder of the type APV-Baker MP19 L/D 15 having the following operating parameters : temperature of the first compartment was 225°C, temperature of the second compartment was 235°C, the twin screw had a rate of 250 revolutions/min and was extruded at a fedd rate of 1.5 kg/h. The extrudate was brought in a hammer mill of type Fitzmill, the mesh of the sieve was 0.125 inch (= 0.32 cm) and revolving speed was 1640 revolutions per minute. The milled extrudate was again brought in a hammer mill, this time with a sieve of mesh 0.063 inch (= 0.16 cm) and a revolving speed of 1640 revolutions per minute. Yield was 1.03 kg (82.4 %).

b) preparation of a tabletting mixture

Microcrystalline cellulose (90.2 g, 24.4 % (w/w)), Crospovidone (25 g, 6.8 % (w/w)), Aerosil (colloidal silicon dioxide) (1.1 g, 0.3 % (w/w)) and Sterotex (3.7 g, 1 % (w/w)) were sieved (mesh width of 850 μm) and mixed together with the milled extrudate (250 g, 67.6 % (w/w)) using a planetary mixer until a homogenous mixture was obtained (10 minutes).

c) Tabletting

Using the mixture obtained in b) round biconvex tablets of 370 mg (die diameter = 10 mm, radius of curvature = 15 mm) were prepared on a Korsch II operating at a speed of 10,000 tablets/hour, a compression pressure of 1500 to 1950 kg /cm^2 (147 - 191.1 MPa). The uncoated tablets had a disintegration time of less than 1 minute in neutral water and hardness = 6.23 daN. The tablets were coated with a coating solution comprising HPMC 2910 5 mPa.s (40 g), propylene glycol (10 g), titanium dioxide (12 g) and tale (8 g) in water (400 g) according to art-known procedures.

Example 2

The process as described in example 1 was repeated, but the blending and tabletting steps were carried out as follows :

Microcelac (141.2 g, 31.4 % (w/w)), Crospovidone (39.2 g, 8.7 % (w/w)) and Aerosil (colloidal silicon dioxide) (1.3 g, 0.3 % (w/w)) were sieved (mesh width of 850 µm) and mixed together with the milled extrudate (250 g, 55.6 % (w/w)) using a planetary mixer until a homogenous mixture was obtained (10 minutes). Then there was added tale (12.9 g, 2.9 % (w/w)), magnesium stearate (1.1 g, 0.24 % (w/w)) and Sterotex (4.3 g, 1 % (w/w)) and the whole was mixed for another 5 minutes. The blend was tabletted on a Korsch II to round bieonvex tablets of 450 mg (die diameter 11.5 mm, radius of curvature = 15 mm). The tablets were coated with a coating solution comprising HPMC 2910 5 mPa.s (40 g), propylene glycol (10 g), titanium dioxide (12 g) and talc (8 g) in water (400 g) according to art-known procedures.

Example 3

The process as described in example 1 was repeated, but the blending and tabletting steps were carried out as follows :

Microcelac (282.4 g, 31.4 % (w/w)), Crospovidone (78.4 g, 8.7 % (w/w)) and Aerosil (colloidal silicon dioxide) (2.6 g, 0.3 % (w/w)) were sieved (mesh width of 850 µm) and mixed together with the milled extrudate (500 g, 55.6 % (w/w)) using a planetary mixer until a homogenous mixture was obtained (10 minutes). Then there was added tale (25.8 g, 2.9 % (w/w)), magnesium stearate (2.2 g, 0.24 % (w/w)) and Sterotex (8.6 g, 1 % (w/w)) and the whole was mixed for another 5 minutes. The blend was tabletted on a Excenterpress Courtoy 27 to oblate biconvex tablets of 900 mg. The length of the die was 19 mm, breadth 9.5 mm, and the radius of curvature 9.57 mm. The tablets were coated with a coating solution comprising HPMC 2910 5 mPa.s (40 g), propylene glycol (10 g), titanium dioxide (12 g) and talc (8 g) in water (400 g) according to art-known procedures.

Example 4 : Dissolution Properties

In-vitro dissolutions studies were performed on the 100 mg tablet formulation of Example 1. The medium was 900 ml water comprising 0.5 % sodium lauryl sulfate at 37°C in Apparatus 2 (USP 23, ⟨711⟩ Dissolution, pp. 1791-1793) (paddle, 100 rpm). The concentration of the active ingredient loviride dissolved in the test medium was determined by removing a 3 ml sample at the indicated time, measuring its absorbance at 266 nm and calculating the concentration therefrom.

The following results were obtained :

Time (min)	Calculated concentration (% w/w) of the active dose						
	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10	84.1	66.3	82.3	83.7	80.5	82.4	79.9
30	100.4	96	100.0	101.5	97.4	97.1	98.8
45	102.6	102.6	103.1	103.9	100.0	99.8	102.0
60	102.1	102.3	103.0	103.3	99.8	99.7	101.7
90	102.9	103.6	104.0	104.1	100.7	99.9	102.5

Example 5 : Pharmacokinetic properties

In this study 12 healthy volunteers in fasting conditions were administered a tablet of example 1 (100 mg loviride). Plasma levels of each of the loviride enantiomers were determined and the following bioavailability data were calculated therefrom.

(-)-loviride : C_{max} = 155 ± 66 ng/ml
AUC_{last} = 1,347 ± 512 ng.h/ml

(+)-loviride : C_{max} = 890 ± 292 ng/ml
AUC_{last} = 18,180 ± 7,197 ng.h/ml

Claims

1. A particle consisting of a solid dispersion comprising

   (a) loviride, or one of its enantiomers, or a mixture of its two enantiomers, and
   (b) one or more pharmaceutically acceptable water-soluble polymers.

2. A particle according to claim 1 having a particle size of less than 600 μm.

3. A particle according to claim 1 or 2 wherein the loviride is in a non-crystalline phase.

4. A particle according to claim 3 wherein the solid dispersion is in the form of a solid solution comprising (a) and (b), or in the form of a dispersion wherein amorphous or microcrystalline (a), or amorphous or microcrystalline (b), or both, are dispersed more or less evenly in another phase of (b), or of (a), or in a solid solution comprising (a) and (b).

5. A particle according to the preceding claims wherein the water-soluble polymer is a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution.

6. A particle according to claim 5 wherein the water-soluble polymer is selected from the group comprising

   - alkylcelluloses such as methylcellulose,
   - hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose,
   - hydroxypropylcellulose and hydroxybutylcellulose,
   - hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
   - carboxyalkylcelluloses such as carboxymethylcellulose,
   - alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
   - carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
   - carboxyalkylcellulose esters,
   - starches,
   - pectines such as sodium carboxymethylamylopectine,
   - chitine derivates such as chitosan,
   - polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,
   - polyacrylic acids and the salts thereof,
   - polymethacrylic acids and the salts thereof, methacrylate copolymers,
   - polyvinylalcohol,
   - polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate
   - polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

7. A particle according to claim 6 wherein the water-soluble polymer is hydroxypropyl methylcellulose HPMC 2910 5 mPa.s.

8. A particle according to claim 7 wherein the weight-by-weight ratio of (a) : (b) is in the range of 1 : 1 to 1 : 8.

9. A particle according to any one of the preceding claims obtainable by melt-extrusion of the components and grinding, and optionally sieving.

10. A particle according to any one of the previous claims consisting of a solid dispersion comprising two parts by weight of loviride and three parts by weight of hydroxypropyl methylcellulose HPMC 2910 5 mPa.s, obtainable by blending said components, extrading the blend at a temperature in the range of 120°C - 300°C, grinding the extrudate, and optionally sieving the thus obtained particles.

11. A particle according to the preceding claims further comprising one or more pharmaceutically acceptable excipients.

12. A pharmaceutical dosage form comprising a therapeutically effective amount of particles as claimed in any one of the preceding claims.

13. A dosage form according to claim 12 adapted for oral administration shaped as a tablet.

14. A dosage form according to claim 12 for immediate release of loviride upon oral ingestion wherein said particles are homogeneously distributed throughout a mixture of a diluent and a disintegrant.

15. A dosage form according to claim 13 or 14 surrounded by a film-coat comprising a film-forming polymer, a plasticizer and optionally a pigment.

16. A dosage form according to claim 14 wherein the diluent is a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75 : 25), and the disintegrant is crospovidone or croscarmellose.

17. A dosage form according to any one of claims 12 to 16 wherein the weight of said particles is at least 40 % of the total weight of the dosage form.

18. A dosage form according to claim 12 comprising by weight based on the total weight of the dosage form :

loviride (200 mg)
HPMC 2910 5 mPa.s (300 mg)
spray-dried lactose monohydrate : microcrystalline cellulose (75 : 25) (282.4 mg)
crospolyvidone (78.4 mg)
talc (25.8 mg)
hydrogenated vegetable oil Type I (8.6 mg)
colloidal anhydrous silica (2.6 mg)
magnesium stearate (2.2 mg), yielding
a tablet core (900 mg), and
HPMC 2910 5 mPa.s (16 mg)
propyleneglycol (4 mg)
talc (3.2 mg)
titanium dioxide (4.8 mg), yielding
a film-coat (28 mg).

19. A dosage form according to any one of claims 12 to 18 from which at least 85 % of the available loviride dissolves within 60 minutes when a dosage form equivalent to 200 mg loviride is tested as set forth in USP test ⟨711⟩ in a USP-2 dissolution apparatus under conditions at least as stringent as the following : 900 ml water comprising 0.5 % sodium lauryl sulfate, 37°C with paddles turning at 100 rpm.

20. A process of preparing particles as claimed in any one of claims 1 to 11 characterized by blending the components, extruding said blend at a temperature in the range of 120 - 300 °C, grinding the extrudate, and optionally sieving the particles.

21. A solid dispersion obtained by melt-extrusion of

(a) loviride, or one of its enantiomers, or a mixture of its two enantiomers, and
(b) one or more pharmaceutically acceptable water-soluble polymers.

22. A process of preparing a pharmaceutical dosage form as claimed in any one of claims 12 to 19 characterized by blending a therapeutically effective amount of particles as claimed in any one of claims 1 to 11 with pharmaceutically acceptable excipients and compressing said blend into tablets.

23. Particles according to any one of claims 1 to 11 for use in preparing a pharmaceutical dosage form for oral administration to a patient suffering from a retroviral infection, wherein said dosage form can be administered at any time of the day independently of the food taken in by said patient.

24. Use of particles according to any one of claims 1 to 11 for the preparation of a pharmaceutical dosage form for oral administration to a patient suffering from a retroviral infection, wherein said dosage form can be administered at any time of the day independently of the food taken in by said patient.

25. A pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form of loviride as claimed in any one of claims 12 to 19, and associated with said package written matter non-limited as to whether the dosage form can be taken with or without food.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 20 1100

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A,D	WO 92 00952 A (JANSSEN) * claims * * page 19, line 23 - page 20, line 17 *	1-25	A61K9/14 A61K9/20
A	WO 94 18963 A (JANSSEN) * the whole document *	1-25	
A	WO 96 00068 A (MERCK) * the whole document *	1-25	
A	WO 96 01110 A (JANSSEN) * the whole document *	1-25	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

A61K

The present search report has been drawn up for all claims

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(54) **ZUBEREITUNG IN FORM EINES WAHLWEISE WIRKSTOFFHALTIGEN MATRIXMATERIAL-HILFSSTOFF COMPOUNDS**

PREPARATION IN FORM OF A MATRIX MATERIAL-AUXILIARY AGENT COMPOUND CONTAINING OPTIONALLY AN ACTIVE SUBSTANCE

PREPARATION SOUS FORME D'UN COMPOSE MATERIAU MATRICIEL-MATIERE AUXILIAIRE RENFERMANT EVENTUELLEMENT UNE MATIERE ACTIVE

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Beschreibung

[0001] Die Erfindung bezieht sich auf eine Zubereitung in Form eines Compounds gemäß Anspruch 1 oder 2, die eine Hilfsstoffphase mit wenigstens einem Hilfsstoff und/oder eine Wirkstoffphase mit wenigstens einem Wirkstoff und eine Phase eines matrixbildenden Materials (im folgenden auch Matrixmaterial genannt) ausgewählt aus Polymer und/oder Lipid, d.h. eine polymere Phase und/oder eine Lipidphase mit wenigstens einem Polymer bzw. Lipid aufweist, und damit auf polymer- und/oder lipidhaltige Retardarzneiformen, Verfahren zu deren Herstellung und deren Verwendung, insbesondere zur Herstellung von Tabletten oder anderen größeren Matrixeinheiten.

[0002] Derartige Compounds sind physikalische Verbindungen von mindestens zwei Ausgangsstoffen und werden insbesondere im pharmazeutischen Bereich eingesetzt.

[0003] Es ist bekannt, zur Erreichung einer kontrollierten, verzögerten oder von physiologischen Parametern unabhängigen Freisetzung von

[0004] Wirkstoffen aus einer Zubereitung, die Ausgangsstoffe derart zu verarbeiten, daß die resultierenden Zubereitungen bzw. die aus diesen Zubereitungen hergestellten Arnzeiformen einen die Freisetzung steuernden Überzug aufweisen (z.B. aus Polymeren wie Polymethacrylate oder organischen Molekülen wie Schellack oder Celluloseacetatphthalat) bzw. alternativ ein aus Polymeren bestehendes Matrixsystem aufweisen.

[0005] Unter Verwendung von Polymeren hergestellte, in der Literatur beschriebene Matrixeinheiten zur kontrollierten Freisetzung sind:

1. Polymerpartikel
(z.B. Pellets, Granulatkörner, Mikropartikel)
2. größere Matrixeinheiten
(z.B. Tabletten, Drageekerne und Implantate).

[0006] Die im folgenden näher beschriebenen Partikel sind dadurch gekennzeichnet, daß der Wirkstoff molekulardispers oder partikulär in der polymeren Phase eingebettet ist.

[0007] Die im folgenden näher beschriebenen größeren Matrixeinheiten müssen in der Regel durch das kostenaufwendige Verfahren der Komprimierung nach vorheriger Granulation hergestellt werden.

Arzneiformen zur kontrollierten Freisetzung unter Verwendung von Polymeren:

[0008] Der die Freisetzung kontrollierende Effekt einer solchen Zubereitung oder Arnzeiform, auch "Controlled Release"-Zubereitung (CR-Zubereitung) genannt, wird einerseits durch die Eigenschaften der polymeren Phase selbst, wie beispielsweise die Benetzbarkeit, die Quellbarkeit oder die Kristallinität, und andererseits durch die Struktur der durch die polymere Phase gebildeten Matrix gesteuert. Diese Matrixstruktur, die homogen oder heterogen ausgebildet sein kann, ist entweder bereits in der Zubereitung selbst vorhanden oder entsteht während der Verarbeitung bei der Zubereitung zur Arzneiform.

[0009] Als die Freisetzung beeinflussende Eigenschaften der polymeren Phase seien hier die Löslichkeitseigenschaften genannt. So sind Polymere bzw. Makromoleküle aufgrund ihrer Unlöslichkeit und/oder Quellbarkeit in wäßrigen Lösungsmitteln geeignet, Wirkstoffe, die in einer Matrix solcher Polymere bzw. Makromoleküle eingebettet sind, durch die Poren der Matrix verzögert freizusetzen. Weiterhin sind Arzneiformen mit Polymerstoffen bekannt, die aufgrund der Löslichkeit der Polymere im Magen- oder Darmsaft eine den Ort der Freisetzung kontrollierende Zubereitung darstellen.

[0010] Bei diesen die Wirkstofffreisetzung kontrollierenden Zubereitungen sind insbesondere zwei Gruppen zu unterscheiden.

[0011] Einerseits sind polymerhaltige Partikel in einer Größenordnung von ca. 0,01 bis 2 mm bekannt, die auch als Mikropartikel (0,05 bis 0,2 mm), Granulatkörner oder Pellets bezeichnet werden. Aber auch die erst seit kürzerer Zeit bekannten Mikropartikel bzw. Mikrosphärulen mit einer typischen Größe von 50 bis 200 µm, Nanopartikel, Nanopellets und Nanosphärulen werden, sofern sie eine polymere Phase aufweisen, der Gruppe der polymerhaltigen Partikel zugeordnet. Die Partikel liegen als eigenständige Freisetzungseinheit in Form einer partikulären Matrix vor, wobei dann bereits die Zubereitung eine Matrixstruktur aufweist.

[0012] Andererseits können die in der vorliegenden Anmeldung beschriebenen Partikel zu größeren Freisetzungseinheiten bzw. größeren Matrixeinheiten vereinigt werden. Diese Weiterverarbeitung wird weiter unten im einzelnen ausgeführt.

[0013] Als Beispiele der partikulären Matrices, deren Partikel eigenständige Freisetzungseinheiten bilden, seien die Dispersion von Mikropartikeln zur parenteralen Injektion, die eine kontrollierte Freisetzung von LH-RH-Analoga erlauben, sowie die Füllung von Pellets in eine Gelatinekapsel bei Handelspräparaten wie Sympathomimetika genannt. Diese werden von Müller, R.H., Hildebrand G.E. (Hrsg.) in "Pharmazeutische Technologie: Moderne Arzneiformen", Wissenschaftliche Verlagsgesellschaft mbh Stuttgart, (1997), von Bauer, K.H., Frömming, K-H., Führer, C. in "Pharmazeutische Technologie"; Georg Thieme Verlag Stuttgart, New York, (1991), sowie von List, P.H. "Arzneiformenlehre" Wissenschaftliche Verlagsgesellschaft mbh Stuttgart, (1986), beschrieben.

[0014] Weiterhin sind in der EP 0 261 677 polymerhaltige Zusammensetzungen beschrieben, die eine verzögerte Freisetzung des Wirkstoffs ermöglichen sollen. Zur Herstellung dieser Zusammensetzungen wird ein Sprühtrocknungsverfahren offenbart, so daß unter Anwendung der Lehre dieser Druckschrift Partikel mit einer

Größe von mindestens 30 µm erhalten werden, die den Wirkstoff in gleichmäßiger Verteilung aufweisen.

[0015] Zur Herstellung solcher Zubereitungen mit partikulärer Matrixstruktur werden in der Literatur mehrere Verfahren beschrieben.

[0016] Bei den Verfahren nach der "solvent evaporation"- oder der "inliquid-drying"-Methode ist das Polymer bzw. der Matrixbildner eine in einem organischen Lösungsmittel lösliche Substanz (z.B. Polymere wie Polylactide, Polylactid/Glycolid). Das Polymer wird in einem organischen Lösungsmittel gelöst, der Wirkstoff wird ebenfalls in der organischen Phase gelöst oder - im Falle unlöslicher Wirkstoffe - dispergiert. Die den Wirkstoff enthaltende Lösung des Polymers bzw. Matrixbildners wird dann in eine wäßrige Tensidlösung gegeben und durch Rühren eine O/W-Emulsion hergestellt. Das organische Lösungsmittel wird dann entfernt und der Matrixbildner präzipitiert. Es entstehen feste Pellets bzw. Mikropartikel. Je nach der Methode zur Entfernung des Lösungsmittels unterscheidet man zwischen der "solvent evaporation"und der "in-liquid-drying"-Methode.

[0017] Diese Verfahren wurden von Speiser, P. in Müller, R.H., Hildebrand, G.E. (Hrsg.) "Pharmazeutische Technologie: Moderne Arzneiformen", Wissenschaftliche Verlagsgesellschaft mbh Stuttgart (1997), von Beck, L.R., Pope, V.Z., Cowsar, D.R., Lewis, D.H., Tice, T.R. in "Evulation of a new three-month injectable contraceptive microsphere system in primates (baboons)", Contracept. Deliv.1 Syst., 1, 79-80 (1980), von Beck, L. R., Flowers, C.E., Pope, V.Z., Tice, T.R. Wilborn, W.H. in "Clinical evaluation of an improved injectable microcapsule contraceptive system" in Amer. J. Obstet. Gynecol. 147 (7), 815-821 (1983) und von Beck, L.R., Pope, V.Z., Flowers, C.E., Cowsar, D.R., Tice, T.R., Lewis, D.H., Dunn, R.L., Moore, A.B., Gilley, R.M. in "Poly (d,l-lactide-coglycolide)/norethisterone microcapsules: An injectable biogradable contraceptive" in Biol. Reprod. 28, 186-195 (1983a) beschrieben.

[0018] Mit diesen Verfahren können sehr feine Partikel im Bereich von wenigen Mikrometern erhalten werden. Nachteilig ist jedoch der große Aufwand, mit dem die Herstellungsmethode verbunden ist, sowie die Belastung der Partikel mit Restlösungsmittel. Aus diesem Grund gibt es auch bisher in Deutschland noch kein Produkt, das nach einer dieser Verfahren hergestellt worden ist und die Zulassungskriterien für ein Arzneimittel erfüllt.

[0019] Alternativ kann man die den Wirkstoff enthaltende Lösung des Polymers bzw. des Matrixbildnersversprühen. Auch hier ist ein Restgehalt an organischen Lösungsmitteln im Produkt aufgrund des Herstellungsverfahrens nicht zu vermeiden. Nach diesem Verfahren hergestellte Produkte, wie z.B. Mikropartikel zur parenteralen Applikation von Bromocriptin, werden von Fahr, A., Kissel, T. in Müller, R.H., Hildebrand, G.E. (Hrsg.), "Pharmazeutische Technologie: Moderne Arzneiformen", Wissenschaftliche Verlagsgesellschaft mbh Stuttgart, (1997) beschrieben. Sie sind auf dem pharmazeutischen Markt. Das Problem des Restlösungsmittelgehalts ist jedoch nur dadurch verdrängt worden, daß hier auch die Freisetzung des toxischen Lösungsmittels verzögert und damit in geringer Menge erfolgt. Mit der pro Tag aus der Matrix freigegebenen Menge bleibt man unter dem maximalen täglich tolerierten Wert.

[0020] Alle bisher genannten Verfahren sind dadurch gekennzeichnet, daß die polymere Phase bzw. der Matrixbildner in einer gelösten Form als Molekül vorliegt und sich in einem organischen Lösungsmittel befindet. Es entstehen partikuläre Zubereitungen, deren polymere Phase den Wirkstoff molekulardispers oder in Form feiner Partikel enthält. Diese Zubereitungen weisen eine sogenannte heterogene Matrixstruktur auf, wie auch von Fahr, A., Kissel, T. in Müller, R.H., Hildebrand, G.E. (Hrsg.), "Pharmazeutische Technologie: Moderene Arnzeiformen", Wissenschaftliche Verlagsgesellschaft mbh Stuttgart, (1997) beschrieben ist.

[0021] Ein weiteres Verfahren zur Herstellung einer partikulären Zubereitung mit polymerer Phase unter Vermeidung der Verwendung von organischen Lösungsmittel wird in der EP 0 361 677 dargestellt. Der nach dieser Druckschrift wasserlösliche Matrixbildner bzw. die polymere Phase wird in Wasser gelöst (z.B. Ethylacrylat/Methacrylat-Copolymer in ammoniakalischer Lösung), der Wirkstoff wird ebenfalls gelöst oder dispergiert und - im Gegensatz zur "solvent evaporation"- und "in liquid-drying"-Methode - anstatt einer O/W - nun eine W/O-Emulsion hergestellt. Dispersionsmedien sind mit Wasser nicht mischbare organische Lösungsmittel, z.B. flüssiges Paraffin oder Methylenchlorid. Der Matrixbildner kann in Wasser gelöst oder auch in der Wasserphase emulgiert werden. Im zweiten Fall wird eine Emulsion in einem mit Wasser nicht mischbaren organischen Lösungsmittel dispergiert. Durch aufwendige azeotrope Destillation von Wasser und organischem Lösungsmittel werden Polymerpartikel ausgefällt, die den Wirkstoff in molekulardisperser oder partikulärer Verteilung einschließen. Die Gewinnung der Partikel erfolgt durch Separation mittels Filtration und anschließendes Waschen.

[0022] In der US-A-5 043 280 wird ein Verfahren zur Herstellung einer partikulären Zubereitung durch Extraktion in überkritischen Gasen beschrieben. Hierbei ist der Matrixbildner - wie bei der "solvent evaporation" - eine in einem organischen Lösungsmittel lösliche Substanz, wie z.B. ein Polymer. Das Polymer wird in einem organischen Lösungsmittel gelöst, und der Wirkstoff wird ebenfalls gelöst oder - im Falle unlöslicher Wirkstoffe - in der organischen Phase dispergiert. Die den Wirkstoff enthaltende Lösung des Matrixbildners wird dann in einer überkritischen Gasphase fein versprüht. Feine Tropfen verteilen sich im überkritischen Gas, das das organische Lösungsmittel aus den Tropfen extrahiert. Als Folge kommt es zur Präzipitation von Partikeln, die den Wirkstoff enthalten.

[0023] Auch diese genannten Verfahren führen zu Zu-

bereitungen, die den Wirkstoff in molekulardisperser bzw. partikulärer Form in der polymeren Phase eingebettet aufweisen. Durch diesen verfahrensbedingten Einschluß des Wirkstoffs in die polymere Phase weist die Außenphase der Zubereitung größtenteils Polymer auf, wodurch auch die pharmazeutischen Eigenschaften, die für eine eventuelle Weiterverarbeitung von Bedeutung sind, festgelegt werden. Ferner weisen die genannten Zubereitungen den Nachteil auf, daß sie nur unter erheblichem Kosten- und Zeitaufwand herstellbar sind.

[0024] DE-A-35 06 276 offenbart ein Verfahren zur Herstellung von Direkttablettiermitteln, wobei Cellulosepulver mit einer heißen Lösung von 50%-iger Lactose in Wasser vermischt und die so erhaltene Mischung abgekühlt wird. Die so erhaltene Masse wird anschließend grannliert und getrocknet. Alternativ kann eine Mischung von mikrokristalliner Lactose mit Cellulose pulver in kattern Wasser aufgeschlämmt und anschließend sprühgetrocknet werden.

[0025] Die Möglichkeit der Weiterverarbeitung partikulärer, polymerhaltiger Zubereitungen zu Arzneiformen, die größere Matrixeinheiten aufweisen, wie beispielsweise zu Tabletten, Drageekernen oder Implantaten ist bekannt. So wird von Müller, R.H., Hildebrand, G. E. (Hrsg.) in Pharmazeutische Technologie: Moderne Arzneiformen", Wissenschaftliche Verlagsgesellschaft mbh Stuttgart, (1997), die Herstellung von LH-RH-Analoga enthaltenden Implantaten beschrieben. Von besonderer Bedeutung ist dabei die Herstellung von Tabletten, da diese Arzneiform viele Vorteile aufweist, wie beispielsweise die Möglichkeit zur Verarbeitung fast aller festen Wirkstoffe, die hohe Dosierungsgenauigkeit, die einfache Einnahme und Handhabung und die gute Lager- und Transportfähigkeit.

[0026] Die Herstellung von Arzneiformen, die größere Matrixeinheiten darstellen, und insbesondere von Tabletten, erfolgt üblicherweise durch Komprimierung. Dabei sind zur Verarbeitung der herkömmlichen polymerhaltigen Zubereitungen in Form der partikulären Matrices mehrere Verfahrensschritte notwendig.

[0027] Zuerst werden die verschiedenen Inhaltsstoffe, wie beispielsweise verschiedene Wirkstoffe, Hilfsstoffe und Polymere homogen vermischt. Anschließend wird die Mischung einer Feuchtgranulation durch Zusatz von Binde-, Kleb- oder Lösungsmitteln unterzogen. Das resultierende Granulat wird zum Entzug der Restfeuchte getrocknet. Die Komprimierung zu Tabletten, Drageekernen oder Implantaten erfolgt dann mit dem trockenen Granulat unter Zusatz von weiteren Hilfsstoffen, wie Fließregulierungs-, Schmier- und Formtrennmitteln.

[0028] Nachteilig ist, daß der Wirkstoff während der Feuchtgranulation über lange Zeit der Feuchtigkeit des Binde-, Kleb- oder Lösungsmittels ausgesetzt wird und während des notwendigen Trocknungsverfahrens zwingend einer erhöhten Temperatur ausgesetzt wird. Weiterhin ist das Verfahren aufgrund der verschiedenen Einzelschritte und hierbei benötigter Vorrichtungen und Geräte mit relativ großem Zeitaufwand verbunden und somit kostenintensiv.

[0029] Die Direkttablettierung von Zubereitungen mit polymeren Bestandteilen, die zur Herstellung von Tabletten ohne polymere Phase aufgrund der niedrigen Kosten und der schnellen Durchführbarkeit bereits häufig angewendet wird, ist bisher aufgrund folgender Schwierigkeiten nicht möglich gewesen.

[0030] Zum einen weisen die Polymere durch überwiegend elastische Verformung ein schlechtes Komprimierverhalten auf, da eine Komprimierung üblicherweise hauptsächlich durch plastische Verformung erreicht wird.

[0031] Zum anderen neigt die Tablettiermischung zu einer unerwünschten Entmischung zwischen pulverisierten Wirkstoffen und/oder Hilfsstoffen und Polymeren aufgrund der unterschiedlichen Oberflächenbeschaffenheit und der daraus resultierenden unterschiedlichen Fließeigenschaften. Bei der Direkttablettierung würden daher durch die fortschreitende Entmischung des Tablettierguts stark inhomogene Tabletten erhalten werden.

[0032] Ein weiteres Problem ist das allgemein schlechte Fließverhalten der Polymere. Dies hat zur Folge, daß ein zufriedenstellender Retardeffekt durch die begrenzte Beimischungsfähigkeit von Polymeren zur Tablettiermischung nicht erreicht wird. In der Literatur wird von McGinity, J.W., Cameron, C.G., Cuff. G.W. in "Controlled-release teophylline tablet formulations containing acrylic resins. I. Dissolution properties of tablets", Drug Development and Industrial Pharmacy, 9 (162), 57-68 (1983) und von Cameron, C.G., McGinity, J.W. in "Controlled-release teophylline tablet formulations containing acrylic resins. II. Combination resin formulations" und "III. Influence of filler excipient"., a.a.O. 13(8), 1409-1427 (1987), a.a.O. 13(2), 303-318 (1987) bei Acrylatpolymeren ein in der Regel maximaler Zusatz von 10 - 15% Polymer in einer Tablettenrezeptur zur Direkttablettierung beschrieben.

[0033] Es sind aber auch Retardarzneiformen bekannt, in denen Lipide verwendet werden. Bei solchen in der Literatur beschriebenen Arzneiformen zur kontrollierten Freisetzung unter Verwendung von Lipiden handelt es sich im wesentlichen um:

1. Suppositorien
2. Vaginalglobuli
3. Pellets zur peroralen Applikation (z.B. Mucosolvan retard).

[0034] Im Vergleich zu Polymeren bieten Lipide folgende Vorteile:

1. gute Verträglichkeit in vivo, insbesondere wenn sie aus physiologischen Fettsäuren aufgebaut sind
2. keine toxikologisch bedenklichen Rückstände aus der Produktion (z.B. Katalysatorrückstände)

3. Steuerung der Abbaugeschwindigkeit über chemische Struktur der Lipide
4. kostengünstig

[0035] Somit sind sie neben Polymeren zur Herstellung von CR-Formulierungen einsetzbare Hilfsstoffe.

Arzneiformen zur kontrollierten Freisetzung unter Verwendung von Lipiden - Zubereitungen aus Compounds:

[0036] Die Herstellung von Suppositorien und Vaginalglobuli erfolgt in der Regel durch Ausgießen der arzneistoffhaltigen Mischung (P.H. List, Arzneiformenlehre, Wissenschaftliche Verlagsgesellschaft 1976).

[0037] Die Herstellung von Suppositorien ist auch durch Komprimieren einer Mischung von Lipidpartikeln und Arzneistoffpulver möglich, eine großtechnische Herstellung bereitet jedoch aufgrund der in der Regel schlechten Fließfähigkeit dieser Mischungen beim Abfüllen in die Preßformen Schwierigkeiten. Primär wird diese Methode daher für die Kleinherstellung im Rezepturmaßstab in der Apotheke beschrieben (K. Münzel, J. Büchi, O.-E. Schultz, Galenisches Praktikum, Wissenschaftliche Verlagsgesellschaft Stuttgart, S. 652, 1959). Eingesetzt werden dabei nur Lipide die bei Körpertemperatur schmelzen oder zumindest erweichen.

[0038] Arzneiformen zur peroralen Applikation sind Pellets, die großtechnisch durch Extrusion geschmolzener Lipide mit einem Extrudor und einer Lochscheibe hergestellt werden (Voigt, Lehrbuch der Pharmazeutischen Technologie, Verlag Chemie, 1975). Nachteilig sind hierbei z.B. die Einarbeitung der Arzneistoffe in das Lipid (z.B. durch Dispergieren oder Lösen), die Thermobelastung der Arzneistoffe bei der Extrusion und die Notwendigkeit der Weiterverarbeitung der Pellets in einem zusätzlich Produktionsschritt (z.B. Einfüllung in Hartgelatinekapseln).

[0039] Die Aufgabe der vorliegenden Erfindung liegt nun darin, eine Zubereitung in Form eines matrixmaterialhaltigen Compounds als Retardarzneizubereitungen zu Verfügung zu stellen, die eine Hilfsstoff- und/oder eine Wirkstoffphase und eine Matrixmaterialphase aufweist. Die Zubereitung soll einen ausreichend großen Matrixmaterialanteil aufweisen, so daß eine kontrollierte Freisetzung des enthaltenen oder bei einer Verarbeitung zu größeren Matrixeinheiten nachträglich hinzugefügten Wirkstoffs ermöglicht wird. Außerdem soll die Zubereitung mittels Direkttablettierung zu größeren Matrixeinheiten verarbeitet werden können. Ferner soll ein Verfahren zur Herstellung dieser Zubereitung bzw. Compounds angegeben werden.

[0040] Die erfindungsgemäße Aufgabe wird durch eine matrixmaterialhaltige Retardarzneiform gelöst, die in Form eines Matrixmaterial-Hilfsstoff-Compounds, Matrixmaterial-Wirkstoff-Compounds und/oder Matrixmaterial-Hilfsstoff-Wirkstoff-Compounds vorliegen, wobei das Matrixmaterial ausgewählt ist aus Polymeren und Lipiden, so daß der Compound eine polymere Phase und/oder Lipidphase und eine Hilfsstoff- und/oder eine Wirkstoffphase aufweist.

[0041] Ein solcher Compound kann durch Direktkomprimierung in seine endgültige Arzneimittelform überführt werden.

[0042] Die Erfindung bezieht sich somit auf polymer- oder lipidhaltige Zubereitungen, die

- in Form eines Compounds vorliegen, der eine polymere bzw. lipide Phase mit wenigstens einem Polymer bzw. Lipid, eine Hilfsstoffphase mit wenigstens einem Hilfsstoff und/oder eine Wirkstoffphase mit wenigstens einem Wirkstoff aufweist.

[0043] Erfindungsgemäß ist erkannt worden, daß die Lösung der Aufgabe durch die in Anspruch 1 beschriebene Zubereitung möglich ist, die

a) eine Hilfsstoffphase mit wenigstens einem Hilfsstoff und/oder eine Wirkstoffphase mit wenigstens einem Wirkstoff und eine polymere Phase mit wenigstens einem Polymer aufweist, wobei die polymere Phase inkohärent ist und die Hilfs- und/oder Wirkstoffphase kohärent ist, oder

b) eine Lipidphase mit wenigstens einem Lipid, eine Hilfsstoffphase mit wenigstens einem Hilfsstoff und/oder eine Wirkstoffphase mit wenigstens einem Wirkstoff aufweist, wobei die Lipid-phase inkohärent ist und die Hilfs- und/oder Wirkstoffphase kohärent ist.

[0044] Insbesondere kann die Polymerphase bzw. die Lipidphase Hilfsund/oder Wirkstoff enthält oder frei davon sein.

[0045] Bei der erfindungsgemäßen Zubereitung kann der Anteil an polymerphase bzw. Lipidphase bezogen auf die Gesamtmenge von Hilfsstoff- und/oder Wirkstoffphase und Polymerphase bzw. Lipidphase zwischen 1 und 98% betragen.

[0046] Insbesondere kann die Zubereitung einen Anteil an Polymer-/Lipidphase von 10 bis 95% aufweisen.

[0047] Ferner kann der Anteil der Polymer-/Lipidphase in der Zubereitung mehr als 15% und höchstens 90% betragen.

[0048] Besonders vorteilhaft zur Ausführung der vorliegenden Erfindung ist es aber, wenn die Polymer-/Lipidphase einen Anteil von 40 bis 70% bezogen auf die Gesamtmenge von Hilfsstoff- und/oder Wirkstoffphase und Polymer-/Lipidphase aufweist.

[0049] Die erfindungsgemäße Zubereitung kann grundsätzlich jede Art von Wirkstoff aufweisen oder frei von Wirkstoff sein. Ferner kann der Wirkstoff der Zubereitung nachträglich, z.B. vor einer Weiterverarbeitung zu größeren Matrixeinheiten zugesetzt werden. Im allgemeinen kann die Zubereitung folgende Wirkstoffgruppen enthalten:

- hydroxylierte Kohlenwasserstoffe
- Carbonylverbindungen wie Ketone (z.B. Haloperidol), Monosaccharide, Disaccharide und Aminozucker
- Carbonsäuren wie aliphatische Carbonsäuren, Ester aliphatischer und aromatischer Carbonsäuren, basisch substituierte Ester aliphatischer und aromatischer Carbonsäuren (z.B. Atropin, Scopolamin), Lactone (z.B. Erythromycin), Amide und Imide aliphatischer Carbonsäuren, Aminosäuren, aliphatische Aminocarbonsäuren, Peptide (z.B. Ciclosporin), Polypeptide, β-Lactamderivate, Penicilline, Cephalosporine, aromatische Carbonsäuren (z. B. Acetylsalicylsäure), Amide aromatischer Carbonsäuren, vinyloge Carbonsäuren und vinyloge Carbonsäureester
- Kohlensäurederivate wie Urethane und Thiourethane, Harnstoff und Harnstoffderivate, Guanidinderivate, Hydantoine, Barbitursäurederivate und Thiobarbitursäurederivate
- Nitroverbindungen wie aromatische Nitroverbindungen und heteroaromatische Nitroverbindungen
- Amine wie aliphatische Amine, Aminoglykoside, Phenylalkylamine, Ephedrinderivate, Hydroxyphenylethanolamine, Adrenalinderivate, Amfetaminderivate, aromatische Amine und Derivate, quartäre Ammoniumverbindungen
- schwefelhaltige Verbindungen wie Thiole und Disulfane, Sulfone, Sulfonsäureester und Sulfonsäureamide
- Polycarbocyclen wie Tetracycline, Steroide mit aromatischem Ring A, Steroide mit alpha,beta-ungesättigter Carbonylfunktion im Ring A und alpha-Ketol-Gruppe (oder Methylketo-Gruppe) am C-17, Steroide mit einem Butenolid-Ring am C-17, Steroide mit einem Pentadienolid-Ring am C-17 und Seco-Steroide
- O-haltige Heterocyclen wie Chromanderivate (z.B. Cromoglicinsäure)
- N-haltige Heterocyclen wie Pyrazolderivate (z.B. Propyphenazon, Phenylbutazon)
- Imidazolderivate (z.B. Histamin, Pilocarpin), Pyridinderivate (z.B. Pyridoxin, Nicotinsäure), Pyrimidinderivate (z.B. Trimetoprim), Indolderivate (z.B. Indometacin), Lysergsäurederivate (z.B. Ergotamin), Yohimbanderivate, Pyrrolidinderivate, Purinderivate (z.B. Allopurinol), Xanthinderivate, 8-Hydroxychinolinderivate, Amino-hydroxy-alkylierte Chinoline, Aminochinoline, Isochinolinderivate (z.B. Morphin, Codein), Chinazolinderivate, Benzopyridazinderivate, Pteridinderivate (z.B. Methotrexat), 1,4-Benzodiazepinderivate, tricyclische N-haltige Heterocyclen, Acridinderivate (z.B. Ethacridin) und Dibenzazepinderivate (z.B. Trimipramin)
- S-haltige Heterocyclen wie Thioxanthenderivate (z. B. Chlorprothixen)
- N,O- und N,S-haltige Heterocyclen wie monocyclische N,0-haltige Heterocyclen, monocyclische N, S-haltige Heterocyclen, Thiadiazinderivate, bicyclische N-S-haltige Heterocyclen, Benzothiadiazinderivate, tricyclische N,S-haltige Heterocyclen und Phenothiazinderivate
- O,P,N-haltige Heterocyclen (z.B. Cyclophosphamid)

[0050] Die folgenden Arzneistoffe (als Salz, Ester, Ether oder in freier Form) sind beispielsweise für eine Einarbeitung geeignet:

Analgetika/Antirheumatika
BTM Basen wie Morphin, Codein, Piritamid, Fentanyl und Fentanylderivate, Levomethadon, Tramadol, Diclofenac, Ibuprofen, Indometacin, Naproxen, Piroxicam, Penicillamin

Antiallergika
Pheniramin, Dimetinden, Terfenadin, Astemizol, Loratidin, Doxylamin, Meclozin, Bamipin, Clemastin

Antibiotika/Chemotherapeutika
hiervon: Polypeptidantibiotika wie Colistin, Polymyxin B, Teicplanin, Vancomycin; Malariamittel wie Chinin, Halofantrin, Mefloquin, Chloroquin, Virustatika wie Ganciclovir, Foscarnet, Zidovudin, Aciclovir und andere wie Dapson, Fosfomycin, Fusafungin, Trimetoprim

Antiepileptika
Phenytoin, Mesuximid, Ethosuximid, Primidon, Phenobarbital, Valproinsäure, Carbamazepin, Clonazepam

Antimykotika

a) intern:
Nystatin, Natamycin, Amphotericin B, Flucytosin, Miconazol, Fluconazol, Itraconazol
b) extern außerdem:
Clotrimazol, Econazol, Tioconazol, Fenticonazol, Bifonazol, Oxiconazol, Ketoconazol, Isoconazol, Tolnaftat

Corticoide (Interna)
Aldosteron, Fludrocortison, Betametason, Dexametason, Triamcinolon, Fluocortolon, Hydroxycortison, Prednisolon, Prednyliden, Cloprednol, Methylpredinsolon

Dermatika

a) Antibiotika:
Tetracyclin, Erythromycin, Neomycin, Gentamycin, Clindamycin, Framycetin, Tyrothricin, Chlortetracyclin, Mipirocin, Fusidinsäure
b) Virustatika wie oben, außerdem:

Podophyllotoxin, Vidarabin, Tromantadin
c) Corficoide wie oben, außerdem:
Amcinonid, Fluprednidien, Alclometason, Clobetasol, Diflorason, Halcinonid, Fluocinolon, Clocortolon, Flumetason, Diflucortolon, Fludroxycortid, Halometason, Desoximetason, Fluocinolid, Fluocortinbutyl, Fluprednidien, Prednicarbat, Desonid

Diagnostika

a) radioaktive Isotope wie Te99m, In111 oder I131, kovalent gebunden an Lipide oder Lipoide oder andere Moleküle oder in Komplexen
b) hochsubstituierte iodhaltige Verbindungen wie z.B. Lipide

Hämostyptika/Antihämorrhagika
Blutgerinnungsfaktoren VIII, IX

Hypnotika, Sedativa
Cyclobarbital, Pentobarbital, Phenobarbital, Methaqualon (BTM), Benzodiazepine (Flurazepam, Midazolam, Nitrazepam, Lormetazepam, Flunitrazepam, Triazolam, Brotizolam, Temazepam, Loprazolam)

Hypophysen-, Hypothalamushormone, regulatorische Peptide und ihre Hemmstoffe
Corticotrophin, Tetracosactid, Choriongonadotropin, Urofollitropin, Urogonadotropin, Somatropin, Metergolin, Bromocriptin, Terlipressin, Desmopressin, Oxytocin; Argipressin, Ornipressin, Leuprorelin, Triptorelin, Gonadorelin, Buserelin, Nafarelin, Goselerin, Somatostatin

Immuntherapeutika und Zytokine
Dimepranol-4-acetatamidobenzoat, Thymopentin, α-Interferon, β-Interferon, γ-Interferon, Filgrastim, Interleukine, Azathioprin, Ciclosporin

Lokalanaesthetika

intern:
Butanilicain, Mepivacain, Bupivacain, Etidocain, Lidocain, Articain, Prilocain,
extern außerdem:
Propipocain, Oxybuprocain, Tetracain, Benzocain

Migränemittel
Proxibarbal, Lisurid, Methysergid, Dihydroergotamin, Clonidin, Ergotamin, Pizotifen

Narkosemittel
Methohexital, Propofol, Etomidat, Ketamin, Alfentanil, Thiopental, Droperidol, Fentanyl

Nebenschilddrüsenhormone, Calciumstoffwechselregulatoren Dihydrotachysterol, Calcitonin, Clodronsäure, Etidronsäure

Opthalmika
Atropin, Cyclodrin, Cyclopentolat, Homatropin, Tropicamid, Scopolamin, Pholedrin, Edoxudin, Idouridin, Tromantadin, Aciclovir, Acetazolamid, Diclofenamid, Carteolol, Timolol, Metipranolol, Betaxolol, Pindolol, Befunolol, Bupranolol, Levobununol, Carbachol, Pilocarpin, Clonidin, Neostimgin

Psychopharmaka
Benzodiazepine (Lorazepam, Diazepam), Clomethiazol

Schilddrüsentherapeutika
1-Thyroxin, Carbimazol, Thiamazol, Propylthiouracil

Sera, Immunglobuline, Impfstoffe

a) Immunglobuline allgemein und spezifisch wie Hepatitis-Typen, Röteln, Cytomegalie, Tollwut, FSME, Varicella-Zoster, Tetanus, Rhesusfaktoren
b) Immunsera wie Botulismus-Antitoxin, Diphterie, Gasbrand, Schlangengift, Skorpiongift
c) Impfstoffe wie Influenza, Tuberkulose, Cholera, Diphterie, Hepatitis-Typen, FSME, Röteln, Hämophilus influenzae, Masern, Neisseria, Mumps, Poliomyelitis, Tetanus, Tollwut, Typhus

Sexualhormone und ihre Hemmstoffe
Anabolika, Androgene, Antiandrogene, Gestagene, Estrogene, Antiestrogene (Tamoxifen etc.)

Zystostatika und Metastasenhemmer

a) Alkylantien wie Nimustin, Melphalan, Carmustin, Lomustin, Cyclophosphamid, Ifosfamid, Trofosfamid, Chlorambucil, Busulfan, Treosulfan, Prednimustin, Thiotepa
b) Antimetabolite wie Cytarabin, Fluorouracil, Methotrexat, Mercaptopurin, Tioguanin
c) Alkaloide wie Vinblastin, Vincristin, Vindesin
d) Antibiotika wie Aclarubicin, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitomycin, Plicamycin
e) Komplexe von Nebengruppenelementen (z. B. Ti, Zr, V, Nb, Ta, Mo, W, Ru, Pt) wie Carboplatin, Cisplatin und Metallocenverbindungen wie Titanocendichlorid
f) Amsacrin, Dacarbazin, Estramustin, Etoposid, Hydroxycarbamid, Mitoxanthron, Procarbazin, Temiposid
g) Alkylamidophospholipide (beschrieben in J. M. Zeidler, F. Emling, W. Zimmermann und H.

J. Roth, Archiv der Pharmazie, 324 (1991), 687)

h) Etherlipide wie Hexadecylphosphocholin, Ilmofosin und Analoga, beschrieben in R. Zeisig, D. Arndt und H. Brächwitz, Pharmazie 45 (1990), 809-818.

[0051] Insbesondere sind zu nennen: Cyclosporine, wie Cyclosporin A, und Cyclosporinderivate sowie Paclitaxel.

[0052] Als Polymer kann die erfindungsgemäße Zubereitung übliche Polymere aufweisen, wie beispielsweise Polyacrylate oder Polymethacrylate (Eudragit E, L, F), Cellulosen und Cellulosederivate (Methylhydroxypropylcellulose, Ethylcellulose, Hydroxypropylcelluloseacetatsuccinat (Aquoat®) oder natürliche Polymere (Schellack, Wachse, Bienenwachs, Glanz-Wachse). Durch die Wahl des Polymers kann die Freisetzungseigenschaft der Zubereitung oder der daraus hergestellten größeren Matrixeinheiten gesteuert werden. So kann durch Einsatz von Methylhydroxypropylcellulose eine im Vergleich zu nicht retardierten Tabletten nur gering verzögerte Freisetzung des Wirkstoffs erreicht werden. Die Verwendung von Eudragit E als Polymer führt zu einer verzögerten Freisetzung des Wirkstoffs bereits im Magen. Weist die Zubereitung Eudragit L bzw. F als Polymer auf, so ist eine kontrollierte Freisetzung des Wirkstoffs erst im Darmbereich möglich.

[0053] Als Lipid kann die erfindungsgemäße Zubereitung übliche Lipide aufweisen, wie beispielsweise natürliche, halbsynthetische und synthetische Triglyceride oder deren Mischungen, Mono- und Diglyceride allein oder in Mischung untereinander oder mit z.B. Triglyceriden, natürliche und synthetische Wachse, Fettalkohole einschließlich ihrer Ester und Ether sowie Lipidpeptide. Insbesondere sind synthetische Mono-, Di- und Triglyceride als Einzelsubstanzen oder in Mischung (z.B. Hartfett), Glycerintrifettsäureester (z.B. Glycerintrilaurat, -myristat, -palmitat, -stearat und -behenat) und Wachse wie z.B. Cetylpalmitat und Cera alba (gebleichtes Wachs, DAB9), Bienenwachs (z.B. Apifil, Apifac geeignet.

[0054] Weitere Lipide, zum Teil mit zusätzlich emulgierenden (SE = self emulsifying; selbstemulgierend) Eigenschaften sind Glycerinbehenat (z.B. Compritol 888 ATO), Glycerintribehenat (Compritol 888), Palmitostearate wie z.B. Glycerinpalmitostearat (z.B. Biogapress Vegetal ATO BM 297, Precirol Ato 5, Geleol), Diethylenglykol-, Propylenglykol-, Ethylenklykol-, Polyglykol- und Propylenglykolpalmitostearat, Stearate wie Glycerinstearat (z.B. Precirol WL 2155 Ato) und Polyglykolstearat, Isostearate, Polyalkohol-Fettsäureester (z.B. Compritol WL 3284), PEG-Behenat (z.B. Compritol HD5 ATO), Cetylpalmitat (z.B. Precifac Ato), Sacharoseester wie Saccharose-Monodistearat und -Monopalmitat (z.B. Sucro-Ester W.E. 15), Saccharose-Distearat (z.B. Sucro-Ester W.E. 7), Polyglycerinester wie Polyglycerinisostearostearat (Lafil WL 3254) und -palmitostearat, Polyglykolisierte Glyceride (z.B. Gelucire, Labrafil, Suppocire), selbstemulgierendes Polyglykolstearat (z.B. Superpolystate), selbstemulgierendes Polyglykolpalmitostearat (z.B. Tefose Serie), Glyceride C_{12}-C_{18} Fettsäuren (z.B. Lipocire) sowie deren Mischungen aus zwei oder mehr Lipiden.

[0055] Durch die Wahl des Lipids kann die Freisetzungseigenschaft der Zubereitung oder der daraus hergestellten größeren Matrixeinheiten gesteuert werden. So kann durch Einsatz von im Darm gut abbaubaren Lipiden die Freisetzung beschleunigt werden, da zusätzlich zur Freisetzung aufgrund von Diffusion aus der Matrix auch Freisetzung aufgrund vom Matrixerosion erfolgt. Mit langsamer abbaubaren Lipiden oder nicht im Magen-Darm-Trakt abbaubaren Lipiden erfolgt die Freisetzung verzögerter. Als relativ schnell durch Pankreas Lipase/Colipase abbaubares Lipid wird Dynasan 114 beschrieben, der Abbau Dynasan 118 erfolgt langsamer (C.Olbrich, R.H. Müller, Proceed. Int. Symp. Controlled Rel. Bioact. Mater., Stockholm, 921-922, 1997).

[0056] Als Hilfsstoffe können insbesondere die folgenden Stoffgruppen verwendet werden:

[0057] Füllstoffe aus dem Bereich der Zucker, wie beispielsweise Disaccharide (Laktose, Saccharose), Monosaccharide (Glukose, Fruktose) oder Polysaccharide (Stärken, Mais- oder Kartoffelstärke, Cellulose, natürliches Cellulosepulver, mikrokristalline Cellulose), Zukkeralkohole, wie beispielsweise Sorbit oder Mannit, oder Calciumphosphate.

[0058] Bindemittel, wie Polyvinylpyrrolidon (PVP, Kollidon CL), Gelatine, Stärkekleister, Cellulosen, Celluloseether oder Zucker.

[0059] Erfindungsgemäß ist festgestellt worden, daß eine Zubereitung in Form eines polymerhaltigen/lipidhaltigen Compounds, die eine Hilfsstoffphase mit wenigstens einem Hilfsstoff und/oder eine Wirkstoffphase mit wenigstens einem Wirkstoff und eine polymere phase/lipide Phase mit wenigstens einem Polymer/Lipid aufweist, wobei die Polymerphase/Lipidphase der Zubereitung inkohärent ist und die Hilfs- und/oder Wirkstoffphase kohärent ist, erhalten wird, wenn die verschiedenen Phasen der Zubereitung zusammen in einer Flüssigkeit suspendiert oder suspendiert und gelöst werden, wobei die Polymerphase/Lipidphase in der Flüssigkeit nicht löslich ist, und diese Suspension anschließend sprühgetrocknet wird.

[0060] Hierbei wird insbesondere eine Zubereitung erhalten, deren Polymerphase/Lipidphase frei von Hilfs- und/oder Wirkstoffphase ist.

[0061] Ebenso ist es möglich, die Suspension in einem Fließbett- oder Wirbelschichttrockner zu trocknen. Dabei werden die Phasen der Zubereitung wiederum zusammen in einer Flüssigkeit suspendiert oder suspendiert und gelöst, wobei die Polymerphase/Lipidphase in der Flüssigkeit nicht löslich ist, und diese Suspension wird anschließend in einem Fließbett- oder Wirbelschichttrockner getrocknet.

[0062] Zur Durchführung des erfindungsgemäßen

Verfahrens werden die entsprechenden Mengen an Polymer/Lipid und Hilfsstoff und/oder Wirkstoff in einer Flüssigkeit mit Hilfe eines hochtourigen Rührers oder eines Dispergators suspendiert oder suspendiert und gelöst, wobei das Polymer/Lipid, im Gegensatz zu den bekannten Verfahren mit Polymerverarbeitung, in der Flüssigkeit nicht lösbar ist, sondern als Festoffpartikel vorliegt. In Abhängigkeit von dem zu suspendierenden Polymer/Lipid ist darauf zu achten, daß bei der Dispergierung keine zu hohen Scherkräfte und Temperaturen auftreten, die zu einer Aggregation bzw. einem Zusammenfließen von Polymerpartikeln/Lipidpartikeln führen.

[0063] Die verwendete Flüssigkeit ist insbesondere demineralisiertes Wasser oder ein wäßriges oder organisches Dispersions- bzw. Suspensionsmittel.

[0064] Die jeweils gewünschte Viskosität der im Sprühtrockner, Fließbett- oder Wirbelschichttrockner zu versprühenden Suspension wird über den prozentualen Feststoff-Anteil gesteuert. Zusätzliche Regulationsmöglichkeiten bestehen bei wasserlöslichen Hilfsstoffen über deren Konzentration und chemische Natur (z. B. Lactose, Hilfsstoffe mit ausgeprägtem viskositätserhöhenden Effekt).

[0065] Eine weitere vorteilhafte Ausgestaltung ist der Zusatz von Netzmittel und/oder Bindemittel und/oder Weichmacher (z.B. Triethylcitrat, Propylenglycol, u.a) zur Suspension. Als Bindemittel sind insbesondere Polyvinylpyrrolidon, Gelatine, Stärkekleister, Cellulose, Celluloseether oder Zucker geeignet. Sie erhöhen die mechanische Festigkeit der Zubereitung. Der Weichmacher erlaubt einen validierungsfähigen Einfluß auf die Plastizität, Verformbarkeit und Verfilmbarkeit des Polymers/Lipids und ermöglicht damit die Steuerbarkeit der Freigabe des Wirkstoffs neben dem Retard-Effekt des Polymers/Lipids an sich. Als Weichmacher können vor allem Triethylcitrat und Propylenglycol eingesetzt werden. Aber auch andere innere und äußere Weichmacher, die als übliche Zusätze zu Polymeren/Lipiden bekannt sind, sind zur Steuerung der Wirkstofffreisetzung geeignet.

[0066] Die Suspension wird anschließend bei Sprühdrücken üblicherweise über 20 bar mit Hilfe geeigneter Ein- und Mehrstoff-Düsen im Sprühturm bei geeigneten Abluft-Temperaturen, in Abhängigkeit von der Sensibilität der Wirk- und Hilfsstoffe sowie von den apparativen Gegebenheiten des Sprühturmes und dessen Peripherie, sprühgetrocknet oder im Fließbett- oder Wirbelschichttrockner getrocknet.

[0067] Die erhaltene Zubereitung kann anschließend, soweit es erforderlich ist, noch nachgetrocknet werden. Hierbei ist eine Nachtrocknung und/oder eine zusätzliche Agglomeration der Zubereitung auf Fließbett- oder Wirbelschichttrocknern möglich.

[0068] Aufgrund des Trocknungsvorgangs im Sprühtrockner, Fließbettoder Wirbelschichttrockner weist die erhaltene Zubereitung eine angenähert sphärische Form auf.

[0069] Es ist erfindungsgemäß erkannt worden, daß die beschriebene Zubereitung, die eine inkohärente Polymerphase/Lipidphase und eine kohärente Hilfsstoff- und/oder Wirkstoffphase aufweist, sich zur Verwendung bei der Herstellung von größeren Matrixeinheiten mit kontrollierten Freisetzungseigenschaften eignet. Hierbei können sämtliche bekannte Verfahren angewendet werden, so daß größere Matrixeinheiten jeder beliebigen Form erhalten werden, wie beispielsweise Tabletten, Pellets oder zylinderförmige Stäbchen. Ebenso können mit der erfindungsgemäßen Zubereitung die bekannten Verfahren zur Herstellung von Extrusionsoder Sphäronisationspellets oder zur Abfüllung der Zubereitung in Kapseln durchgeführt werden.

[0070] Ferner ist erkannt worden, daß sich die erfindungsgemäße Zubereitung insbesondere zur Herstellung von größeren Matrixeinheiten und/oder Tabletten mit kontrollierten Freisetzungseigenschaften mittels Direkttablettierung eignet. Dies ist trotz des hohen Polymeranteils/Lipidanteils der Zubereitung möglich, da durch das erfindungsgmäße Verfahren unter anderem eine sehr gute Fließeigenschaft und ein verbessertes Komprimierverhalten der Zubereitung erreicht wird.

[0071] Vorteilhaft ist insbesondere die Herstellung von Tabletten mit-. tels Direkttablettierung aus einer wirkstofffreien Zubereitung, die mit wenigstens einem Wirkstoff und bei Bedarf mit weiteren Hilfsstoffen gemischt wird, sowie aus einer wirkstoffhaltigen Zubereitung, die unter Umständen zusätzlich noch mit wenigstens einem Wirkstoff und soweit erforderlich mit weiteren Hilfsstoffen gemischt werden kann.

[0072] Neben den üblichen Tabletten sind insbesondere auch Drageekerne, Film- oder Manteltablettenkerne oder zylinderförmige Stäbchen durch Direkttablettierung bzw. direkte Komprimierung erhältlich.

[0073] Ferner kann die erfindungsgemäße Zubereitung zur Herstellung größerer Matrixeinheiten verwendet werden, die verschiedene Wirkstoffe oder den gleichen Wirkstoff in unterschiedlichen Dosen aufweisen (z. B. Schichttabletten), wobei jeder Wirkstoff oder jede Dosis einen eigenen, von den anderen Wirkstoffen oder Dosen unabhängigen Freisetzungszeitpunkt aufweist. Hierzu wird eine wirkstoffhaltige erfindungsgemäße Zubereitung, die auch zusätzlich noch wenigstens einen Hilfsstoff aufweisen kann, mit wenigstens einem weiteren oder demselben Wirkstoff, falls erforderlich unter Zusatz von Hilfsstoffen, wie beispielsweise Füll-, Formtrenn- oder Bindemitteln, gemischt. Die Mischung wird dann mittels Direkttablettierung oder nach anderen bekannten Verfahren zu größeren Matrixeinheiten verarbeitet. Dies ist besonders bei inkompatiblen Wirkstoffen vorteilhaft, da diese Vorgehensweise zu einer räumlichen Trennung der Wirkstoffe in der Arzneiform führt.

[0074] Durch die Verwendung der erfindungsgemäßen Zubereitung in einem Verfahren zur Herstellung von größeren Matrixeinheiten werden Modifikationen des Freisetzungsprofils ermöglicht, da der oder die Wirkstoffe in der größeren Matrixeinheit unterschiedlich stark als Funktion der Polymermenge/Lipidmenge eingeschlos-

sen sind und somit unterschiedlich schnell freigesetzt werden.

[0075] Die erfindungsgemäße Verwendung der Zubereitung zur Direkttablettierung weist insbesondere den Vorteil auf, daß die Wirkstoffe und/oder Hilfsstoffe durch den angewandten Trocknungsvorgang gegenüber der herkömmlichen Feuchtgranulierung, die bisher als Vorstufe zur Komprimierung von polymerhaltigen Zubereitungen erforderlich gewesen ist, nur sehr kurze Zeit der Feuchtigkeit ausgesetzt werden. Die Temperaturbelastung ist bei den genannten Trockungsverfahren steuerbar und sogar auszuschalten, wenn im Luftstrom bei Raumtemperatur getrocknet wird.

[0076] Zur Herstellung größerer Matrixeinheiten nach bekannten Verfahren sei beispielsweise die Herstellung von Pellets angeführt. Dazu wird die erfindungsgemäße Zubereitung unter Zusatz adäquater Hilfsstoffe mit einem für die Pelletherstellung üblichen Extruder extrudiert und über eine anschließende Sphäronisation in Kügelchen von Pelletgröße überführt. Alternativ kann die Herstellung über einen Lochwalzenkompaktor mit angeschlossenem Pelltierbehälter erfolgen. Mögliche Geräte sind Spheronizer® und Marumizer®. Ebenso können diese Pellets durch Einsatz eines Pelletiertellers aus der beschriebenen Zubereitung hergestellt werden.

[0077] Diese Pellets können ebenso wie die Zubereitung selbst beispielsweise in Kapseln abgefüllt oder zu größeren Einheiten verpreßt werden.

[0078] Die Erfindung wird im folgenden anhand von Ausführungsbeispielen und Figuren näher erläutert. Alle Prozentangaben beziehen sich auf das Gewicht.

Beispiele

1. Herstellung einer Lactose-Ethylcellulose-Zubereitung (50:50):

[0079] Beide Komponenten werden mit Hilfe eines Rührers in demineralisiertem Wasser dispergiert. Die Dispersion wird bei einem Feststoffgehalt von bis zu 40 Prozent und einem Sprühpumpen-Druck von 30-50 bar in einem Labor-Sprühturm bei Abluft-Temperaturen zwischen 70 und 100 Grad Celsius versprüht.

[0080] Das Ergebnis ist ein gut fließfähiges Sprüh-Agglomerat bestehend aus Lactose und Ethylcellulose in einer Korngrößenverteilung zwischen 1 und 630 µm, wobei der Hauptanteil von 50-80% zwischen 63 und 400 µm liegt.

[0081] Die so hergestellte Zubereitung zeichnet sich insbesondere aufgrund ihres Merkmals, daß die polymere Phase inkohärent und die Hilfsstoff- und/oder Wirkstoffphase kohärent ist, sowie ihrer angenähert sphärischen Form und ihrer Oberflächenbeschaffenheit (Kavitäten, Lakose) als sehr gut mit Wirkstoff misch- und beladbar aus.

[0082] Bei lipophilen Wirkstoffen kann die Freisetzungsdauer der Wirkstoffe bei direkter Mischung mit der Zubereitung bis zum Faktor drei gegenüber nicht retardierten Tabletten verlängert werden. Die Freisetzungsdauer kann wiederum durch Veränderung des Polymer-Anteiles in der Tablettiermasse, z.B. durch.Zumischen eines Füllstoffes der Typen Stärke und Laktose variiert werden.

2. Herstellung einer Acetylsalicylsäure (ASS) aufweisenden Lactose-Ethylcellulose-Zubereitung:

[0083] Die Herstellung erfolgt wie in 1. beschrieben, die Mischung der Komponenten Lactose:Ethylcellulose: ASS erfolgt im Gewichtsverhältnis 45:45:10.

3. Herstellung einer Tablette aus einer Acetylsalicylsäure (ASS) aufweisenden Zubereitung:

[0084] Die unter 1. hergestellte wirkstofffreie Lactose-Ethylcellulose-Zubereitung wird mit ASS im Verhältnis 90:10 gemischt, der Mischung wird 0,5% Aerosil und 1% Magnesiumstearat zugesetzt und direkttablettiert.

4. Herstellung einer Tablette aus eine Acetylsalicylsäure (ASS) aufweisenden Zubereitung:

[0085] Der unter 2. hergestellten ASS-beladenen Lactose-Ethylcellulose-Zubereitung werden 0,5% Aerosil und 1% Magnesiumstearat zugesetzt und direkttablettiert.

5. Herstellung einer Paracetamol-Lactose-Ethylcellulose-Zubereitung (20:40:40):

[0086] Alle Komponenten werden in demineralisiertem Wasser dispergiert und auf eine gewünschte pumpen- und druckabhängige Vikosität eingestellt. Es erfolgt die Versprühung nach den oben beschriebenen Verfahren. Die so hergestellte Zubereitung ist aufgrund ihrer Pulvereigenschaften unmittelbar für die Direkttablettierung geeignet, wobei durch den variabel einstellbaren Prozentanteil an Polymer - durch Zumischung von weiteren Hilfsstoffen, variable Tablettenhärte - die Freigabe des Wirkstoffes im gewünschten Umfang verzögert werden kann.

6. Herstellung eines Compritol-Trehalose-Compounds:

[0087] Compritol 888 ATO (Glyceroltribehenat) wurde geschmolzen, in heißes Wasser nach Zusatz von 1,2% Poloxamer 188 eingegossen und darin mittels eines hochtourigen Ultra-Turrax dispergiert. Nach Erkalten wurde in der wäßrigen Lipidpartikeldispersion Trehalose gelöst, so daß sich als Endkonzentration 10% Lipid und 3 % Trehalose ergab. Diese Mischung wurde in einem Mini-Büchi sprühgetrocknet (Inlet-Temperatur: 110 °C, Outlet-Temperatur: 50°C; Sprüh-Flow: 600 Normliter). Es wurde ein rieselfähiges Lipid-Hilfsstoff-Compound erhalten.

7. Herstellung einer Tablette aus Compound mit 1% Paracetamol:

[0088] 9 Teile des in Beispiel 1 beschriebenen Lipid-Trehalose-Compounds wurde unter Zusatz von 0,1 Teil Paracetamol und unter Zumischung von 0,5% Aerosil 200 und 0,5% Magnesiumstearat auf einer Korsch-Excenterpresse direkt komprimiert. Tablettensollgewicht 505 mg.

8. Herstellung einer Tablette aus Compound mit 10% Paracetamol:

[0089] 13 Teile des in Beispiel 6 beschriebenen Lipid-Trehalose-Compounds wurden mit 3 Teilen Trehalose gemischt, dieser Mischung 10% Paracetamol zugesetzt und unter Zumischung von 0,5% Aerosil 200 und 0,5% Magnesiumstearat auf einer Korsch-Excenterpresse direkt komprimiert. Tablettensollgewicht 505 mg.

9. Freisetzung aus einer Tablette aus Compound mit 10% Paracetamol:

[0090] Die Freisetzung von Paracetamol aus der in Beispiel 8 hergestellten Tablette wurde mit der Paddle-Methode nach der United States Pharmacopeia bestimmt, Freisetzungsmedium: Wasser, Temperatur 37 °C. Die erhaltenen Freisetzungskurven zeigen Figur 5 und 6.

Kurze Erläuterung der Figuren:

Figur 1:

[0091] In Figur 1 ist die Herstellung einer erfindungsgemäßen Zubereitung über ein Compound nach dem erfindungsgemäßen Verfahren dargestellt: Der Matrixbildner (z.B. Polymerpartikel/Lipidpartikel) wird in Wasser dispergiert, der Hilfsstoff und/oder Wirkstoff wird ebenfalls in der Wasserphase gelöst bzw. dispergiert und die Suspension wird versprüht, wobei das Wasser durch Trocknen entfernt wird. Es entsteht eine Zubereitung, die selbst aus kleinen Polymerpartikeln/Lipidpartikeln zusammengesetzt ist, wobei die Zwischenräume mit dem Hilfsstoff (links oder mit Hilfsstoff- und Wirkstoff gefüllt sind (rechts). Die Zubereitung weist eine inkohärente polymere/lipide Phase und eine kohärente Hilfs- und/oder Wirkstoffphase auf.

Figur 2:

[0092] Figur 2 zeigt ein Beispiel für die Verwendung der erfindungsgemäßen Zubereitung zur Herstellung größerer Matrixeinheiten. Die wirkstofffreie Zubereitung (z.B. aus Polymer und Lactose bzw. aus Lipid und Flowlac 100- sprühgetrocknete Lactose, Fa. Meggle, Deutschland) wird mit dem Wirkstoff (in Pulverform) gemischt, gegebenenfalls Tablettierhilfsstoffe soweit erforderlich zugesetzt und die Mischung direkttablettiert.

Figur 3a:

[0093] Aus dem Stand der Technik bekanntes O/W-Emulsionsverfahren: Hier ist ein Tropfen eines organischen Lösungsmittels mit darin gelöstem Matrixbildner (z.B. Polymer) in einer Wasserphase dispergiert (O/W-Emulsion), wobei der Wirkstoff in der organischen Phase gelöst (links) oder bei unlöslichem Wirkstoff dispergiert ist (rechts). Weitere Erklärung siehe Text.

Figur 3b:

[0094] Aus dem Stand der Technik bekanntes W/O-Emulsionsverfahren: Hier ist ein Tropfen Wasser mit darin gelöstem Matrixbildner (z.B. wasserlösliches Polymer) in einer organischen Phase dispergiert (O/W-Emulsion), wobei der Wirkstoff in der wäßrigen Phase gelöst (links) oder bei unlöslichem Wirkstoff dispergiert ist (rechts). Weitere Erklärung siehe Text.

Figur 4:

[0095] Figur 4 zeigt das erfindungsgemäße Verfahren zur Herstellung der erfindungsgemäßen Zubereitung. Die polymere Phase/Lipidphase ist nicht gelöst, sondern in Wassertropfen dispergiert bzw. suspendiert, die durch Sprühen in einer Gasphase verteilt werden. Ein Hilfsstoff (z.B. Lactose, links) oder ein Hilfsstoff und ein Wirkstoff (rechts) sind ebenfalls im Wassertropfen gelöst oder dispergiert bzw. suspendiert. Nach Entfernen des Wassers entsteht eine wirkstofffreie Hilfsstoff-Polymer/Lipid-Zubereitung (links) oder eine Wirkstoff-Hilfsstoff-polymer/Lipid-zubereitung (rechts), wobei die polymere Phase/Lipidphase in beiden Fällen inkohärent ist.

Figuren 5 und 6:

[0096] Freisetzung von Paracetamol aus einer Tablette bei Verwendung der erfindungsgemäßen Zubereitung (Beispiel 4). Darstellung der freigesetzten Menge als Funktion der Zeit (Figur 5) und als Funktion der Wurzel aus der Zeit (Figur 6).

Patentansprüche

1. Zubereitung in Form eines matrixmaterialhaltigen Compounds mit einer Hilfsstoffphase mit wenigstens einem Hilfsstoff und/oder einer Wirkstoffphase mit wenigstens einem Wirkstoff, **dadurch gekennzeichnet, daß** das Matrixmaterial ausgewählt ist aus Polymeren, wobei im Fall von Cellulosematerialien diese Cellulosematerialien Cellulosederivate sind, und Lipiden, die Polymerphase und/oder die Lipidphase der Zubereitung inkohärent und die

Hilfs- und/oder Wirkstoffphase der Zubereitung kohärent ist.

2. Zubereitung in Form eines matrixmaterialhaitigen Compounds mit einer Hilfsstoffphase mit wenigstens einem Hilfsstoff und/oder einer Wirkstoffphase mit wenigstens einem Wirkstoff, **dadurch gekennzeichnet, daß** das Matrixmaterial ausgewählt ist aus Polymeren, wobei im Fall von Cellulose der Anteil der Matrixmaterialphase der Zubereitung 70 bis 98% beträgt, und Lipiden, die Polymerphase und/oder die Lipidphase der Zubereitung inkohärent und die Hilfs- und/oder Wirkstoffphase der Zubereitung kohärent ist.

3. Zubereitung nach Anspruch 1 oder 2, **dadurch gekennzeichnet, daß** die Matrixmaterialphase der Zubereitung Hilfs- und/oder Wirkstoff enthält oder frei davon ist.

4. Zubereitung nach einem der Ansprüche 1 bis 3, **dadurch gekennzeichnet, daß** der Anteil der Matrixmaterialphase der Zubereitung 1 bis 98% beträgt.

5. Zubereitung nach einem der Ansprüche 1 bis 4, **dadurch gekennzeichnet, daß** der Anteil der Matrixmaterialphase der Zubereitung 10 bis 95% beträgt.

6. Zubereitung nach einem der Ansprüche 1 bis 5, **dadurch gekennzeichnet, daß** der Anteil der Matrixmaterialphase der Zubereitung mehr als 15% und höchstens 90% beträgt.

7. Zubereitung nach einem der Ansprüche 1 bis 6, **dadurch gekennzeichnet, daß** der Anteil der Matrixmaterialphase der Zubereitung 40 bis 70% beträgt.

8. Zubereitung nach einem der Ansprüche 1 bis 7, **dadurch gekennzeichnet, daß** die polymere Phase ein Polyacrylat und/oder ein Polymethacrylat und/oder die Lipidphase natürliche, halbsynthetische und synthetische Triglyceride oder deren Mischungen, Mono- und Diglyceride allein oder in Mischung untereinander oder mit Triglyceriden, natürliche und synthetische Wachse, Fettalkohole einschließlich ihrer Ester und Ether sowie Lipidpeptide, insbesondere synthetische Mono-, Di- und Triglyceride als Einzelsubstanzen oder in Mischung, speziell Hartfett, Glycerintrifettsäureester, speziell Glycerintrilaurat, -myristat, -palmitat, -stearat und -behenat, und Wachse, speziell Cetylpalmitat und Cera alba (gebleichtes Wachs, DAB9), Bienenwachs enthält.

9. Zubereitung nach einem der Ansprüche 1 bis 8, **dadurch gekennzeichnet, daß** die Polymerphase ein Polyacrylat und/oder ein Polymethacrylat, ein Cellulosederivat oder natürliches Polymer und/oder die Lipidphase natürliches Lipid enthält.

10. Zubereitung nach einem der Ansprüche 1 bis 9, **dadurch gekennzeichnet, daß** sie mindestens einen Wirkstoff enthält.

11. Zubereitung nach einem der Ansprüche 1 bis 10, **dadurch gekennzeichnet, daß** die Hilfsstoffphase wenigstens einen Füllstoff, insbesondere ausgewählt aus Monosacchariden, Disacchariden, Polysacchariden, Zuckeralkoholen und Calciumphosphat, und/oder wenigstens ein Bindemittel, insbesondere ausgewählt aus Polyvinylprrolidon, Gelatine, Stärkekleister, Cellulosen, Celluloseethern und Zuckern aufweist.

12. Zusammensetzung nach einem der vorhergehenden Ansprüche, **dadurch gekennzeichnet, daß** sie in Form eines durch Direktkomprimierung herstellbaren Preßlings vorliegt.

13. Verfahren zur Herstellung einer Zubereitung in Form eines matrixmaterialhaltigen Compounds nach einem der Ansprüche 1 bis 12, **dadurch gekennzeichnet, daß** die Phasen der Zubereitung zusammen in einer Flüssigkeit suspendiert oder suspendiert und gelöst werden, wobei die Matrixmaterialphase in der Flüssigkeit nicht löslich ist, und diese Suspension anschließend sprühgetrocknet wird.

14. Verfahren zur Herstellung einer Zubereitung in Form eines matrixmaterialhaltigen Compounds nach einem der Ansprüche 1 bis 12, **dadurch gekennzeichnet, daß** die Phasen der Zubereitung zusammen in einer Flüssigkeit suspendiert oder suspendiert und gelöst werden, wobei die Matrixmaterialphase in der Flüssigkeit nicht löslich ist, und diese Suspension anschließend in einem Fließbett- oder Wirbelschichttrockner getrocknet wird.

15. Verfahren nach Anspruch 13 oder 14, **dadurch gekennzeichnet, daß** die Flüssigkeit ein wäßriges oder organisches Suspensionsmittel ist.

16. Verfahren nach einem der Ansprüche 13 bis 15, **dadurch gekennzeichnet, daß** der Suspension wenigstens ein Bindemittel und/oder wenigstens ein Netzmittel und/oder wenigstens ein Weichmacher zugesetzt wird.

17. Verwendung der Zubereitung in Form eines matrixmaterialhaltigen Compounds nach einem der Ansprüche 1 bis 12 zur Herstellung von größeren Matrixeinheiten mit kontrollierten Freisetzungseigenschaften nach bekannten Verfahren.

18. Verwendung der Zubereitung in Form eines matrixmaterialhaltigen Compounds nach einem der An-

sprüche 1 bis 12 zur Herstellung von Tabletten und/ oder größeren Matrixeinheiten mit kontrollierten Freisetzungseigenschaften mittels Direkttablettierung.

Claims

1. Preparation in the form of a compound containing a matrix material with an auxiliary-substance phase comprising at least one auxiliary substance and/or an active-substance phase comprising at least one active substance, **characterized in that** the matrix material is selected from polymers, where, in the case of cellulose materials, these cellulose materials are cellulose derivatives, and lipids, where the polymer phase and/or the lipid phase of the preparation is incoherent and the auxiliary-substance phase and/or active-substance phase of the preparation is coherent.

2. Preparation in the form of a compound containing a matrix material with an auxiliary-substance phase comprising at least one auxiliary substance and/or an active-substance phase comprising at least one active substance, **characterized in that** the matrix material is selected from polymers, where, in the case of cellulose, the proportion of the matrix-material phase of the preparation is from 70 to 98%, and lipids, where the polymer phase and/or the lipid phase of the preparation is incoherent and the auxiliary-substance phase and/or active-substance phase of the preparation is coherent.

3. Preparation according to Claim 1 or 2, **characterized in that** the matrix-material phase of the preparation comprises an auxiliary substance and/or active substance or is free therefrom.

4. Preparation according to one of Claims 1 to 3, **characterized in that** the proportion of the matrix-material phase in the preparation is from 1 to 98%.

5. Preparation according to one of Claims 1 to 4, **characterized in that** the proportion of the matrix-material phase in the preparation is from 10 to 95%.

6. Preparation according to one of Claims 1 to 5, **characterized in that** the proportion of the matrix-material phase in the preparation is greater than 15% and at most 90%.

7. Preparation according to one of Claims 1 to 6, **characterized in that** the proportion of the matrix-material phase in the preparation is from 40 to 70%.

8. Preparation according to one of Claims 1 to 7, **characterized in that** the polymeric phase comprises a polyacrylate and/or a polymethacrylate, and/or the lipid phase comprises natural, semisynthetic and synthetic triglycerides or mixtures thereof, mono- and diglycerides, alone or in a mixture with one another or with triglycerides, natural and synthetic waxes, fatty alcohols, including esters thereof, and ethers, as well as lipid peptides, in particular synthetic mono-, di- and triglycerides as individual substances or in the form of a mixture, especially hydrogenated fat, glycerol trifatty acid esters, especially glycerol trilaurate, trimyristate, tripalmitate, tristearate and tribehenate, and waxes, especially cetyl palmitate and cera alba (bleached wax, DAB9), or beeswax.

9. Preparation according to one of Claims 1 to 8, **characterized in that** the polymer phase comprises a polyacrylate and/or a polymethacrylate, a cellulose derivative or natural polymer, and/or the lipid phase comprises natural lipid.

10. Preparation according to one of Claims 1 to 9, **characterized in that** it comprises at least one active substance.

11. Preparation according to one of Claims 1 to 10, **characterized in that** the auxiliary-substance phase comprises at least one filler, in particular selected from monosaccharides, disaccharides, polysaccharides, sugar alcohols and calcium phosphate, and/or at least one binder, in particular selected from polyvinylpyrrolidone, gelatine, starch glue, celluloses, cellulose ethers and sugars.

12. Composition according to one of the preceding claims, **characterized in that** it is in the form of a pressing which can be produced by direct compression.

13. Process for the production of a preparation in the form of a compound containing a matrix material according to one of Claims 1 to 12, **characterized in that** the phases of the preparation are suspended or suspended and dissolved together in a liquid, where the matrix-material phase is insoluble in the liquid, and this suspension is subsequently spray-dried.

14. Process for the production of a preparation in the form of a compound containing a matrix material according to one of Claims 1 to 12, **characterized in that** the phases of the preparation are suspended or suspended and dissolved together in a liquid, where the matrix-material phase is insoluble in the liquid, and this suspension is subsequently dried in a fluidized-bed drier.

15. Process according to Claim 13 or 14, **character-**

ized in that the liquid is an aqueous or organic suspension medium.

16. Process according to one of Claims 13 to 15, **characterized in that** at least one binder and/or at least one wetting agent and/or at least one plasticizer is added to the suspension.

17. Use of the preparation in the form of a compound containing a matrix material according to one of Claims 1 to 12 for the production of larger matrix units having controlled release properties by known processes.

18. Use of the preparation in the form of a compound containing a matrix material according to one of Claims 1 to 12 for the production of tablets and/or larger matrix units having controlled release properties by means of direct tabletting.

Revendications

1. Composition sous la forme d'un composite contenant un matériau de matrice avec une phase agent auxiliaire contenant au moins un agent auxiliaire et/ou une phase principe actif contenant au moins un principe actif, **caractérisée en ce que** le matériau de matrice est choisi parmi les polymères, dans lesquels, lorsqu'il s'agit de matériaux cellulosiques, ces matériaux cellulosiques sont des dérivés de la cellulose, et parmi les lipides, et **en ce que** la phase polymère et/ou la phase lipidique de la préparation est incohérente et la phase agent auxiliaire et/ou la phase principe actif de la préparation est cohérente.

2. Composition sous la forme d'un composite contenant un matériau de matrice avec une phase agent auxiliaire contenant au moins un agent auxiliaire et/ou une phase principe actif contenant au moins un principe actif, **caractérisée en ce que** le matériau de matrice est choisi parmi les polymères, dans lesquels, dans le cas de la cellulose, la proportion de la phase matériau de matrice de la préparation est de 70 à 98%, et parmi les lipides, et **en ce que** la phase polymère et/ou la phase lipidique de la préparation est incohérente et la phase agent auxiliaire et/ou la phase principe actif de la préparation est cohérente.

3. Composition selon la revendication 1 ou 2, **caractérisée en ce que** la phase matériau de matrice de la préparation contient un agent auxiliaire et/ou un principe actif ou bien en est dépourvue.

4. Composition selon l'une des revendications 1 à 3, **caractérisée en ce que** la proportion de la phase matériau de matrice dans la préparation est de 1 à 98%.

5. Composition selon l'une des revendications 1 à 4, **caractérisée en ce que** la proportion de la phase matériau de matrice dans la préparation est de 10 à 95%.

6. Composition selon l'une des revendications 1 à 5, **caractérisée en ce que** la proportion de la phase matériau de matrice dans la préparation est supérieure à 15% et au maximum égale à 90%.

7. Composition selon l'une des revendications 1 à 6, **caractérisée en ce que** la proportion de la phase matériau de matrice dans la préparation est de 40 à 70%.

8. Composition selon l'une des revendications 1 à 7, **caractérisée en ce que** la phase polymère contient un polyacrylate et/ou un polyméthacrylate et/ou **en ce que** la phase lipidique contient des triglycérides naturels, semi-synthétiques et synthétiques ou des mélanges de ceux-ci, des mono- et diglycérides seuls ou mélangés entre eux ou avec des triglycérides, des cires naturelles et synthétiques, des alcools gras, y compris leurs esters et leurs éthers, ainsi que des peptides lipidiques, en particulier des mono-, di- et triglycérides synthétiques seuls ou en mélange, notamment des graisses durcies, des triesters d'acides gras avec le glycérol, en particulier les trilaurate, trimyristate, tripalmitate, tristéarate et tribéhénate de glycérol, et des cires, notamment le palmitate de cétyle et la cire blanche (Cera alba, DAB9), la cire d'abeilles.

9. Composition selon l'une des revendications 1 à 8, **caractérisée en ce que** la phase polymère contient un polyacrylate et/ou un polyméthacrylate, un dérivé de la cellulose ou un polymère naturel et/ou **en ce que** la phase lipidique contient un lipide naturel.

10. Composition selon l'une des revendications 1 à 9, **caractérisée en ce qu'**elle contient au moins un principe actif.

11. Composition selon l'une des revendications 1 à 10, **caractérisée en ce que** la phase agent auxiliaire contient au moins une matière de charge, en particulier choisie parmi les monosaccharides, les disaccharides, les polysaccharides, les alcools de sucres et le phosphate de calcium, et/ou au moins un liant, en particulier choisi parmi la polyvinylpyrrolidone, la gélatine, la colle d'amidon, les celluloses, les éthers de cellulose et les sucres.

12. Composition selon l'une au moins des revendications précédentes, **caractérisée en ce qu'**elle se présente sous la forme d'une pièce moulée suscep-

tible d'être obtenue par compression directe.

13. Procédé de fabrication d'une composition sous la forme d'un composite contenant un matériau de matrice selon l'une des revendications 1 à 12, **caractérisé en ce que** les phases de la composition sont mises en suspension ensemble dans un liquide ou bien mises en suspension et dissoutes, la phase matériau de matrice n'étant pas soluble dans le liquide, et cette suspension est ensuite séchée par pulvérisation.

14. Procédé de fabrication d'une préparation sous la forme d'un compound contenant un matériau de matrice selon l'une des revendications 1 à 12, **caractérisé en ce que** les phases de la préparation sont mises en suspension ensemble dans un liquide ou bien mises en suspension et dissoutes, la phase matériau de matrice n'étant pas soluble dans le liquide, et cette suspension est ensuite séchée dans un sécheur à lit fluidisé.

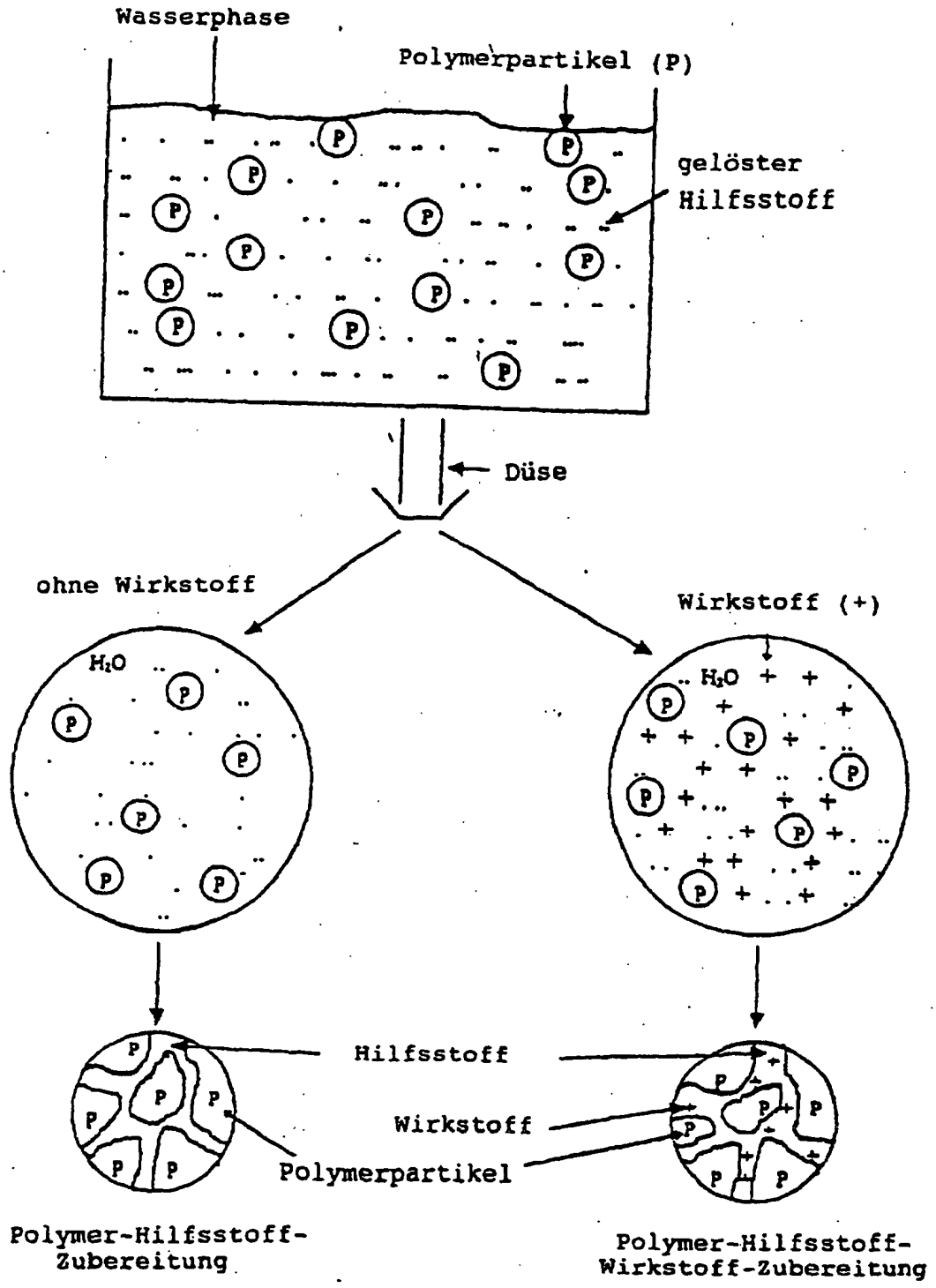
15. Procédé selon la revendication 13 ou la revendication 14, **caractérisé en ce que** le liquide est un agent de suspension aqueux ou organique.

16. Procédé selon l'une des revendications 13 à 15, **caractérisé en ce que** l'on ajoute à la suspension au moins un liant et/ou au moins un agent mouillant et/ou au moins un plastifiant.

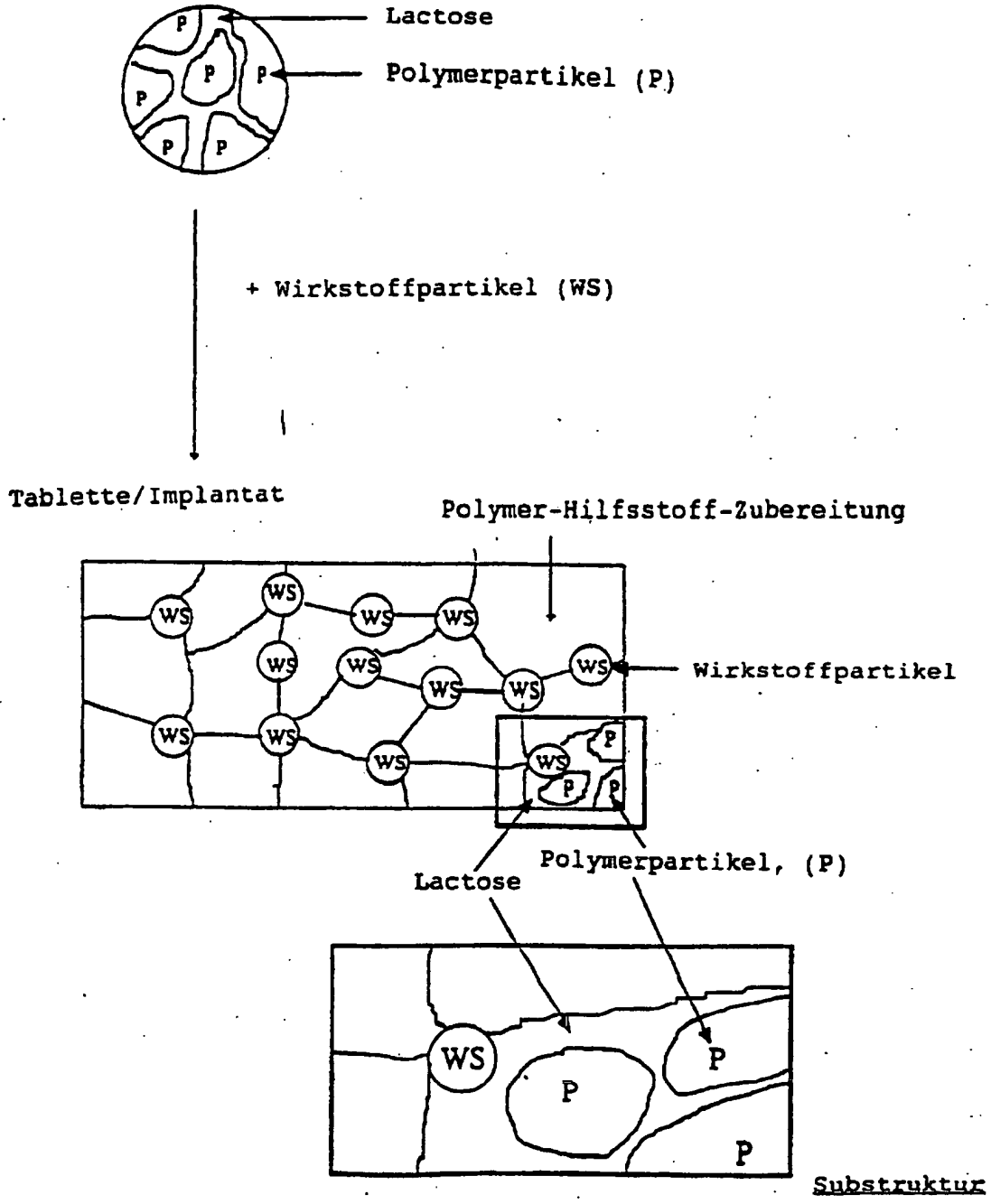
17. Utilisation de la composition sous la forme d'un composite contenant un matériau de matrice selon l'une des revendications 1 à 12 pour la fabrication d'unités de matrice de plus grande taille ayant des propriétés de libération contrôlée selon des procédés connus.

18. Utilisation de la composition sous la forme d'un composite contenant un matériau de matrice selon l'une des revendications 1 à 12 pour la fabrication de comprimés et/ou d' unités de matrice de plus grande taille ayant des propriétés de libération contrôlée par pastillage direct.

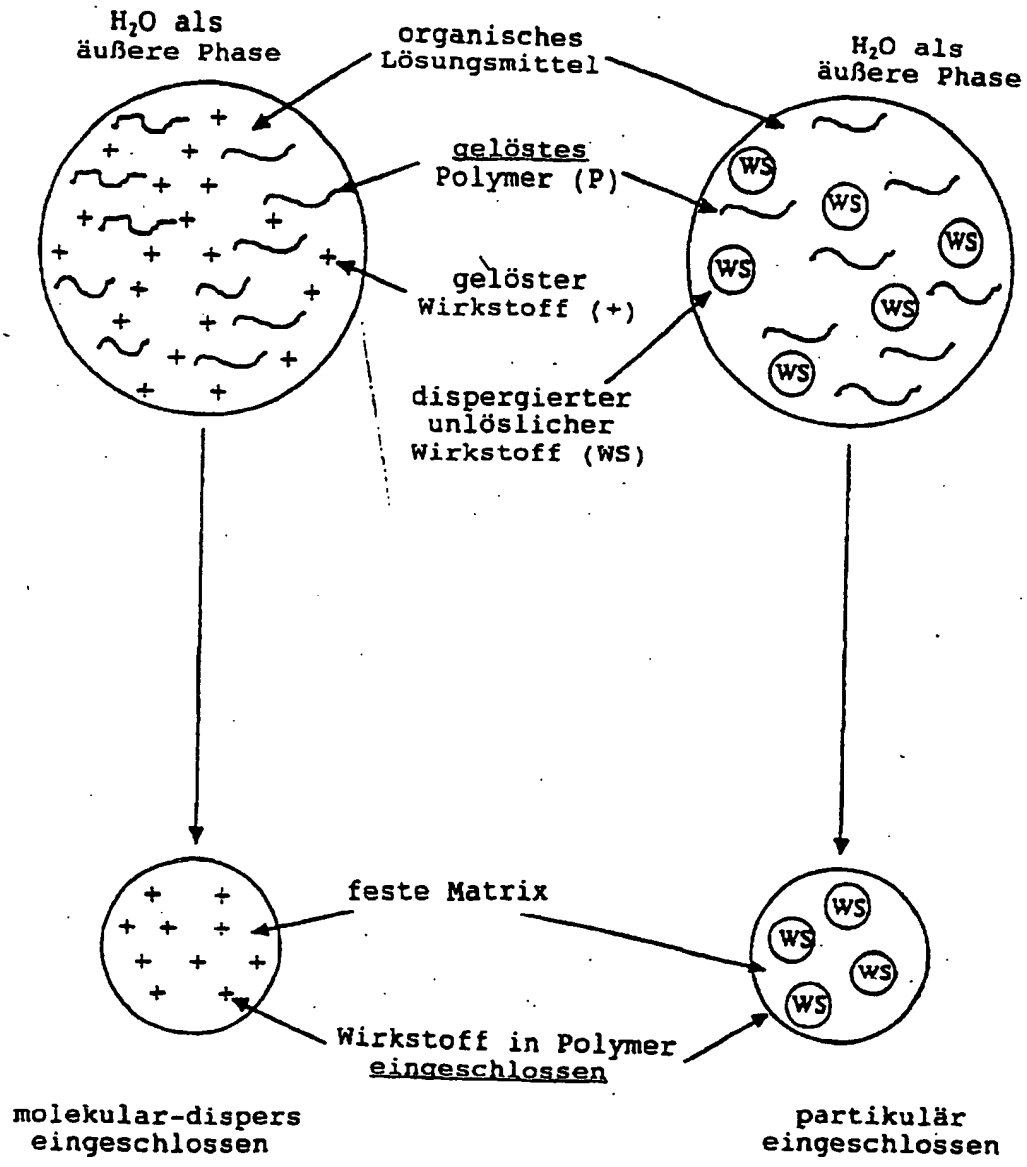
FIGUR 1: Herstellung der Zubereitung in Form eines Pellets



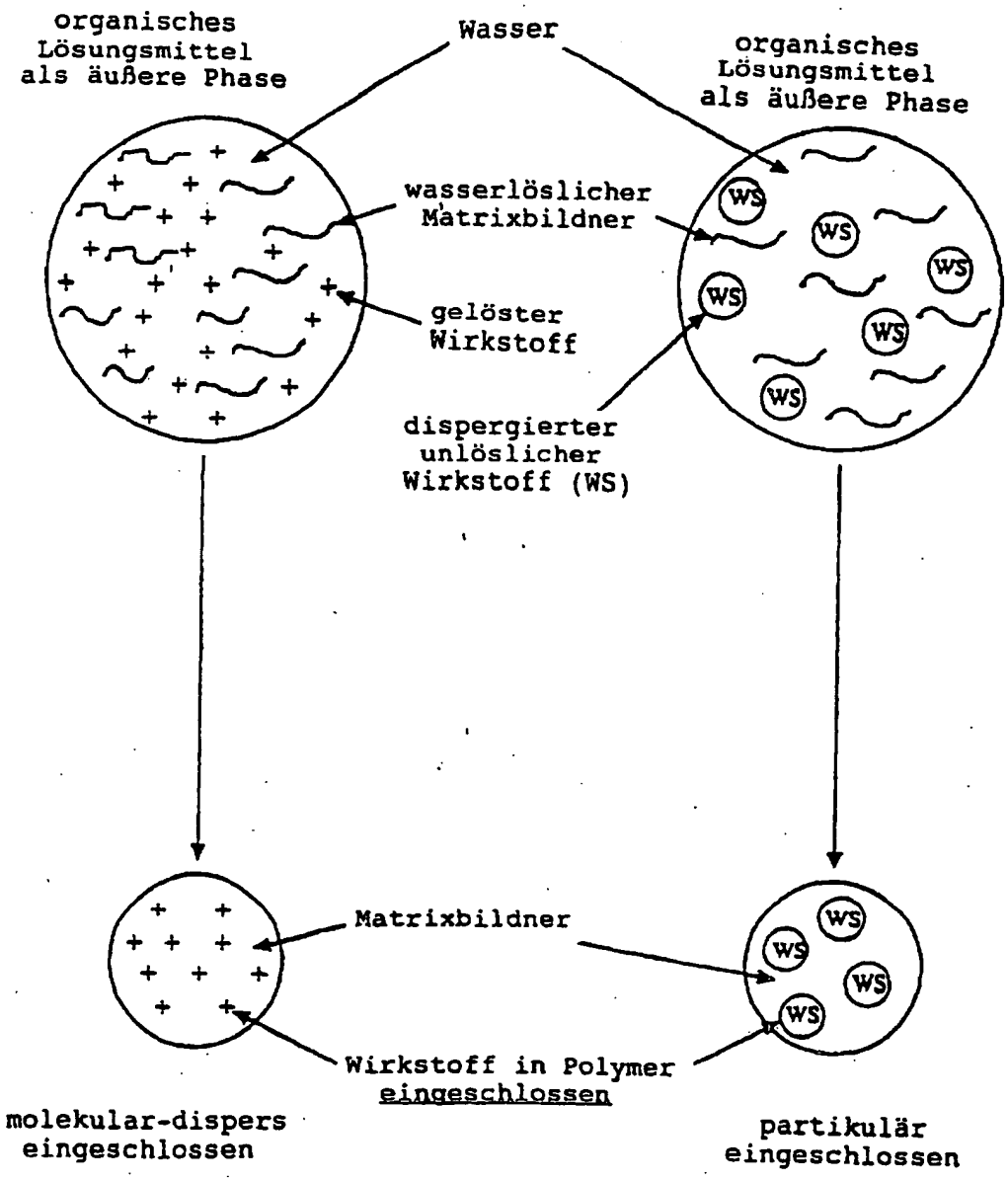
FIGUR 2: Herstellung größerer Matrixeinheiten



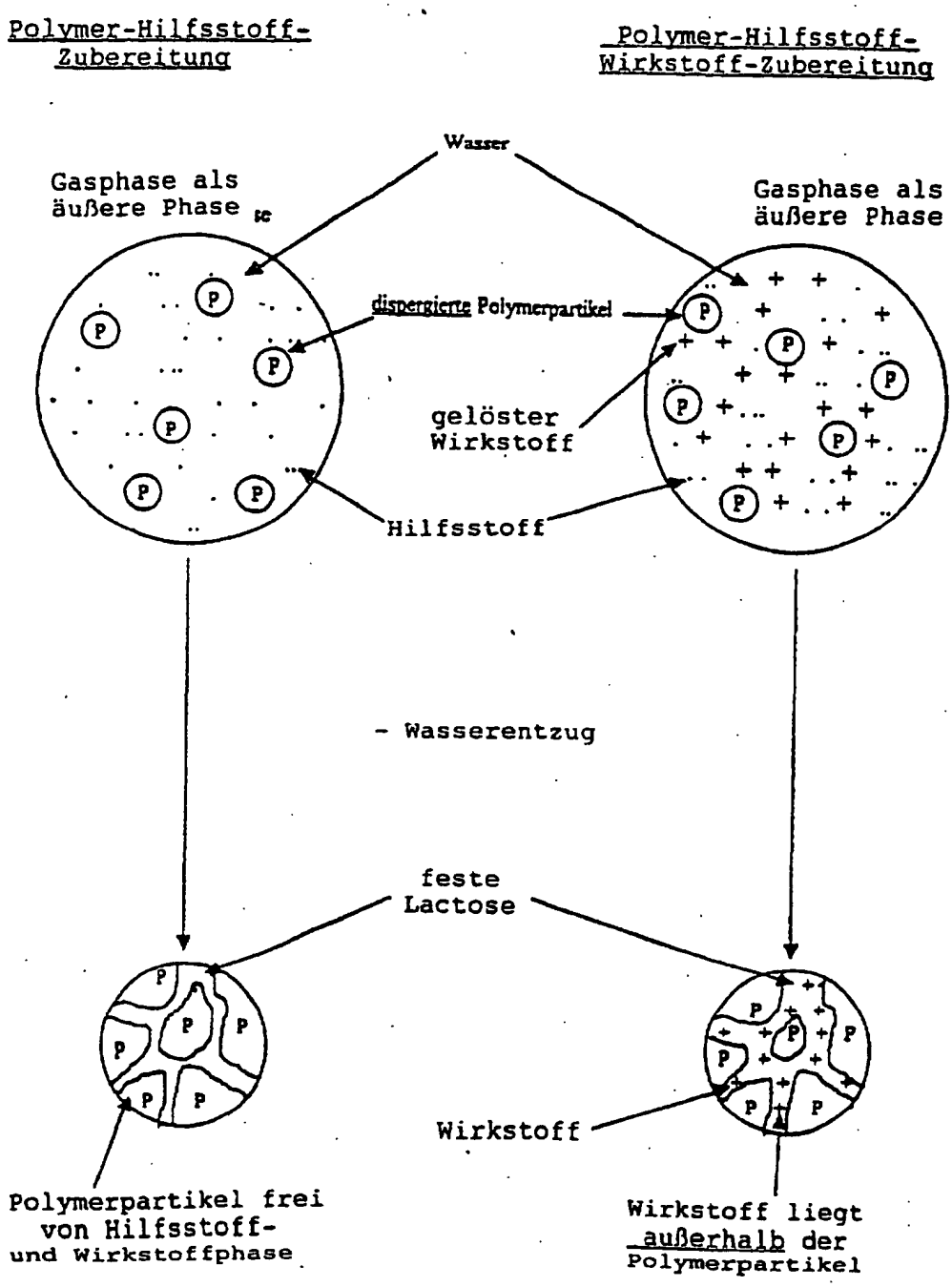
FIGUR 3a: O/W-Emulsionsverfahren (Stand der Technik)



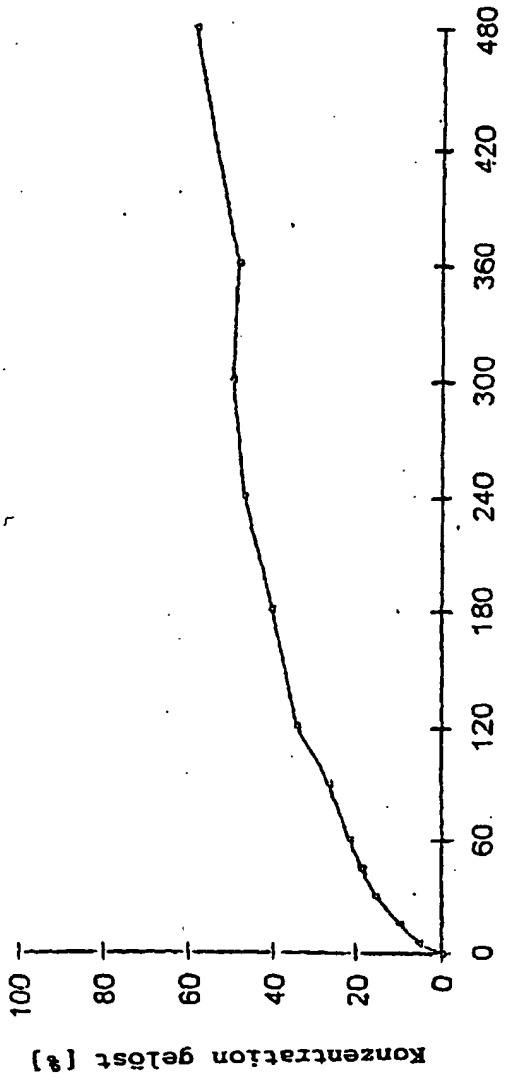
FIGUR 3b: W/O-Emulsionsverfahren (Stand der Technik)



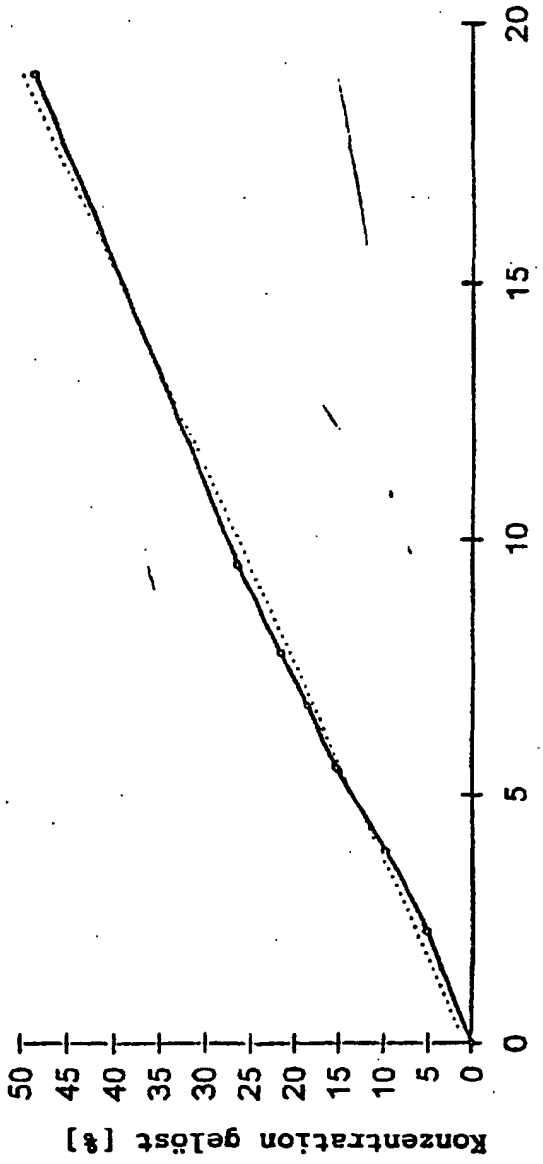
FIGUR 4: Erfindungsgemäßes Verfahren



Abbildungen zu Lipid-Compounds /1



Figur 5: Freisetzung von Paracetamol aus tablettierter Mischung aus sprühgetrocknetem Lipid-Trehalose-Compound (9 Teile) plus Paracetamol (1 Teil) unter Zumischung von 0,5 % Aerosil 200 und 0,5 % Magnesiumstearat. (Tablettengewicht: 500 mg, Zusammensetzung Lipid-Trehalose-Compound Compritol 888 ATO 10 Teile plus 3 Teile Trehalose).



Figur 6: Wurzel-Zeit Diagramm der Freisetzungskurve aus Figur 5 zur Belegung der Matrixfreisetzung (gestrichelte Linie = Trendlinie)

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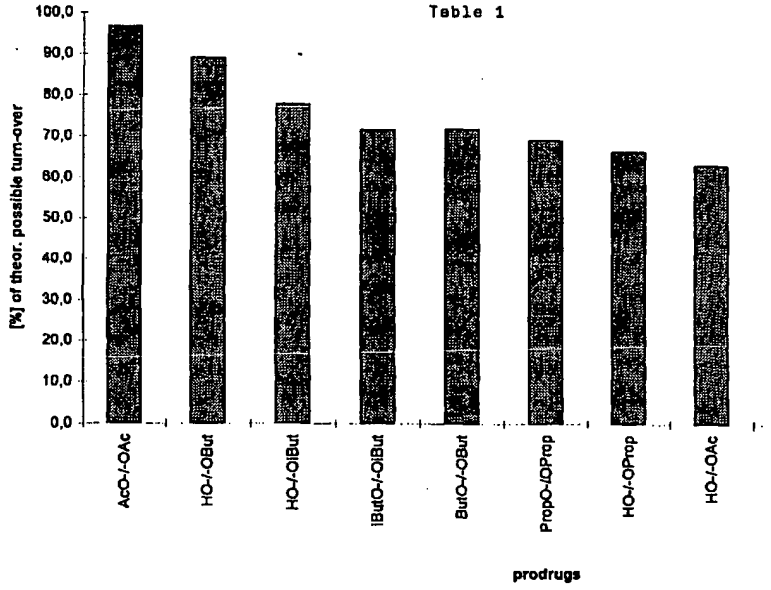
(54) Novel derivatives of 3,3-diphenylpropylamines

(57) The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly the invention concerns to provide novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h

Table 1



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Description

[0001] The present invention relates to novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. A further object of the invention is to provide novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

[0002] More particularly, the present invention relates to certain prodrugs of 3,3-diphenylpropylamines while avoiding on administration to a mammal a high variation in bioavailability and formation of active metabolites which can result in a substantial variation in response - too low efficacy or too much side effects - for the subjects on the suggested therapy.

[0003] In man, normal urinary bladder contractions are mediated mainly through cholinergic muscarinic receptor stimulation. There is reason to believe that muscarinic receptors mediate not only normal bladder contractions but also the main part of the contractions in the overactive bladder resulting in symptoms as urinary frequency, urgency and urge incontinence. For this reason antimuscarinic drugs have been instituted as a treatment of bladder over activity.

[0004] Among the antimuscarinic drugs available on the market, oxybutynin is currently regarded as the gold standard for pharmacological treatment of urge incontinence and other symptoms related to bladder over activity. The effectiveness of oxybutynin has been demonstrated in several clinical studies but the clinical usefulness of oxybutynin is limited due to antimuscarinic side effects. Dryness of the mouth is the must common experienced side effect which may be severe enough to result in poor compliance or discontinuation of treatment (Andersson, K.-E., 1988, Current concepts in the treatment of disorders of micturition, Drugs 35, 477-494; Kelleher et al. 1994).

[0005] Tolterodine is a new, potent and competetive, muscarinic receptor antagonist intended for the treatment of urinary urge incontinence and detrusor hyperactivity. Preclinical pharmacological data show that tolterodine exhibits a favourable tissue selectivity in vivo for the urinary bladder over the effect on the salivation (Nilvebrant et al, 1997, Tolderodine - a new bladderselective antimuscarinic agent, Eur. J. Pharmacol. 327 (1997), 195-207), whereas oxybutynin exhibits the reversed selectivity. Tolterodine is equipotent to oxybutynin at urinary bladder muscarinic receptors and the favourable tissue selectivity of tolterodine demonstrated in the preclinical studies has been confirmed in clinical studies.. Thus a good clinical efficacy has been combined with a very low number of incidences of dry mouth and antimuscarinic side effects.

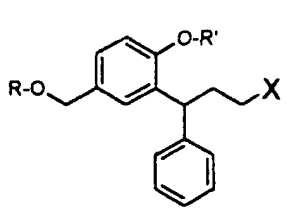
[0006] A major metabolite of tolterodine, the 5-hydroxymethyl derivative is also a potent muscarinic receptor antagonist and the pharmacological in vitro and in vivo profiles of this metabolite is almost identical to those of tolterodine (Nilvebrant et al, 1997, Eur. J. Pharmacol. 327 (1997), 195-207). Combined pharmacological and pharmacokinetic data indicate that it is most likely that the metabolite give a major contribution to the clinical effect in most patients.

[0007] The document WO 94/11337 discloses that the active metabolite of tolterodine is suggested as a new drug for urge incontinence. Administration of the active metabolite directly to patients has the advantage compared to tolterodine that only one active principle (compound) has to be handled by the patient which normally should result in a lower variation in efficacy and side effects between patients and lower risk of interaction with other drugs.

[0008] However, the introduction of an additional hydroxy group in the tolterodine results in an increased hydrophilic property of the new compounds (3,3-diphenylpropylamines) compared to the parent compounds which normally results in a lower absorption/bioavailability. In a method to circumvent this disadvantage different prodrugs of the metabolite have been synthetized and tested for their absorption/bioavailability data.

[0009] It is an object of the present invention to provide novel derivatives of 3,3-diphenylpropylamines. It is an further object of the present invention to provide new derivatives of 3,3-diphenylpropylamines which will be more useful as prodrugs for treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms while avoiding the disadvantage of a too low absorption/bioavailability after oral administration of the drugs or an unfavourable metabolism.

[0010] The novel compounds of the present invention are represented by the general Formula (I)



(I)

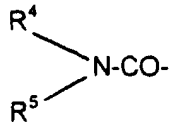
wherein R indepently signifies:

a) R^1 represents the residues hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl or allyl; or

b) R^2 represents the residues formyl, acetyl, propionyl, isobutyryl, butyryl, valeroyl, pivaloyl, benzoyl; or

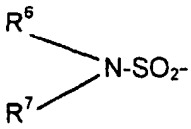
c) R^3 represents the residues CH_3OCO-, C_2H_5-OCO-, C_3H_7OCO-, $(CH_3)_3COCO$-, benzoylacyl, benzoylglycyl, glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl; or

d) a group consisting



of wherein R^4 and R^5 indepently represent the residues hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

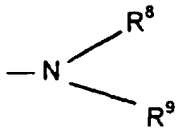
e) a group consisting



of wherein R^6 and R^7 indepently represent the residues methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl; or

f) an ester of inorganic acids such as sulfuric acid, phosphoric acid;

X represents a tertiary amino group of Formula Ia



(Ia)

wherein R^8 and R^9 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen, R' represents hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, alkyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, if R is hydrogen R' will not represent hydrogen or methyl
and

their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

[0011] The compounds of Formula (I) can form salts with physiologically acceptable acids, organic and inorganic. Furthermore the aforementioned compounds comprise the free bases as well as the salts thereof. Examples of such acid

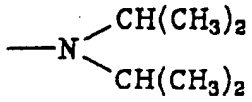
addition salts include the hydrochloride, hydrobromide and the like.

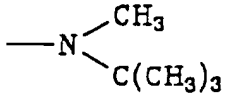
[0012] When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

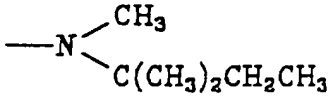
[0013] Preferably each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

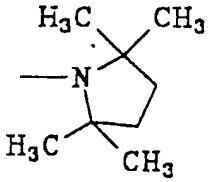
[0014] According to an other embodiment of the invention at least one of R^8 and R^9 comprises a branched carbon chain.

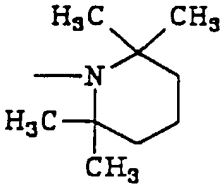
[0015] Presently preferred tertiary amino groups X in Formula I include the following groups a) to h):

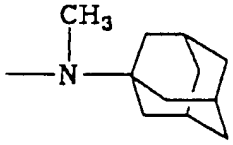
a) 

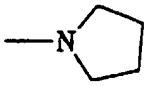
b) 

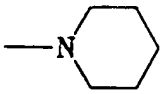
c) 

d) 

e) 

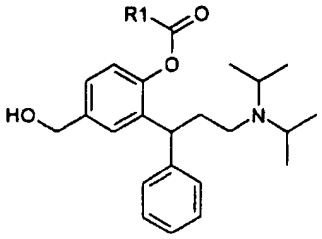
f) 

g) 

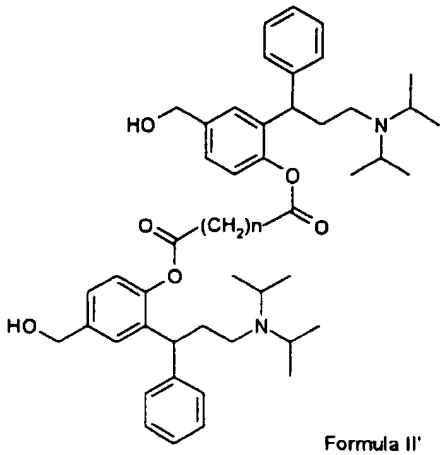
h) 

[0016] Preferred compounds according to the present invention are:

A) Phenolic monoesters represented by the general Formulae II and II'



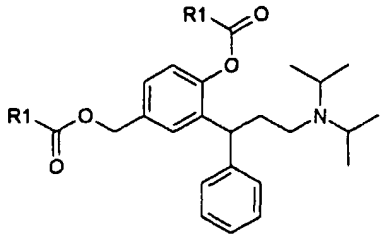
Formula II



Formula II'

Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester
Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester
Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester
Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester

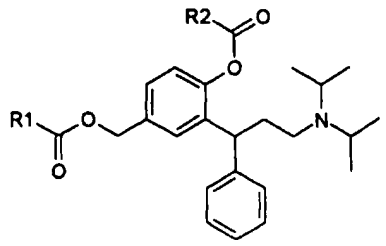
B) Identical diesters represented by the general Formula III



Formula III

Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester
Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester
n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester
2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester
Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester

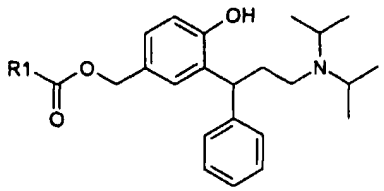
C) Mixed diesters represented by the general Formula IV



Formula IV

Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester
Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester
Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)benzyl ester
2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester

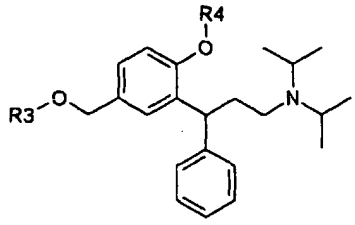
D) Benzylic monoesters represented by the general Formula V



Formula V

Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester

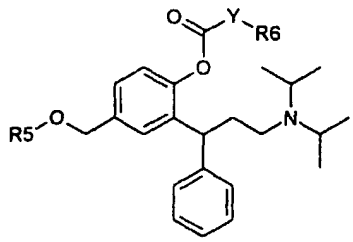
E) Ethers and silyl ethers represented by the general Formula VI



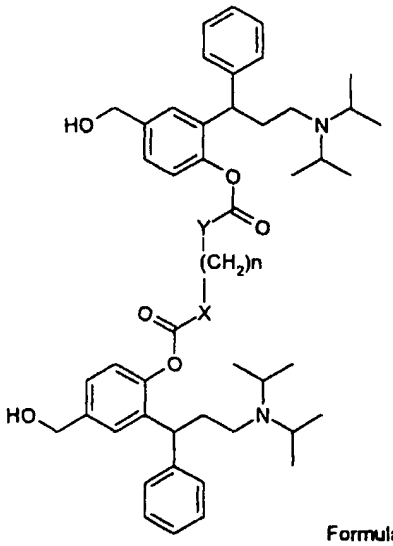
Formula VI

2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol
Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester
Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester
2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol
Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)propyl]-amine
[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol
Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine
Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine
(4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]methanol
Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol
Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
{3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)phenyl]-3-phenylpropyl}-diisopropylamine
[4-(tert.-Butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]methanol
Acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
4-(tert.-Butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)phenol
{3-[2-(tert.-Butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)phenyl]-2-phenylpropyl}-diisopropylamine
Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester

F) Carbonates and carbamates represented by the general Formulae VII and VII'



Formula VII



Formula VII'

N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester

N-Phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester
{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester

[0017] The compounds of formula (I) may, in accordance with the present invention be prepared by per se conventional methods. Methods for preparing substituted 3,3-diphenylpropylamines as disclosed by this invention may be synthesized according to methods as described in the document PCT/SE93/00927.

[0018] The invention will be further illustrated by the following non-limiting examples and pharmacological tests.

[0019] The following starting materials and preffered Examples illustrate the invention:

I. Experimental

1. General

[0020] All compounds were fully characterized by ^{1}H and ^{13}C NMR spectroscopy. The chemical shifts reported (^{13}C NMR, ppm) refer to the solvents $CDCl_3$ (77.10 ppm), CD_3OD (49.00 ppm) or hexadeuterio dimethylsulphoxide (DMSO-d_6, 39.70 ppm) respectively. Thin-layer chromatography (tlc, R_f values reported) was conducted on precoated 5x10 cm E. Merck silica gel plates (60F254), spots were visualized by fluorescence quenching or spaying with alkaline potassium permanganate solution. Solvent systems: (1), ethyl acetate/n-hexane (30/70, v/v-%); (2), toluene/acetone/methanol/acetic acid (70/5/20/5, v/v-%); (3), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (4), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (5), ethyl acetate/n-hexane/2-propanol/triethylamine (60/40/20/1, v/v-%); (6), ethyl acetate/triethylamine (90/10, v/v-%). Gas chromatography-mass spectrometry (GC-MS): spectra (m/z values and relative abundance reported) were recorded on a Finnigan TSQ 700 triple mass spectrometer in the positive (P-CI) or negative (N-CI) chemical ionization mode using methane or ammonia as reactant gas. Hydroxylic compounds were analyzed as their trimethylsilyl ether derivatives.

2. Synthesis of Intermediates A and B

[0021] An icecooled solution of 4-bromophenol (69.2g) and cinnamoyl chloride (66.8g) in dichloromethane (150ml) was treated with triethylamine (40.6g). After stirring for 18h at room temperature the mixture was washed with water (250ml), 1M aqueous HCl, and dried over anhydrous sodium sulphate. Evaporation in vacuum left solid *3-phenylacrylic acid 4-bromophenyl ester* (121.0g, 99.8% yield), m.p. 113.3 °C, tlc (1) 0.83. NMR($CDCl_3$): 116.85, 118.87, 123.49, 128.38, 129.06, 130.90, 132.49, 134.02, 147.07, 149.84, 165.06.

[0022] A portion of the ester (60.0g) was dissolved in a mixture of acetic acid (60ml) und concentrated sulphuric acid (18ml) and refluxed for 2h. After cooling, the reaction mixture was poured into ice water and the product was was isolated by extraction with ethyl acetate. Evaporation of the solvent and recrystallization of the residue from boiling I ethanol (150ml) yielded 26.3g (43.8% yield) of pure, crystalline *6-bromo-4-phenylchroman-2-one,* m.p. 117.8 °C, tlc (1) 0.67. NMR ($CDCl_3$): 36.56, 40.51, 117.29, 118.87, 127.47, 127.89. 128.33, 129.32, 131.07, 131.79, 139.42, 150.76, 166.84.

[0023] A suspension consisting of 6-bromo-4-phenylchroman-2-one (85.0g), anhydrous potassium carbonate (46.7g), sodium iodide (20.5g) and benzyl chloride (40.6g) in methanol (350ml) and acetone (350ml) was refluxed for 3h. After evaporation of the solvents the residue was extracted with diethyl ether (2 x 300ml) and the extract was washed with water (2 x 200ml) and aqueous sodium carbonate. Drying (Na_2SO_4) and rotoevaporation left 121.8g (102.1 % crude yield) of *3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* as a light yellow oil, tlc (1) 0.77. NMR ($CDCl_3$): 39.22, 40.53, 51.63, 70.16, 113.10, 113.77,126.46, 126.92, 127.88, 128.08, 128.34, 128.45, 130.31, 130.55, 134.41, 136.44, 142.37, 154.94, 172.08.

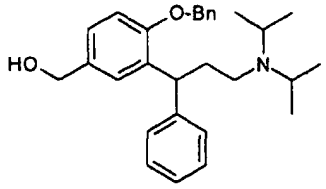
[0024] A solution of the propionate (121.0g) in 350ml of dry tetrahydrofuran was slowly added under an atmosphere of nitrogen to a suspension of lithium aluminiumhydride (7.9g) in tetrahydrofuran (350ml). After stirring at room temperature for 18h, 20% aqueous HCl was added dropwise and the product was isolated by repeated extraction with diethyl ether. The combined extracts were gradually washed with hydrochloric acid, sodium hydroxide solution, distilled water, and then dried (Na_2SO_4) to give a light yellow viscous oil (108.8g, 96.3% yield) after evaporation which gradually crystallized, m.p. 73.8 °C, tlc (1) 0.47, *3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol*. NMR ($CDCl_3$): 37.52, 39.52, 60.84, 70.54, 113.54, 113.83, 126.29, 127.30, 127.51, 129.99, 128.24, 128.38, 129.99, 130.88, 135.69, 136.40, 143.53, 155.12.

[0025] A cooled (5 °C) solution of 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol (108.0g) in dichloromethane (300ml) war treated with pyridine (79.4ml) and than p-toluenesulphonyl chloride (60.6g) in dichloromethane (200ml). After 18h at room temperature the solvent was removed in vacuum and the residue extracted diethyl ether. The extract was washed with hydrochloric acid, water, and dried over anhydrous sodium sulphate to give *toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester* as a light yellow oil after concentration under reduced pressure (140.3g, 93.6% yield), tlc (1) 0.66. NMR ($CDCl_3$): 21.67, 33.67, 39.69, 68.58, 70.28, 113.21, 113.76, 126.47, 127.84, 128.10, 128.25, 128.41, 128.51, 129.81, 130.26, 130.42, 132.91, 134.39, 136.41, 142.16, 155.07.

[0026] A solution of the toluenesulphonate (139.3g) in acetonitrile (230ml) and N,N-diisopropylamine (256g) was refluxed for 97h. The reaction mixture was then evaporated to dryness and the residue thus formed was partitioned between diethyl ether (500ml) and aqueous sodium hydroxide (2M, 240ml). The organic phase was washed twice with water (250ml) and then extracted with 1M sulphuric acid. The aqueous phase was adjusted to about pH 12-13 and reextracted with ether (500ml). The organic phase was washed with water, dried (Na_2SO_4) and evaporated to provide *[3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine* as a brown and viscous syrup (94.5g, 77.9% yield), tlc (2) 0.49. NMR ($CDCl_3$): 20.65, 20.70. 36.70, 41.58, 43.78, 48.77, 70.24, 113.52, 126.02, 127.96, 128.20, 128.36, 129.82, 130.69, 136.34, 136.76, 144.20, 155.15.

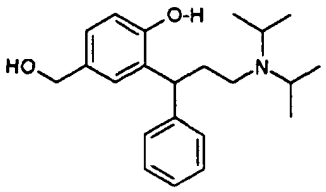
[0027] An ethereal Grignard solution, prepared from the above amine (22.8g), ethyl bromide (17.4g) and magnesium (6.1g) under an atmosphere of nitrogen was diluted with dry tetrahydrofuran (200ml) and then cooled to -60 °C. Powdered solid carbon dioxide (ca. 50g) was the added in small portions and the green reaction mixture was warmed at room temperature. After the addition of an aqueous solution of ammonium chloride (200ml, 10%) and adjustment of the aqueous phase to pH 0.95, a white solid was recovered by filtration to provide *4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)benzoic acid hydrochloride* (14.7g, 64.3% yield), m.p. 140 °C (dec.), tlc (2) 0.33. NMR (CD_3OD): 17.07, 18.77, 33.55, 43.27, 56.50, 71.50, 112.89, 124.10, 127.94, 129.07, 129.25, 129.34, 129.59, 129.66, 130.18, 131.60, 132.78, 137.60, 143.30, 161.11, 169.70.

[0028] The hydrochloride was converted into its methyl ester (MeOH, trace sulphuric acid, 6h reflux) and the free base thus obtained (28g) was dissolved in dry diethyl ether (230ml). This solution was slowly (2h) dropped under an nitrogen atmosphere to a suspension of lithium aluminium hydride (1.8g) in ether (140ml). After stirring for 18h, the reaction was quenched by the addition of water (4.7ml). The organic phase was dried over anhydrous sodium sulphate, filtered and evaporated to dryness to provide *[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (26g, 98.9% yield), as an oil which gradually crystallized, m.p. 86.4 °C, tlc (2) 0.32, **Intermediate A**. NMR ($CDCl_3$): 20.53, 20.61, 36.87, 41.65, 44.14, 48.82, 65.12, 70.09, 111.80, 125.77, 125.97, 126.94, 127.55, 128.08, 128.37, 128.44, 133.27, 134.05, 134.27, 137.21, 144.84.



(Intermediate A)

[0029] A solution of Intermediate A (9.1g) in methanol (100ml) was hydrogenated over Raney-nickel (4.5g) under ambient conditions. After 5h thin layer chromatography indicated complete hydrogenolysis. The catalyst was filtered off and the solution evaporated to dryness to leave an oil (6.95g, 96.5% yield) which gradually solidified, *2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol*, m.p. 50 °C, tlc (2) 0.15, **Intermediate B**. NMR ($CDCl_3$): 19.42, 19.83, 33.22, 39.62, 42.27, 48.27, 65.19, 118.32, 126.23, 126.55, 127.47, 128.33, 132.50, 144.47, 155.38. Hydrochloride: colourless crystalls, m.p. 187-190 °C (with decomposition)



(Intermediate B)

3. Examples

a) Phenolic monoesters

aa) General Procedure

[0030] A stirred solution of *2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol* (Intermediate B, 1.71g, 5.01 mmol) and acid chloride (5.00 mmol carboxylic acid monochloride for compounds of Formila II, 2.50 mmol for compounds of Formula II') in 60 ml of dichloromethane was cooled to 0 °C and then triethylamine (0.502g,4.96 mmol for compounds of Formula II, 1.05g, 9.92 mmol for compounds of Formula II'), dissolved in 10 ml of dichloromethane, was added dropwise during 5-10 mm. Stirring was continued for 18h at room temperature, and then the mixture was washed successively with water (25 ml), aqueous sodium hydrogen carbonate (5%, 25 ml), and water (25 ml). The organic phase was then dried (sodium sulphate) and evaporated under reduced pressure and a low temperature. The oily residues thus formed were finally exposed to high vacuum (2-4 hrs.) to remove traces of residual solvents. The esters of Formula II or II' were obtained as viscous colourless to light yellow syrups in purities between 90% and 99% (tlc, HPLC, NMR).

bb) Salt formation (Example hydrochloride)

[0031] A cooled (0 °C) solution of 4.94 mmol amino base in 30 ml of dry diethyl ether was treated under an atmosphere of nitrogen with 4.70 mmol (monoamines of Formula II) or 9.4 mmol (diamines of Formula II') ethereal (1M) hydrochloric acid. The oily precipitation was washed repeatedly with dry ether and then evaporated in high vacuum. The residual product solidificated in most cases as an amorphous foam. The highly hygroscopic solids show a wide melting range above 100 °C (with decomposition).

Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.47 (4), NMR ($CDCl_3$): 20.36, 20.68, 20.97, 36.59, 42.35, 43.83, 48.76, 64.58, 122.69, 125.61, 126.22, 126.71, 127.96, 128.34, 136.82, 138.97, 143.73, 147.77, 169.24; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 456.8 (100%), 398.4 (4%)

Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.52 (4); NMR ($CDCl_3$): 20.44, 20.64, 27.67, 36.67, 42.21, 43.87, 48.78, 64.70, 122.71, 125.62, 126.52, 126.78, 127.97, 128.53, 136.86, 138.82, 143.82, 147.86, 172.68; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 470.38 (100%), 398.4 (4%)

n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.43 (4); NMR ($CDCl_3$): 13.77, 18.40, 20.43, 20.51, 20.59, 36.15, 36.82, 42.16, 43.90, 48.83, 49.20, 64.58, 122.66, 125.98, 126.17, 126.74, 127.33, 127.94, 128.33, 136.79, 138.91, 143.82, 171.88; GC-MS/N-CI (methane, trimethylsilyl derivative): 482.3 (20%), 412.3 (100%), 340.1 (33%), 298.1 (89%), 234.7 (15%); GC-MS/P-CI (methane, trimethylsilyl derivative): 484.5 (100%), 468.4 (62%), 394.3 (22%); ; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 484.4 (100%), 398.4 (3%)

Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.43(4); NMR ($CDCl_3$): 18.99, 19.11, 20.54, 34.21, 36.88, 41.84, 43.91, 48.78, 64.61, 122.54, 125.57, 126.14, 126.81, 127.94, 128.34, 136.84, 138.84, 143.89, 147.85, 175.36;

2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.49 (1); NMR ($CDCl_3$): 20.46, 20.66, 26.53, 27.34, 37.12, 39.21, 41.46, 43.98, 48.81, 64.65, 122.42, 125.58, 126.16, 126.92,

128.37, 134.27, 136.92, 138.82, 143.97, 148.02, 176.97; ; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 498.8 (100%), 482.5 (10%), 398.4 (4%)

Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.52 (4); NMR ($CDCl_3$): 20.42, 20.62, 36.95, 41.72, 42.27, 48.23, 64.83, 122.74, 125.33, 127.36, 127.89, 127.97, 128.38, 129.34, 130.64, 131.15, 131.83, 136.87, 138.90, 143.82, 147.74, 164.77

Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester, R_f 0.38 (4); NMR (CDCl3): 20.52, 20.62, 20.69, 36.95, 41.84, 42.82, 43.89, 48.23, 64.83, 123.37, 127.36, 127.97, 128.42, 128.38, 129.06, 131.55, 137.50, 138.90, 148.23, 148.32, 160.54

Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester, R_f 0.40 (4)
NMR (CDCl3): 20.54, 20.63, 20.73, 30.69, 36.91, 41.80, 43.92, 48.20, 64.81, 122.60, 127.41, 127.93, 128.39, 129.31, 131.80, 136.73, 138.92, 143.82, 148.17, 168.01

Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester, R_f 0.43; NMR (CDCl3): 20.47, 20.60, 32.87, 36.93, 41.82, 43.90, 48.22, 64.81, 64.83, 122.85, 122.85, 127.39, 127.99, 128.35, 129.31, 131 .84, 136.98, 138.94, 143.80, 147.40, 147.40, 169.05

Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester, R_f 0.43; NMR (CDCl3): 20.64, 23.40, 34.37, 36.95, 41.84, 43.88, 48.25, 64.87, 122.88, 127.34, 127.97, 128.39, 129.33, 131.80, 136.99, 138.94, 143.82, 147.65, 168.72

b) Identical diesters

[0032] Identical diesters (Formula III) were prepared and worked-up as described above with the exeption that 2.4 mmol of both triethylamine and acyl chloride (R^1-COCl) were used. The physical properties were similar to the bases and salts described above.

Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, R_f 0.65 (4) This diester was prepared from mixed formic acetic anhydride and Intermediate B as described for other substrates previously (F: Reber, A. Lardon, T. Reichstein, *Helv. Chim. Acta* **37**: 45 - 58 [1954])

Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, R_f 0.76 (4);; GC-MS/P-CI (ammonia): 426.3 (100%), 368.3 (22%); GO-MS/P-CI (methane, trimethylsilyl derivative): 426.4 (64%), 410.3 (16%), 366.3 (100%); hydrochloride, NMR ($DMSOd_6$): 16.50, 16.76, 18.05, 20.94, 21.04, 27.02, 31.39, 41.28, 45.26, 53.80,65.21,123.39, 126.84, 127.61, 127.85, 128.70, 134.41, 135.49, 142.68, 148.20, 169.32, 170.42

Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester, R_f 0.82 (4); NMR ($CDCl_3$): 20.53, 20.73, 21.14, 27.66, 36.73, 42.10, 43.68, 48.65, 65.75, 122.65, 126.10, 127.01, 127.70, 128.34, 128.78, 133.73, 136.81, 143.76, 148.45, 172.45, 174.21; ; GO-MS/P-CI (ammonia): 454.8 (100%), 438.5 (9%), 382.4 (27%)

n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, R_f 0.86 (4); NMR ($CDCl_3$): 13.70, 13.76, 18.44, 20.53, 20.69, 21.13, 36.14, 36.76, 37.09, 42.08, 43.73, 48.71, 65.64, 122.81, 125.97, 126.97, 127.92, 128.35, 128.77, 133.78, 136.99, 143.76, 148.41, 171.68, 173.40; ; GC-MS/P-CI (ammonia): 482.8 (100%), 396.4 (67%)

Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester, R_f 0.83 (4); NMR ($CDCl_3$): 18.97, 19.10, 20.64, 20.67, 34.01, 34.23, 36.98, 41.72, 43.70, 48.65, 65.61, 122.50, 126.18, 126.73, 127.92, 128.13, 128.36, 133.90, 137.01, 143.85, 148.41, 175.17, 176.81; GC-MS/N-CI (methane,): 480.3 (15%); GC-MS/P-CI (methane): 482.5 (63%), 466.4 (18%), 394.3 (100%)

2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester, R_f 0.96 (4); NMR ($CDCl_3$): 20.44, 20.75, 27.09, 27.24, 37.18, 38.68, 39.15, 41.25, 43.66, 48.20, 65.50, 122.36, 126.32, 127.22, 127.48, 127.83, 128.29, 133.99, 136.98, 143.87, 148.37, 176.70, 178.10; GC-MS/P-CI (methane): 510.5 (76%), 494.5 (21%), 408.4 (100%)

Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, R_f 0.69 (4); NMR (CDCl3): 20.62, 36.95, 41.72, 43.89, 48.23, 66.76, 122.22, 125.33, 127.36, 127.62, 127.89, 127.89, 127.97, 128.38, 129.49, 130.52, 130.64, 131.15, 131.22, 131.98, 136.38, 137.66, 143.82, 148.95, 164.77, 166.60

c) Mixed diesters

[0033] Mixed diesters (Formula IV) were prepared by acylation of the respective benzylic or phenolic monoesters. Workup and physical properties corresponded to the bases and salts described above.

Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, R_f 0.76 (4); NMR ($CDCl_3$): 20.62, 20.91, 33.25, 42.20, 42.28, 48.23, 70.71, 122.96, 127.36, 127.97, 128.38, 128.73, 132.02, 135.41, 137.11, 143.81, 149.35, 161.34, 168.95

Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, R_f 0.74 (4); NMR ($CDCl_3$): 20.60, 36.93, 41.72, 43.89, 48.23, 70.71, 122.50, 125.33, 127.30, 127.89, 127.97, 128.36, 129.57, 130.65, 131.13, 132.05, 135.41, 136.66, 143.80, 149.15, 161.35, 164.78

Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, R_f 0.77 (4); NMR ($CDCl_3$): 18.99, 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 126.76, 127.14, 127.94, 128.39, 128.84, 133.55, 137.04, 143.84, 148.56, 170.84, 175.18;

2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-*phenylpropyl)-benzyl ester*, R_f 0.80 (4); NMR ($CDCl_3$): 20.63, 20.93, 27.19, 33.25, 37.49, 42.21, 42.25, 48.22, 67.37, 123.18, 127.36, 127.84, 128.39, 131.16, 137.34, 143.84, 148.29, 168.93, 178.40

2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)phenyl ester, R_f 0.81 (4); NMR ($CDCl_3$): 20.60, 20.79, 27.09, 36.93, 37.35, 41.85, 42.29, 48.25, 65.91, 122.36, 127.37, 127.99, 128.39, 129.38, 132.69, 136.00, 136.85, 143.80, 170.45, 176.60

d) Benzylic monoesters

[0034] A mixture consisting of Intermediate B (80 mg, 0.23 mmol), vinyl ester (0.4 ml), tert.-butyl methylether (18 ml), and lipase enzyme (1.0 g) was gently shaken at room temperature. Benzylic formate, acetate, and n-butyrate were prepared from the corresponding vinyl ester donors using SAM I lipase (Amano Pharmaceutical Co.). Benzoylation was achieved with vinyl benzoate in the presence of Lipozym IM 20 (Novo Nordisk), whereas pivalates and isobutyrates were obtained from the corresponding vinyl esters under catalysis of Novozym SP 435 (Novo Nordisk). Tlc analysis indicated after 2 - 24 h complete disappearence of the starting material (R_f = 0.45 (3). The mixture was filtered and then evaporated under high vacuum (< 40 °C) to give the carboxylic acid (R^1-CO_2H) salts of the respective benzylic monoesters as colourless to light yellow oils.

Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.25 (2); NMR ($CDCl_3$): 19.43, 33.24, 39.61, 42.25, 48.21, 68.44, 118.09, 127.34, 127.66, 128.31, 128.39, 133.97, 144.47, 156.63, 161.32

Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.26 (2); NMR ($CDCl_3$): 19.45,20.96, 33.26, 39.63, 42.27, 48.23, 48.23, 63.59, 118.00, 127.36, 128.33, 128.33, 128.48, 128.48, 128.53, 129.13, 131.59, 133.88, 144.49, 155.74, 170.44

Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.45 (2); NMR ($CDCl_3$): 19.02, 19.43, 27.58, 33.20, 39.61, 42.25, 48.21, 64.08, 118.30, 125.30, 127.03, 127.39, 128.31, 130.12, 134.22, 144.51, 155.64, 173.22

Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.54 (2); NMR ($CDCl_3$): 13.58, 18.40, 19.45, 33.29, 35.88, 39.65, 42.23, 48.25, 63.96, 118.32, 124.55, 126.20, 127.35, 128.32, 129.91, 134.22, 144.50, 155.60, 169.05

Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.56 (4); NMR ($CDCl_3$): 19.09, 19.45, 33.28, 33.59, 39.65, 42.29, 48.25, 64.63, 118.35, 125.35, 127.03, 127.38, 128.35, 128.49, 129.79, 134.22, 144.52, 155.65, 175.48

2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.61 (4); NMR ($CDCl_3$): 19.41, 27.15, 33.24, 37.46, 39.61, 42.25, 48.21, 65.10, 118.30, 125.32, 127.00, 127.34, 128.31, 129.42, 134.18, 144.47, 155.61, 178.39

Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.77 (4); NMR ($CDCl_3$):18.01, 19.40, 33.24, 39.60, 42.40, 48.20, 66.93, 117.13, 127.18, 127.81, 128.33, 129.98, 130.17, 132.96, 133.58, 142.33, 156.95, 166.60

e) Ethers and silyl ethers

[0035] A mixture of Intermediate B (3.4g, 10 mmol), methanesulphonic acid (2 ml, 31 mmol), and alcohol R^3-OH, (50 - 150 ml) was stirred at room temperature until no starting material was detectable (2 - 24 h). After evaporation to dryness (< 35 °C) the residue was redissolved in aqueous sodium hydrogen carbonate solution (100 - 200 ml, 5 %, w/v) and the solution was extracted with ethyl acetate (75 ml). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to give bases of Formula VI (R^4 = H) as colourless to light yellow oils.

[0036] Mixed ester ether derivatives, e.g. of Intermediate A, were prepared by benzylic acylation of phenolic ethers, such as Intermediate A, according to the procedure described for Examples of the structure of Formula IV.

Hydrochlorides:

[0037] Molar equivalents of bases of Formula VI (R^4 = H), dissolved in tert.-butyl methylether, and ethereal hydrochloric acid were combined at room temperature. Oily precipitates were separated and dried in vacuum, crystalline hydrochlorides were isolated and recrystallized from acetonitrile to give colourless crystalline material.

2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol, R_f 0.61 (4); GC-MS/P-CI (methane, trimethylsilyl derivative): 428.4 (100%), 412.3 (49%), 396.3 (52%); hydrochloride: amorphous hygroscopic colourless solid; m. p. 161 °C; NMR (CD_3OD): 17.39/18.75 (broad signals), 33.79, 43.13, 56.47, 58.00, 75.59, 116.19, 120.79, 127.62, 129.04, 129.14, 129.42, 129.55, 130.43, 144.32, 155.85

2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol, R_f 0.72 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 444.8 (100%), 398.4 (6%); hydrochloride: m. p 158 - 161 °C, NMR (CD_3OD): 15.43, 17.12, 18.82, 33.80. 56.49, 66.49, 73.62, 116.19, 127.63, 128.99, 129.13, 129.36, 129.55, 130.58, 130.75, 144.32, 155.77

2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethyl-phenol, NMR ($CDCl_3$): 18.62, 19.44, 23.10, 33.24, 39.61, 42.26, 48.22, 71.87, 73.94, 117.78, 124.95, 127.35, 127.57, 128.32, 128.47, 133.66, 134.23, 144.48, 155.25

2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethyl-phenol, NMR ($CDCl_3$): 19.44, 22.32, 33.27, 39.65, 42.29, 48.25, 69.28, 72.10, 117.90, 127.38, 128.03, 128.41, 131.10, 133.76, 134.37, 144.51, 154.65

2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethyl-phenol, NMR ($CDCl_3$): 13.75, 19.44, 19.75, 32.24, 33.28, 39.60, 42.20, 48.20, 72.45, 117.87, 125.50, 127.29, 128.39, 133.70, 134.30, 144.47, 155.36

Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethyl-phenyl ester, NMR ($CDCl_3$): 19.99, 20.62, 20.90, 33.33, 42.30, 48.21, 58.41, 75.94, 122.92, 127.37, 127.95, 128.35, 131.85, 136.99, 138.81, 143.88, 147.88, 168.95

Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethyl-phenyl ester, NMR ($CDCl_3$): 15.49, 19.94, 20.95, 33.23, 42.25, 48.25, 65.70, 73.73, 122.63, 127.46, 127.95, 128.36, 131.65, 136.79, 139.71, 143.80, 147.66, 168.99

2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol, NMR ($CDCl_3$): 0.10, 0.10, 19.40, 19.43, 33.25, 39.65, 42.25, 48.20, 64.93, 117.90, 124.90, 126.60, 127.35, 128.35, 128.48, 133.80, 137.15, 144.49, 155.28

Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]amine, NMR ($CDCl_3$): 0.10, 0.10, 0.29, 0.29, 19.40, 19.53, 33.28, 41.19, 42.27, 48.25, 66.40, 121.37, 127.36, 128.25, 128.50, 136.42, 144.10, 154.98

[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol, NMR ($CDCl_3$): 0.29, 0.33, 19.40, 19.53, 33.27, 41.16, 42.27, 48.23, 65.22, 118.04, 124.99, 126.52, 127.30, 128.25, 134.16, 136.80, 144.14 155.06

Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine, NMR ($CDCl_3$): 0.28, 0.32, 19.39, 19.43, 33.28, 41.22, 42.33, 48.19, 58.40, 75.95, 117.68, 124.92, 126.60, 127.35, 128.25, 128.55, 134.00, 136.47, 144.16, 155.09

Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine, NMR ($CDCl_3$): 0.28, 0.31, 15.50, 19.42, 19.58, 33.29, 41.17, 42.25, 48.20, 65.70, 72.48, 117.50, 124.75, 126.39, 127.39, 128.25, 128.50, 134.99, 136.28, 144.19, 154.28

[4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]methanol, R_f 0.65 (3)

Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, NMR ($CDCl_3$): -4.92, -5.00, 19.40, 19.49, 20.40, 20.83, 23.49, 33.25, 41.22, 42.25, 48.25, 72.55, 81.55, 121.24, 124.88, 127.40, 128.26, 128.48, 128.44, 133.37, 135.74, 144.11, 155.20

4-(tert.-Butyl-dimethylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol, R_f 0.70 (3); GC-MS/N-CI (methane, trimethylsilyl derivative): 526.5 (59%), 454.3 (100%), 412.2 (14%), 340.1 (42%); GC-MS/P-CI (methane, trimethylsilyl derivative): 528.6 (100%), 512.5 (85), 470.43 (10%), 396.3 (31%)

Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)phenyl ester, NMR ($CDCl_3$): -4.77, -4.88, 19.15, 20.65, 20.93, 24.77, 33.25, 42.20, 48.20, 67.90, 122.79, 125.15, 127.44, 127.90, 128.41, 136.99, 140.55, 143.85, 147.86, 168.95

{3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine, R_f 0.94 (3); GC-MS/N-CI (methane): 568.6 (62%), 454.3 (100%), 438.2 (10%), 340.2 (58%), 324.8 (16%), 234.7 (78%); GC-MS/P-CI (methane): 570.6 (70%), 554.5 (52%), 512.5 (18%), 438.4 (24%)

Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, R_f 0.56 (5); GC-MS/P-CI (ammonia): 474.4 (100%), 416.4 (54%); NMR ($CDCl_3$): 20.44, 20.56, 21.07, 36.73, 41.53, 44.01, 48.79, 66.43, 70.00, 111.61, 125.75, 127.34, 127.55, 127.76, 127.90, 128.03, 128.27, 128.39, 133.98, 136.98, 144.63, 156.05, 170.94

Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, R_f 0.87 (4); NMR ($CDCl_3$):20.54, 20.60, 36.80, 41.51, 43.95, 48.67, 66.83, 70.04, 111.66, 125.76, 127.35, 127.45, 127.78, 128.06, 128.27, 128.30, 128.42, 128.85, 129.66, 130.55, 132.86, 134.05,137.03, 144.75, 156.08, 166.46; GC-MS/P-CI (ammonia): 536.5 (100%), 416.4 (42%)

Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, R_f 0.77 (4); NMR ($CDCl_3$): 19.01, 20.62, 20.65, 34.04, 36.85, 41.54, 43.97, 48.71, 66.15, 70.06, 111.62, 125.79, 125.96, 126.97, 127.24, 127.55, 127.81, 128.08, 128.34, 128.45, 134.05, 137.10, 144.79, 156.00, 177.01); GC-MS/P-CI (ammonia): 502.4 (100%), 416.4 (49%)

f) Carbamates and Carbonates

[0038] A solution of 4.0 mmol of Intermediate B or benzylic ether (Formula VI, R^4 = H) in dichloromethane (20 ml) was treated at room temperature for 16 h with isocyanate (4.8 mmol) or diisocyanate (2.2 mmol). After washing with 10 ml aqueous sodium hydrogen carbonate (5%, w/v), drying (Na_2SO_4) and evaporation the oily residue was redissolved in tetrahydrofuran (10 ml). Addition of ethereal hydrochloric acid and evaporation to dryness in high vacuum gave crystalline or amorphous carbamate hydrochlorides. Bis-carbamates were prepared in like manner using Intermediate B and excess isocyanate (4.8 mmol) and toluene as solvent at 65 °C over 18 h.
Carbonates were prepared and worked-up according to the methods described for the preparation of compounds of Formula II to IV. Alkyl chloroformates were used as acylation reagents.

N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester, R_f 0.38 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 486.8 (100%), 413.4 (5%), 398.4 (6%); hydrochloride: m. p. 64 °C (with decomposition); NMR (DMSO-d_6): 15.16, 16.68, 18.05, 18.13, 25.33, 31.26, 35.46, 53.94, 62.65, 67.22, 123.04, 125.70, 126.72, 127.86, 128.67, 135.42, 136.02, 140.07, 142.98, 147.53, 154.52

N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester, NMR ($CDCl_3$): 20.52, 20.61, 36.91, 39.44, 42.25, 48.22, 62.66, 118.36, 119.46, 123.50, 125.32, 127.11, 127.99, 130.15, 132.63, 139.65, 141.33, 145.16, 152.21, 156.00

N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester, R_f 0.36 (3), NMR ($CDCl_3$): 15.00, 19.23, 19.40, 33.26, 36.00, 39.62, 42.35, 48.12, 65.95, 118.30, 125.45, 127.08, 128.33, 130.37, 134.24, 144.44, 155.44, 157.74

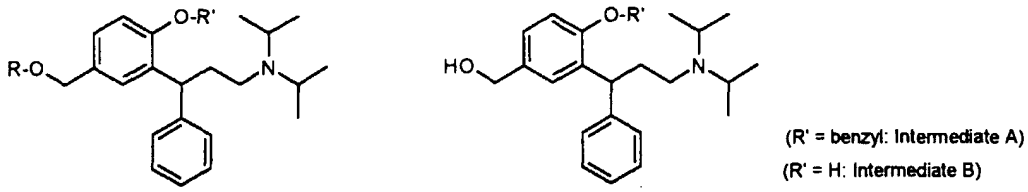
{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester, (Formula VII', X = Y = NH, n = 4) R_f 0.60 (6); dihydrochloride: m. p. 142.5 - 145.6 °C

Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester, R_f 0.67 (4)

Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester, R_f 0.87 (4)

4. The respective prodrugs (Formula I) or pharmaceutically acceptable salts thereof were prepared also from Intermediate A or Intermediate B by the following methods:

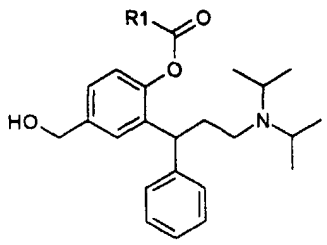
[0039]



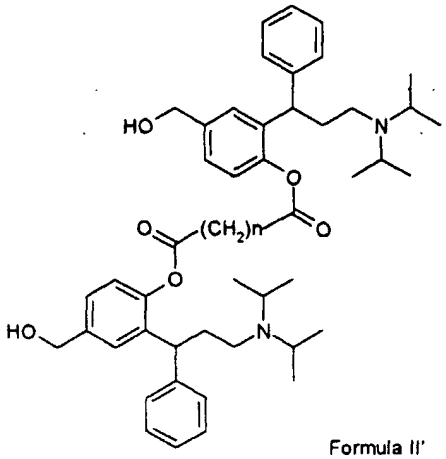
Formula I

a) Phenolic monoesters

[0040] Treatment of Intermediate B with an equivalent of an acylating agent (e.g. acyl halogenide or acyl anhydride) in an inert solvent and in the presence of an condensating agent (e.g. amine) provides phenolic monoesters of Formula II or Formula II' (n = 0-12), respectively, if polyfunctional acylating agents (e.g. acid chlorides of dicarboxylic acids) are used.



Formula II

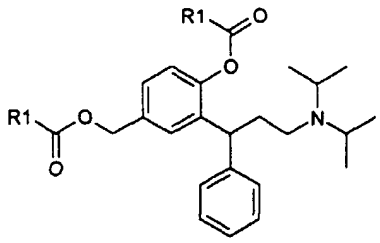


Formula II'

[0041] Alternatively, structures of Formula II or II' may be obtained by regioselective deprotection of a protected benzylic hydroxy group (chemically or enzymatically: T. W. Greene, P. G. M. Wuts, „*Protective Groups in Organic Chemistry*", 2nd Ed., J. Wily & Sons, New York 1991).

b) Identical diesters

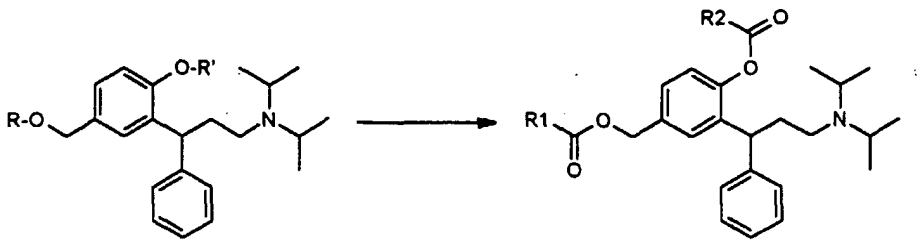
[0042] Di-acyl compounds are readily accessible if an at least two molar excess of acylation agent is used in the above-mentioned conversions of Intermediates A or B or, more general, on treatment of compounds of Formula I with acylating agents in the presence of suitable catalysts.



Formula III

c) Mixed diesters

[0043] Acylation of compounds of the general Formula I wherein R and R' are different substituents selected from the group consisting of hydrogen, acyl residues or protecting groups that are cleavable under the acylation reaction conditions yields mixed diesters of Formula IV, where R^1 and R^2 are different.

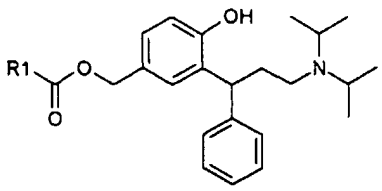


Formula I

Formula IV

d) Benzylic monoesters

[0044] Moreover, the invention refers to the preparation of phenols with *para* acyloxymethyl substituents (Formula V). These compounds can be prepared in several chemical steps from intermediates such as Formula I, where R represents hydrogen and R' is hydrogen or any suitable protective group which can be removed by known methods (T. W. Greene, P. G. M. Wuts, „*Protective Groups in Organic Chemistry*", 2nd Ed., J. Wily & Sons, New York 1991) in the presence of the newly introduced substituent R^1CO. It was found, however, in the present invention that the benzylic substituent R^1CO can be introduced more conveniently and in only one step if Intermediate B is treated at room temperature and under anhydrous conditions with activated esters (e.g. vinyl acylates, isopropenyl acylates) in the presence of enzymes such as lipases or esterases.

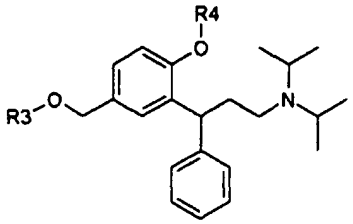


Formula V

e) Ethers and silanyl esters

[0045] Regioselective modification of the *benzylic hydroxy groups* is achieved either by acid or base treatment of benzylic acylates in the presence of suitable hydroxy reagents (e.g. alcohols) or by catalytic ether formation as described in the literature for other benzylic substrates (J. M. Saa, A. Llobera, A. Garcia-Raso, A. Costa, P. M. Deya; J. Org. Chem. **53**: 4263-4273 [1988]). Both free benzylic alcohols such as Intermediates A and B or Formulas II or VI (in which R^3 hydrogen) or Formula VII (in which R^5 is hydrogen) as well as benzylic acylates such as Formula III, IV, V may serve as starting materials for the preparation of benzylic ethers (B. Loubinoux, J. Miazimbakana, P. Gerardin; Tetrahedron Lett. **30**: 1939-1942 [1989]).

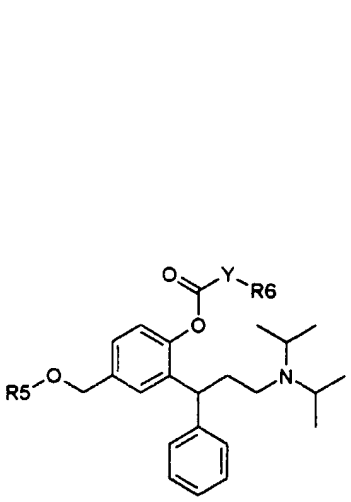
Likewise the *phenolic hydroxy groups* are readily transformed into phenyl ethers (R^4 = alkyl) using alkylating agents such as e.g. alkyl halogenides, alkyl sulphates, alkyl triflates or employing Mitsunobu type reaction conditions (Synthesis **1981**, 1-28). Similarly, both phenolic and alcoholic monosilyl ethers are obtained by regioselective silylation or by desilylation of bis-silyl ethers of Intermediate B as described for other compounds in the literature (J. Paladino, C. Guyard, C. Thurieau, J.-L. Fauchere, Helv. Chim. Acta **76**: 2465-2472 [1993]; Y. Kawazoe, M. Nomura, Y. Kondo, K. Kohda, Tetrahedron Lett. **26**: 4307-4310 [1987]).



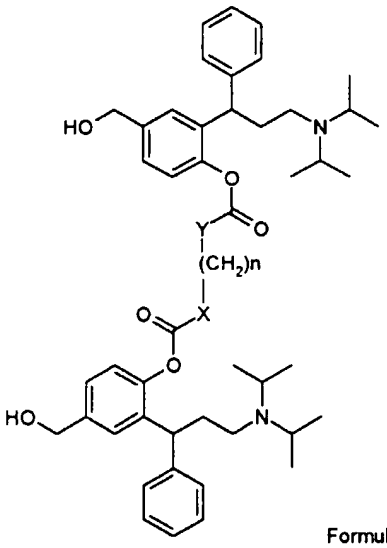
Formula VI

f) Carbamates and Carbonates

[0046] Other reactive reagents which can be used in the reaction of the hydroxy groups of Intermediates A or B, Formulas II, II', V, or VI (R^3 or R^4 = hydrogen) shown above are, for example, other activated carbonyl compounds or carbonyl precursor reagents.
Preferably, haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates, isothiocyanates can be used. The coupling reactions can be carried out in inert solvents over periods of several hours at temperatures from -10 °C to the refluxing temperature of the solvent or reagent used to provide compounds of the general Formula VII where R^5 represents hydrogen, alkyl, aliphatic or aromatic acyl, or carbamoyl, and Y and R^6 represent O, S, NH and alkyl or aryl, respectively.
Polyfunctional reagents give the corresponding derivatives. For example, diisocyanates or di-carbonylchlorides provide compounds of Formula VII' where X, Y have the meaning of O, S, or NH and n is zero to twelve.



Formula VII



Formula VII'

[0047] The compounds of formula (I) can be used as pharmaceutically active substances, especially as antimuscannic agents.
[0048] The compounds of formula (I) can be used for preparing pharmaceutical formulations containing at least one of said compounds.

II. Pharmaceutical composition of the present invention

[0049] In accordance with the present invention, the compounds of formula (I), in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of formula (I) in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

[0050] The composition according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

[0051] The compounds according to the invention may be used in a patch formulation. The compounds can be administered transdermally with a reduced incidence of side effects and improved individual compliance.

[0052] The compounds and compositions can, as mentioned above, be used for the treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 5 mg, adminstered singly or multiply in doses e.g. from about 0,05 mg to about 200 g each.

III. Incubations of different compounds of the invention with human liever S 9-fraction.

[0053] A pooled human liver S 9-preparation was used to show the in-vitro metabolism of different compounds of the invention and to prove the generation of the active metabolite by enzymatic process.

[0054] The pooled human liver S 9-preparation was delivered by Gentest, Woburn, MA, USA.

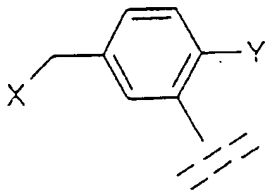
[0055] The analysis was performed by a routine High Pressure Liquid Cromatography (HPLC) method with UV-detection.

[0056] The incubation results expressed in (%) of theoretical turn-over are presented in Table 1.

[0057] They ranged from 96 to 63,2 %. The formation of the active metabolite is dependent on the substituents both at the benzylic and phenolic side of the respective compounds.

Explanation:

[0058] The prodrugs introduced in the assay show the following chemical structure:

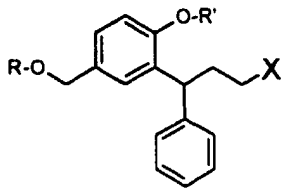


chemical structure X-/-Y

AcO-/-OAc	means	acetate
HO-/-OBut	means	hydroxy and butyrate
HO-/-OiBut	means	hydroxy and iso-butyrate
iButO-/-OiBut	means	iso-butyrate
ButO-/-OBut	means	butyrate
PropO-/-OProp	means	propyrate
HO-/-OProp	means	hydroxy and propyrate
HO-/-OAc	means	hydroxy and acetate

Claims

1. 3,3-Diphenylpropylamines of Formula I:



(I)

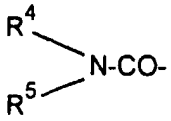
wherein R indepently signifies:

a) R^1 represents the residues hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl or allyl; or

b) R^2 represents the residues formyl, acetyl, propionyl, isobutyryl, butyryl, valeroyl, pivaloyl, benzoyl; or

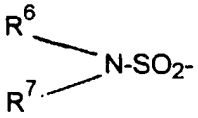
c) R^3 represents the residues CH_3OCO-, C_2H_5-OCO-, C_3H_7OCO-, $(CH_3)_3COCO$-, benzoylacyl, benzoylglycyl, glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl; or

d) a group consisting of



wherein R^4 and R^5 indepently represent the residues hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl and wherein R^4 and R^5 may form a ring together with the amine nitrogen;
or

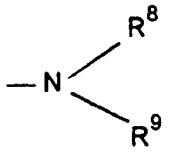
e) a group consisting of



wherein R^6 and R^7 indepently represent the residues methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl; or

f) an ester of inorganic acids such as sulfuric acid, phosphoric acid;

X represents a tertiary amino group of Formula Ia



(Ia)

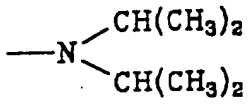
wherein R^8 and R^9 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms and wherein R^8 and R^9 may form a ring together with the amine nitrogen, R' represents hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, alkyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, if R is hydrogen R' will not represent hydrogen or methyl
and

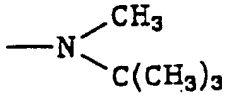
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

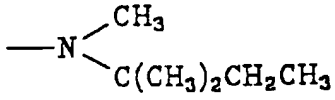
2. 3,3-Diphenylpropylamines according to claim 1, wherein each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

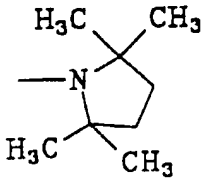
3. 3,3-Diphenylpropylamines according to claim 1 or 2, wherein at least one of R^8 and R^9 comprises a branched carbon chain.

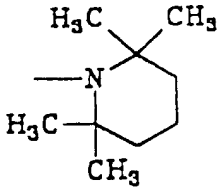
4. 3,3-Diphenylpropylamines according to any one of claims 1 to 3, wherein X signifies any of the following groups a) to h):

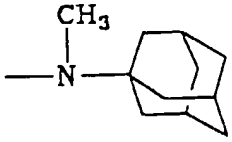
a) 

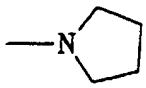
b) 

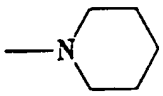
c) 

d) 

e) 

f) 

g) 

h) 

5. 3,3-diphenylpropylamines, their salts with physiologically acceptable acids, their free bases or salts thereof, racemates and individual enantiomers thereof which are definied as

Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenyl ester
Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester
Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethy-phenyl] ester
Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester
Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester
Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester

Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester
n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester
2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester
Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester
Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester
Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol
Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester
Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester
2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol
Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)propyl]-amine
[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol
Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine
Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine
[4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol
Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol
Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
{3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)phenyl]-3-phenylpropyl}-diisopropylamine
[4-(tert.-Butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol
Acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
4-(tert.-Butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol
{3-[2-(tert.-Butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)phenyl]-2-phenylpropyl}-diisopropylamine
Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester
N-Phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester
{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester

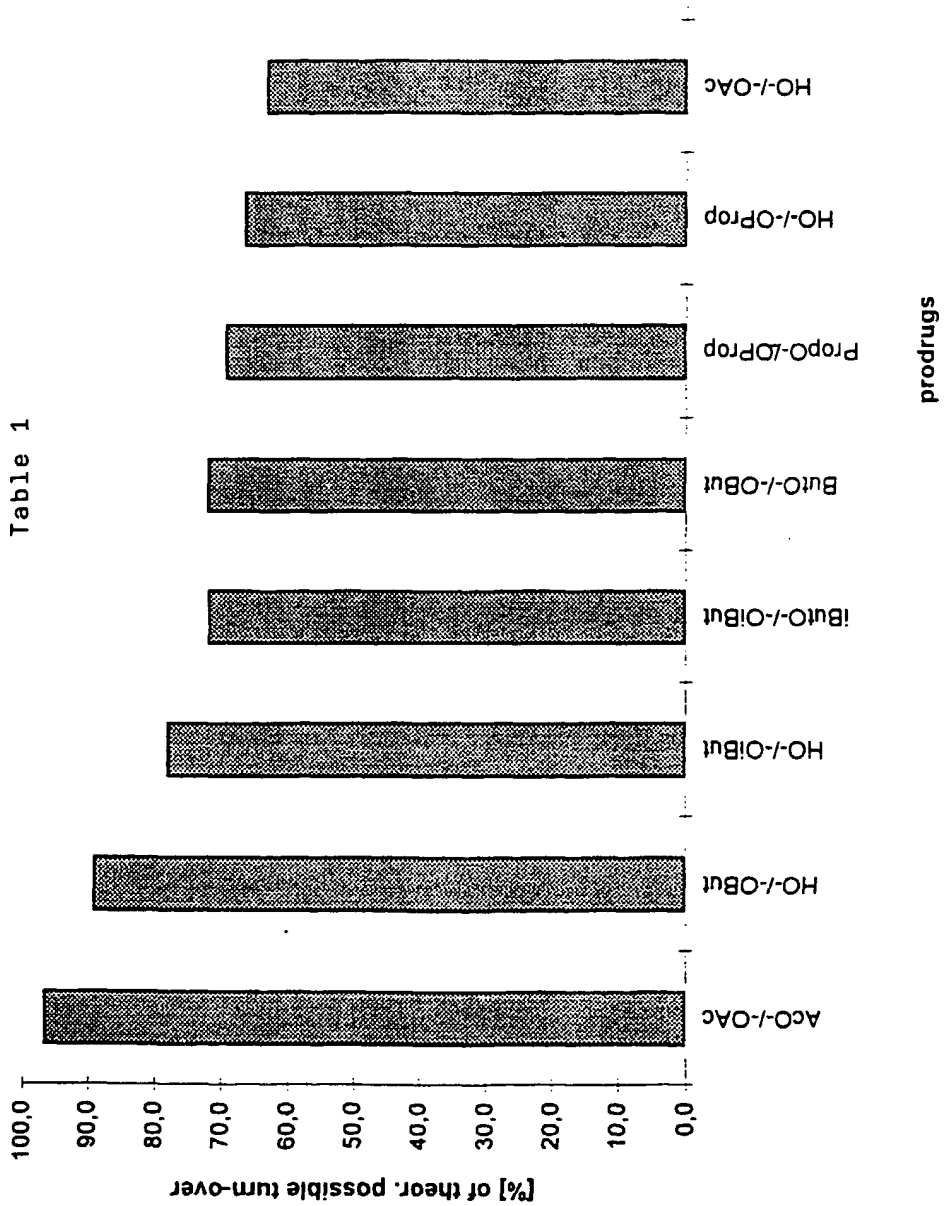
6. 3,3-Diphenylpropylamines according to any one of claims 1 to 5 for use as pharmaceutically active substances, especially as antimuscarinic agents.

7. A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to any one of claims 1 to 6 and preferably a compatible pharmaceutical carrier.

8. Use of a 3,3-diphenylpropylamine according to any one of claims 1 to 7 for preparing an antimuscarinic drug.

Table 1

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h



European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 98 10 8608

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X,D	WO 94 11337 A (KABI PHARMACIA AB ;JOHANSSON ROLF ARNE (SE); MOSES PINCHAS (SE); N) 26 May 1994 * page 12, line 35 - page 13, line 15 * ---	1-4,6-8	C07C1/00 C07C217/62 C07C217/48 C07C219/28 C07C219/22
A	WO 89 06644 A (KABIVITRUM AB) 27 July 1989 * abstract * ---	1-8	C07D207/06 C07D295/06 C07C271/08
A,D	LISBETH NILVEBRANT ET AL.: "Tolterodine - a new bladder-selective antimuscarinic agent" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 327, 1997, pages 195-207, XP002079629 * the whole document * -----	1,7,8	C07F7/18 C07C307/02 A61K31/135 A61K31/325 A61K31/40 A61K31/435

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07C
C07D
C07F
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	5 October 1998	Rufet, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 98 10 8608

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

05-10-1998

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 5382600 A	17-01-1995

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

1,025,041

PATENT SPECIFICATION

NO DRAWINGS

1,025,041

Inventor: JOSEF KLOSA

Date of Application and filing Complete Specification: Feb. 21, 1964.
No. 7418/64.

Complete Specification Published: April 6, 1966.

Index at acceptance:—C2 C(1G5B, 1G6B1, 1G6B3, 1H1A3, 1H1C2, 2A2, 2A5, 2A7, 2A13, 2A14, 2B3A2, 2B3B, 2B3F, 2B3G1, 2B3G8, 2B3G9, 2R17, 3A13C3C, 3A13C10H, B4A2, B4A4, B4D, B4M); **A5** B2S

Int. Cl.:—C 07 c, d // A 61 k

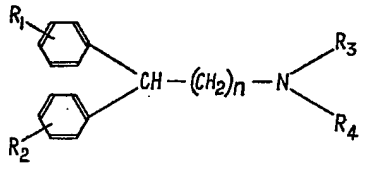
COMPLETE SPECIFICATION

Process for the manufacture of Diphenylalkylamines

We, FARBWERKE HOECHST AKTIENGESELLSCHAFT, vormals Meister Lucius & Brüning, a body corporate recognised under German Law, of 6230 Frankfurt (M)-Hoechst, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

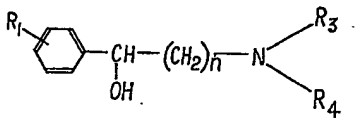
The present invention relates to a process for the manufacture of diphenylalkylamines which have a beneficial physiological effect, especially on the heart and on blood circulation. The invention also relates to processes for the manufacture of pharmaceutical preparations, having cardiac and circulatory action containing diphenylalkylamines or their physiologically tolerable salts as the active ingredients.

The present invention provides diphenylalkylamines of the formula



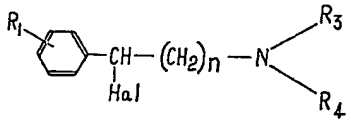
(I)

in which R_1 and R_2, which may be identical or different, represent hydrogen, an alkyl group having 1—3 carbon atoms, an alkoxy group having 1—3 carbon atoms, or halogen, especially chlorine, R_3 represents hydrogen or an alkyl group having 1—3 carbon atoms, and R_4 represents hydrogen, an alkyl group having 1—4 carbon atoms, an aralkyl group having up to 4 carbon atoms in the alkylene chain which may be substituted in the phenyl nucleus by alkyl or alkoxy groups each having 1—3 carbon atoms, or in which R_3 and R_4 together with the nitrogen atom form a morpholino, piperidino or pyrrolidino ring, and n is 1 or 2, by reacting a 1-phenyl-1-hydroxy-alkylamine of the formula



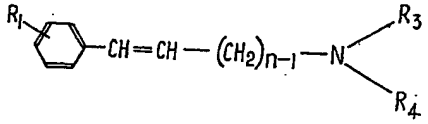
(II)

or a 1-phenyl-1-halogenoalkylamine of the formula



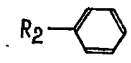
(III)

in which Hal represents a halogen atom, preferably a chlorine atom, or a 1-phenyl-1,2-unsaturated alkenylamine of the formula



(IV)

in which R_1, R_3 and R_4 and n have the meanings given above, with an aryl compound of the formula



(V)

in which R_2 has the meaning given above, in

[*Pric*

the presence of Friedel-Crafts catalysts such for example as gallium trichloride, boron trifluoride or, preferably, aluminium trichloride.

The following phenylalkyl compounds may be used as one reactant in the process of the present invention:

1 - phenyl - 1 - hydroxy - 3 - (1 - phenyl-propyl - (2) - amino) - propane,
1 - *p* - methoxy - phenyl - 1 - hydroxy - 3-(1 - phenyl - propyl - (2) - amino) - propane,
1 - *m* - chlorophenyl - 1 - hydroxy - 3 - (1-phenyl - propyl - (2) - amino) - propane,
1 - *o* - tolyl - 1 - hydroxy - 3 - (1 - phenyl-propyl - (2) - amino) - propane,
1 - phenyl - 1 - hydroxy - 3 - (1 - *m* - methoxy - phenyl - propyl - (2) - amino) - propane,
1 - phenyl - 1 - hydroxy - 3 - (1 - phenyl-butyl - (2) - amino) - propane,
1 - phenyl - 1 - hydroxy - 3 - (2 - phenyl-ethylamino) - propane,
1 - phenyl - 1 - hydroxy - 3 - (1- phenyl-propyl - (2) - methylamino) - propane,
1 - phenyl - 1 - hydroxy - propylamine - (3),
1 - phenyl - 1 - hydroxy - ethylamine - (2),
1 - phenyl - 1 - hydroxy - 3 - isopropyl-amino - propane,
1 - phenyl - 1 - hydroxy - 2 - morpholino-ethane, and the analogous
1 - phenyl - 1 - chloro - compounds and
1 - phenyl - 1,2 - unsaturated compounds.

As the second reactant in the process of the present invention, there may be mentioned, for example, benzene, toluene, chlorobenzene, methoxybenzene, ethoxybenzene and isopropylbenzene.

The reaction is carried out in a suitable solvent. As solvent there may be used, the second reactant in the process, which is then to be used in excess, or as an inert solvent, nitrobenzene or chlorinated hydrocarbons such as for example as carbon tetrachloride or tetrachloroethane.

The reaction is carried out at a temperature in the range of 50 and 200°C, preferably in the range of 60 and 140°C. In practice, the reaction is carried out at the boiling temperature of the solution used.

In an advantageous method for carrying out the process of the present invention, the selected 1-phenyl-1-hydroxy-alkylamine is converted with a Lewis acid, for exemple, aluminium chloride, in a suitable solvent, for example, benzene, and with the aid of an appropriate halogenating agent, preferably an acid chloride of sulphur, for example, thionyl chloride, into the corresponding chloride; the hydrochlorides of the 1-phenyl-1-chloro-compounds thus obtained are generally well crystallizable. The 1-phenyl-1-chloroalkyl-amines thus obtained are condensed at elevated temperature in one of the mentioned solvents containing the desired reactant and the Friedel-Crafts catalyst to yield the diphenyl-alkyl-amines. These two process steps may be carried out in one vessel.

According to another advantageous method of operation, the 1-phenyl-1-hydroxy-alkyl-amines can be reacted directly with the second reactant in the solvents mentioned above. The reaction may be carried out in the same way starting from the mentioned 1-phenyl-1,2-unsaturated alkylamine compounds.

As basic compounds, the products of the present invention may be converted into the corresponding salts by reacting them with inorganic or organic acids, preferably physiologically tolerable inorganic or organic acids. As inorganic acids, there may be used for example, hydrohalic acids, for example hydrochloric acid, sulphuric acid, phosphoric acid or amido-sulphonic acid. As organic acids, there may be used, for example, acetic acid, propionic acid, lactic acid, glycolic acid, gluconic acid, maleic acid, succinic acid, tartaric acid, salicyclic acid, or citric acid.

The products of the present invention may be administered parenterally or orally, as such or in the form of their salts, if desired or required in admixture with pharmaceutically usual carriers, if desired, in unit dosage form. In the case of oral application, they may be used preferably as tablets or dragees into which they, as the active substances, have been made up with the usual carriers such as lactose, starch, tragacanth and magnesium stearate.

The processes hitherto known and used for the preparation of the products of the invention are difficult and time-consuming. Some of the starting materials required for these processes are difficulty accessible. The present process makes the products more readily available as it may be carried out on the scale required for industrial use.

The following Examples illustrate the invention.

EXAMPLE 1

15.1 g of 1-phenyl-1-hydroxy-propylamine-(3) were boiled for 30 minutes with 14.5 g of phenylacetone in 50 cc of benzene and the water formed was removed by distillation with benzene. The oily residue was then taken up in 30 cc of methanol and 5 cc of water. 1.5 g of sodium boron hydride was introduced portionwise into this solution, during which time the temperature of the reaction mixture rose to 40—50°C. The reaction mixture was then heated for 30 minutes on the water bath and the solvent was removed by distillation. The oily residue was extracted with ether and alcoholic hydrochloric acid was added to the ether extract until the mixture was turbid. 25 g of 1-phenyl-1-hydroxy-3-(1-phenyl-propyl-(2)-amino)-propane-hydrochloride crystallized; the compound was found to melt at 144—146°C.

25 g of the compound thus obtained were introduced portionwise, at room temperature, into a solution of 40 cc of thionyl chloride in 80 cc of benzene. A strong evolution of hydrogen chloride and sulphur dioxide set in. After some time, the hydrochloride of 1-phenyl-1-chloro - 3 - (1 - phenyl - propyl - (2) - amino) - propane crystallized. Separation was completed by the addition of ether. 24 g of the compound which showed a melting point of 138—144°C were obtained. 10 g of this hydrochloride were suspended in 40 cc of benzene and 8 g of anhydrous aluminium chloride were added, the temperature being at about 50°C. The whole was then heated for 30 minutes under reflux. After cooling, the reaction mixture was poured in a mixture of 20 cc of concentrated hydrochloric acid, 10 cc of water and 100 g of ice. After several hours standing and after addition of ether, the hydrochloride of 1,1-diphenyl-3-(1-phenyl-propyl-(2)-amino)-propane crystallized in almost colourless crystals. The crude yield was 11.2 g; the compound was found to melt at 186—188°C (from aqueous methanol 190—192°C).

EXAMPLE 2

15 g of 1-phenyl-1-hydroxy-propylamine-(3) were introduced portionwise into a mixture of 16 cc of thionyl chloride and 30 cc of benzene. The whole was heated for 20 minutes under reflux on the water bath. After several hours standing, crystallization was completed by the addition of ether. 18.5 g of 1 - phenyl - 1 - chloro - propylamine - (3)-hydrochloride having a melting point of 110—112°C were obtained. 10 g of the hydrochloride thus obtained were suspended in 40 cc of benzene and 12 g of anhydrous aluminium chloride were added portionwise. After heating for 30 minutes on the water-bath, the reaction mixture was poured in a mixture of hydrochloric acid, water and ice. The hydrochloride of 1,1-diphenyl-propylamine-(3) melting at 206—209°C crystallized out. The yield was 12 g. After recrystallization from water, the product was found to melt at 217—218°C.

EXAMPLE 3

10 g of 1-phenyl-1-hydroxy-2-morpholino-ethane were dissolved in 30 cc of benzene. 15 g of anhydrous aluminium chloride were added portionwise in such a manner that the reaction mixture did not boil. The reaction mixture was then heated for 30 minutes on a water bath. After cooling, it was poured in a mixture of ice, water and concentrated hydrochloric acid. After some minutes, 1,1-diphenyl - 2 - morpholino - ethane - hydrochloride crystallized out. The yield was 14.6 g. After recrystallization from a mixture of isopropanol and ether, the compound was found to melt at 211—213°C.

EXAMPLE 4

8 g of anhydrous aluminium chloride were introduced in a solution of 5 g of 1-phenyl-1-hydroxy-2-benzylamino-ethane in 20 cc of toluene in such a manner that the toluene did not boil. The reaction mixture was then heated for 30 minutes to boiling temperature and after cooling it was poured into a mixture of ice, water and concentrated hydrochloric acid. 1-phenyl-1-*p*-tolyl-2-benzyl-amino-ethane-hydrochloride crystallized in a yield of 92%. By recrystallization from a mixture of isopropanol and ether, there were obtained colourless needles melting at 203—205°C.

EXAMPLE 5

12 g of styrene oxide were mixed with 13.5 g of 1-phenyl-propylamine-(2) and heated for several hours to 100—120°C. 1 - phenyl - 1 - hydroxy - 2 - (1 - phenyl-propyl - (2) - amino) - ethane was obtained in the form of an almost colourless oil. 20 g of anhydrous aluminium chloride were added portionwise to a solution of this oil in 80 cc of benzene. The mixture was heated for 30 minutes under reflux to the boiling temperature on the water bath and, after cooling, it was poured into a mixture of ice, water and hydrochloric acid. The hydrochloride of 1,1-diphenyl - 2 - (1 - phenyl - propyl - (2)-amino) - ethane separated in the form of an oil. The free base was isolated by addition of soda lye and extraction with ether. After addition of an alcoholic solution of maleic acid, the maleate, which was found to melt at 168—170°C, crystallized in a yield of 88%.

EXAMPLE 6

4 cc of water were added to a solution of 14 g of 1-phenyl-1-hydroxy-2-amino-ethane and 13.7 g of phenylacetone in 40 cc of methanol and subsequently 1.5 g of sodium boron hydride were added portionwise. After a one hour standing at room temperature, the reaction mixture was concentrated by evaporation under reduced pressure. The oily residue was taken up in 40 cc of toluene, 20 g of anhydrous aluminium chloride were added portionwise and the mixture was further treated as described in Example 5. 1 - phenyl - 1 - *p* - tolyl - 2 - (1 - phenyl-propyl - (2) - amino) - ethane in the form of a colourless oil was obtained. After addition of maleic acid, the maleate which was found to melt at 166—168°C. was obtained.

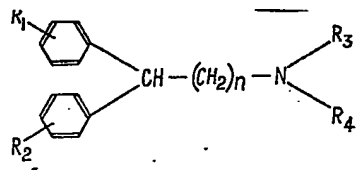
EXAMPLE 7

30 g of anhydrous aluminium chloride were added portionwise to a suspension of 29 g of 1 - phenyl - 2 - cinnamylamino - propane-hydrochloride melting at 237—240°C (prepared by condensation of cinnamic aldehyde with 1-phenyl-propyl-amine-(2) and reduction of the Schiff-base thus obtained with sodium boron hydride) in 100 cc of benzene and the reaction mixture was subsequently heated for 45 minutes to the boiling temperature. After the reaction mixture had cooled, it was

poured in a mixture of ice and hydrochloric acid as described in Example 1. After addition of ether, the crystals were separated by filtration, dissolved in methanol in order to separate mineral salts and then the compound was precipitated by the addition of water. 26.5 g of 1,1-diphenyl-3-(1-phenyl-propyl-(2)-amino)-propane-hydrochloride were obtained; the compound was found to melt at 190—192°C after recrystallization from isopropanol.

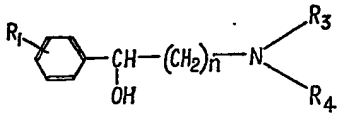
WHAT WE CLAIM IS:—

1. A process for the manufacture of diphenylalkylamines of the formula



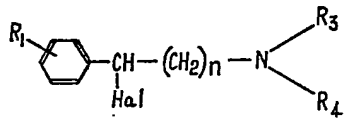
(I)

in which R_1 and R_2, which may be identical or different, represent hydrogen, an alkyl group having 1—3 carbon atoms, an alkoxy group having 1—3 carbon atoms, or halogen, R_3 represents hydrogen or an alkyl group having 1—3 carbon atoms, and R_4 represents hydrogen, an alkyl group having 1—4 carbon atoms, an aralkyl group having up to 4 carbon atoms in the alkylene chain which may be substituted in the phenyl nucleus by alkyl or alkoxy groups having 1—3 carbon atoms, or in which R_3 and R_4 together with the nitrogen atom form a morpholino, piperidino or pyrrolidino ring, and n represents 1 or 2, wherein a 1-phenyl-1-hydroxy-alkylamine of the formula



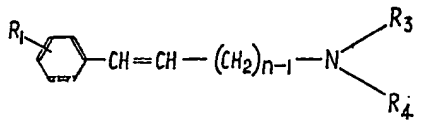
(II)

or a 1-phenyl-1-halogenoalkylamine of the formula



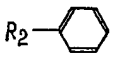
(III)

in which Hal represents a halogen atom, or a 1-phenyl-1,2-unsaturated alkenylamine of the formula



(IV)

in which R_1, R_3 and R_4 and n have the meaning given above, is reacted with an aryl compound of the formula

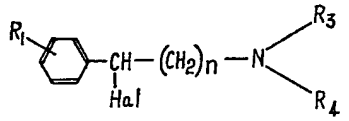


(V)

in which R_2 has the meaning given above, in the presence of Friedel-Crafts catalysts.

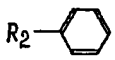
2. A process as claimed in claim 1, in which R_1 or R_2 represents or both R_1 and R_2 represent chlorine.

3. A process as claimed in claim 1 or claim 2, in which a 1-phenyl-1-chloroalkylamine of the formula



(III)

in which R_1, R_3, R_4, and n have the meanings given in claim 1 and Hal represents chlorine is reacted with an aryl compound of the formula



(V)

in which R has the meaning given in claim 1, in the presence of Friedel-Crafts catalysts.

4. A process as claimed in any one of claims 1 to 3, wherein the Friedel-Crafts catalyst is aluminium trichloride.

5. A process as claimed in any one of claims 1 to 4, wherein the Friedel-Crafts catalyst is gallium trichloride or boron trifluoride.

6. A process as claimed in claim 1, wherein 1-phenyl-1-hydroxy-3-(1-phenyl-propyl-(2)-amino)-propane is used as a reactant.

7. A process as claimed in claim 1, wherein 1 - *p* - methoxy - phenyl - 1 - hydroxy-3 - (1 - phenyl - propyl - (2) - amino) - propane is used as a reactant.

8. A process as claimed in claim 1, wherein 1 - *m* - chloro - phenyl - 1 - hydroxy - 3 - (1-

phenyl - propyl - (2) - amino) - propane is used as a reactant.

9. A process as claimed in claim 1, wherein 1 - *o* - tolyl - 1 - hydroxy - 3 - (1 - phenyl-propyl - (2) - amino) - propane is used as a reactant.

10. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - 3 - (1 - *m*-methoxy - phenyl - propyl - (2) - amino)-propane is used as a reactant.

11. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - 3 - (1 - phenyl-butyl - (2) - amino) - propane is used as a reactant.

12. A process as claimed in claim 1, wherein 1 - phenyl - 1- hydroxy - 3 - (2 - phenyl-ethylamino) - propane is used as a reactant.

13. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - 3 - (1-phenyl - propyl - (2) - methylamino) - propane is used as a reactant.

14. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - propylamine-(3), is used as a reactant.

15. process as claimed in claim 1, wherein 1 - phenyl - hydroxy - ethylamine-(2), is used as a reactant.

16. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - 3 - isopropyl-amino - propane, is used as a reactant.

17. A process as claimed in claim 1, wherein 1 - phenyl - 1 - hydroxy - 2 - morpholino-ethane, is used as a reactant.

18. A process as claimed in any one of claims 6 to 17, wherein instead of the 1-phenyl-1-hydroxy alkylamine there is used the corresponding 1-phenyl-1-chloroalkylamine.

19. A process as claimed in any one of claims 6 to 17, wherein instead of the 1-phenyl-1-hydroxyalkylamine there is used the corresponding 1-phenyl-alken-1,2-ylamine.

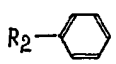
20. A process as claimed in any one of claims 1 to 19, wherein benzene, toluene, chlorobenzene, methoxybenzene, ethoxy-benzene, or isopropylbenzene is used as second reactant.

21. A process as claimed in any one of claims 1 to 20, carried out at a temperature within the range of 50 to 200°C.

22. A process as claimed in claim 21, carried out at a temperature within the range of 60 to 140°C.

23. A process as claimed in any one of claims 1 to 22, carried out in an inert solvent.

24. A process as claimed in any one of claims 1 to 23, wherein an excess of the reaction component of the formula



where R_2 has the meaning given in claim 1, is used as a solvent.

25. A process as claimed in claim 23 or claim 24, carried out at the boiling temperature of the solution used.

26. A process as claimed in claim 1 carried out substantially as described in any one of the Examples herein.

27. Diphenylalkylamines whenever prepared by the process claimed in any one of claims 1 to 26.

28. 1,1 - diphenyl - 3 - (1 - phenyl-propyl - (2) - amino)propane whenever prepared by a process as claimed in claim 1.

29. 1,1 - diphenyl - propylamine - (3) whenever prepared by a process as claimed in claim 1.

30. 1,1 - diphenyl - 2 - morpholino ethane whenever prepared by a process as claimed in claim 1.

31. 1 - phenyl - 1 - *p* - tolyl - 2 - benzyl-aminoethane whenever prepared by a process as claimed in claim 1.

32. 1,1 - diphenyl - 2 - (1 - phenyl-propyl - (2) - amino)ethane whenever prepared by a process as claimed in claim 1.

33. 1 - phenyl - 1 - *p* - tolyl - 2 - (1-phenyl - propyl - (2) - amino - ethane whenever prepared by a process as claimed in claim 1.

34. 1,1 - diphenyl - 3 - (1 - phenyl-propyl - (2) - amino)propane whenever prepared by a process as claimed in claim 1.

35. A salt of a diphenylalkylamine claimed in any one of claims 27 to 34, the diphenyl-alkylamine having been prepared by a process as claimed in claim 1.

36. A physiologically tolerable salt of a diphenylalkylamine claimed in any one of claims 27 to 34, the diphenylalkylamine having been prepared by a process as claimed in claim 1.

37. Pharmaceutical preparations containing a diphenylalkylamine as claimed in any one of claims 27 to 34 in admixture or conjunction with a pharmaceutically acceptable excipient.

38. Pharmaceutical preparations containing a physiologically tolerable salt of a diphenyl-alkylamine as claimed in claim 36, in admixture or conjunction with a pharmaceutically acceptable excipient.

39. Pharmaceutical preparations as claimed in claim 37 or claim 38 in unit dosage form.

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(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The present invention provides a solid pharmaceutical composition, e.g. in form of a tablet, powder or capsule, comprising e.g. a cyclosporin.

Pharmaceutical Compositions

The present invention relates to novel galenic compositions, in particular novel galenic compositions comprising a poorly water-soluble drug, e.g. a cyclosporin.

Cyclosporins present highly specific difficulties in relation to administration generally and galenic composition in particular, including in particular problems of stability, drug bioavailability, and variability in inter- and intra-patient dose response.

In order to meet these and related difficulties, in GB patent publication no. 2 222 770 and no. 2 257 359, galenic compositions are disclosed comprising a cyclosporin as active ingredient and which take the form of, inter alia, an emulsion, e.g. microemulsion, or emulsion, e.g. microemulsion, pre-concentrate. Microemulsion pre-concentrates have been developed for commercial use under the trademark Neoral® which may be orally administered in the form of drink solutions or soft gelatine capsules.

There remains a need for formulations comprising a poorly water-soluble drug, e.g. cyclosporin, that can be orally administered in solid form, e.g. tablet, powder or capsules, which is stable and exhibit consistent and effective absorption. Conveniently, the tablets or capsules are of a volume that allows convenient administration, e.g. easy swallowing.

The poorly water soluble drug preferably is a lipophilic drug, e.g. a cyclosporin. The term "poorly water soluble", as used herein, is understood to mean a solubility in water at 20°C of less than 1, e.g. 0.01, % weight/volume, e.g. a sparingly soluble to very slightly soluble drug as described in Remington: The Science and Practice of Pharmacy, 19th Edition, Ed. A.R. Gennaro, Mack Publishing Company, US, 1995, vol. 1, p 195.

Cyclosporins to which the present invention applies are any of those having pharmaceutical utility, e.g. as immunosuppressive agents, anti-parasitic agents and agents for the reversal of multi-drug resistance, as known and described in the art, in particular Cyclosporin A (also known as Ciclosporin), Cyclosporin G, [O-(2-hydroxyethyl)-(D)Ser]^{8}-Ciclosporin, and [3'-dehydroxy-3'-keto-MeBmt]^{1}-[Val]^{2}-Ciclosporin. Cyclosporin A is preferred.

In one aspect the present invention provides a composition according to the present invention wherein the cyclosporin is Cyclosporin A.

In accordance with the present invention it has now surprisingly been found that particularly suitable galenic compositions containing a poorly water-soluble drug, e.g. a cyclosporin, having particularly interesting bioavailability characteristics and reduced variability in inter- and intra-subject bioavailability parameters, e.g. in the form of tablets, capsules or powder, are obtainable using a solid polymer and/or a solid surfactant.

The present invention provides in one aspect a solid pharmaceutical composition, e.g. in form of a tablet, a powder or a capsule, comprising
(1) a poorly water soluble drug, e.g. a cyclosporin, and
(2) a polymer which is solid at room temperature.

The polymer is preferably one which can exist in the form of a, e.g. flowable, powder, having a melting point of e.g. above 40°C, preferably having a melting point and/or a glass transition temperature of above about 80°C.

In accordance with the present invention, it has surprisingly been found that suitable cyclosporin-containing compositions and compositions containing other poorly water-soluble drugs may be obtained based on polymers (2) which are solid at room temperature. The polymer is for example a pH dependent or non-pH dependent polymer. The polymer preferably is a hydrophilic polymer. Conveniently one or a mixture of polymers may be used.

Suitable pH-independent polymers include

2.1 polyvinyl pyrrolidone. A preferred example may be PVP K30, having an approx. molecular weight of 50 000 Daltons, or PVP K12, having an approx. molecular weight of 2 500 Daltons, as known and commercially available under the trade name Kollidon® or Plasdone® (Fiedler, "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", Editio Cantor Verlag Aulendorf, Aulendorf, 4th revised and expanded edition (1996), 1, , p.1256);

2.2 cellulose derivatives such as hydroxypropylmethylcellulose, preferably having a molecular weight of from 10 000 to 1 500 000 Daltons, as known and commercially available under the trade names Pharmacoat® or Methocel® (Fiedler, loc. cit., p.790). A

preferred example may be as known and commercially available under the name HPMC 3 cP.

Suitable pH-dependent polymers include:

2.3 cellulose derivatives such as hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate or cellulose acetate phthalate. Preferably, hydroxypropylmethylcellulose phthalate may be used as known and commercially available, e.g. from Shin-Etsu, under the name HPMCP HP50, having a viscosity of 190±20 cP, a methoxy content of 20.0-25.0%, hydroxypropyl content of 5.0-10.0%, and a carboxybenzoyl content of 20.0-24.0%, or HPMCP HP55, having a viscosity of 240±20 cP, a methoxy content of 18.0-22.0%, hydroxypropyl content of 4.0-9.0%, and a carboxybenzoyl content of 27.0-35.0% (Fiedler, loc. cit., p.762). Preferably, hydroxypropylmethylcellulose acetate succinate (HPMCAS) may be used as known and commercially available, e.g. from Shin-Etsu. Preferably, cellulose acetate phthalate may be used as known and commercially available, e.g. from Eastman Chemical Company, US, under the trade name C-A-P.

2.4 poly(meth)acrylates, preferably having a molecular weight from about 100 000 to about 400 000 Daltons. Preferably, the polymer is a copolymer which is resistant to gastric juice and soluble in intestinal juices, e.g. a copolymer formed from monomers selected from the group consisting of methacrylic acid, methacrylic acid esters, acrylic acid and acrylic acid esters, or e.g. a copolymer formed from butyl methacrylate, (2-dimethylaminoethyl)methacrylate, and methyl methacrylate, e.g. as those known and commercially available under the trade mark Eudragit® from Röhm Pharma GmbH. Especially preferred polymers are the 1:1 copolymer formed from monomers selected from the group consisting of methacrylic acid and methacrylic acid lower alkyl esters, such as the 1:1 copolymer formed from methacrylic acid and methyl methacrylate, available under the trade mark Eudragit® L, e.g. Eudragit® L100, having a molecular weight of about 135 000 Daltons, and the 1:1 copolymer of methacrylic acid and acrylic acid ethyl ester as known and commercially available under the trade mark Eudragit® L100-55, having a molecular weight of about 250 000 Daltons, and the 1:2:1 copolymer formed from butyl methacrylate, (2-dimethylaminoethyl)methacrylate, and methyl methacrylate, available under the trade mark Eudragit® E, having a molecular weight of about 150 000 Daltons.

Although any pharmaceutically acceptable components selected from the group of polymers specified above may be used in the composition of the invention, certain components are preferred. These include polyvinyl pyrrolidones, e.g. PVP K12/K30, hydroxypropylmethyl-cellulose phthalates, e.g. HPMCP HP50/55, or 1:1 copolymers formed from methacrylic acid and methyl methacrylate, e.g. Eudragit® L100 and L 100-55. Conveniently, one or a mixture of these polymers may be used.

pH-Dependent polymers preferably dissolve at a pH of below about 6, e.g. below about 5.

In the pharmaceutical compositions of the present invention, in a further alternative aspect the constitutional ratio of poorly water-soluble drug (e.g. cyclosporin) : polymer may be from about (10 to 50) : (90 to 50), e.g. 10 : 90, 20 : 80, 30 : 70, or 50 : 50.

The present invention provides in another aspect a solid pharmaceutical composition, e.g. in form of a tablet, a powder or a capsule, comprising
(1) a poorly water soluble drug, e.g. cyclosporin, and
(3) a surfactant which is solid at room temperature.

The present invention provides in a further aspect a solid pharmaceutical composition, e.g. in form of a tablet, a powder or a capsule, consisting of or consisting essentially of
(1) a poorly water-soluble drug, e.g. cyclosporin, and
(3) a surfactant, which is solid at room temperature.

The surfactant (3) is preferably one which can exist in the form of a, e.g. flowable, powder, having a melting point of e.g. above 40°C.

The surfactant (3) is for example nonionic, ionic or amphoteric surfactant. Preferably, the surfactants have solubilizing power for the poorly water-soluble drug, e.g. cyclosporins. In one embodiment the invention provides a composition as described above wherein the surfactant is ionic, e.g. surfactants such as listed below under (3.5). In another embodiment the invention provides a composition as described above wherein the surfactant is nonionic, e.g. surfactants such as listed below under (3.1)-(3.4) and (3.6)-(3.12).

Conveniently one or a mixture of the following surfactants may be used:

3.1 polyoxyethylene alkyl ethers; preferably the alkyl ethers are of C_{12} to C_{18} alcohols. Preferably the polymer number is from about 2 to about 150, e.g. about 5 to about 150. Preferably the polymers are polyoxyethylene glycol ethers. Preferred examples include polyoxyl 2-, 10- or 20-cetyl ether or polyoxyl 23-lauryl ether, or polyoxyl 20-oleyl ether, or polyoxyl 2-, 10-, 20- or 100-stearyl ether, as known and commercially available e.g. under the trade mark Brij® from Uniqema. An especially preferred product of this class is e.g. Brij® 35 (polyoxyl 23 lauryl ether), Brij® 58, Brij® 78P (polyoxyl 20 stearyl ether), or Brij® 98 (polyoxyl 20 oleyl ether) and polyethoxylated (20) cetyl ether, e.g. Nikkol® BC-20 TX, (H. Fiedler, loc. cit., pp. 259; "Handbook of Pharmaceutical Excipients", 2nd Edition, Editors A. Wade and P. J. Weller (1994), Joint publication of American Pharmaceutical Association, Washington, USA and The Pharmaceutical Press, London, England, page 367).

Similar products which may also be used are polyoxyethylene-polyoxypropylene-alkyl ethers, e.g. polyoxyethylene-polyoxypropylene- ethers of C_{12} to C_{18} alcohols, e.g. polyoxyethylen-20-polyoxypropylene-4-cetylether which is known and commercially available under the trade mark Nikkol PBC® 34, from e.g. Nikko Chemicals Co., Ltd. (Fiedler, loc. cit., vol. 2, pp. 1239).

3.2 polyethoxylated fatty acid esters. Preferably the molecular weight is from about 600 to about 18 000 Daltons. Preferably the polymerization number is from about 8 to about 400. Preferably the fatty acid is of 12 to 20 carbon atoms, e.g. stearic acid, e.g. of the type known and commercially available under the trade name Myrj® from Uniqema (Fiedler, loc. cit., vol. 2, pp. 1042). An especially preferred product of this class is Myrj® 52 having a D^{25} of about 1.1, a melting point of about 40 to 44°C, an HLB value of about 16.9, an acid value of about 0 to 1 and a saponification no. of about 25 to 35, or Myrj® 53, or Myrj® 59 (polyethyleneglycol-100-stearate), e.g. from Uniqema.

3.3 polyethoxylated sorbitan monostearates, e.g. as known and commercially available under the trade name Tween® 61 from Uniqema (Fiedler, loc. cit., vol. 2, pp. 1616).

3.4 polyethoxylated distearates, e.g. as known and commercially available under the trade name Atlas® G 1821 from Uniqema (Fiedler, loc. cit., vol. 2, pp. 206), or Nikko® CDS-6000P from Nikko Chemicals Co., Ltd.

3.5 anionic surfactants, e.g. those based on an alkali metal salt (e.g. of sodium);

3.5.1 sodium alkyl sulfates e.g. sodium C_8-C_{18}alkyl sulfates, e.g. sodium C_{10}-C_{18}alkyl sulfates, e.g. sodium lauryl sulfate, which is also known as sodium dodecyl sulfate and which is commercially available, e.g. under the trade name Texapon K12® from Henkel KGaA (Fiedler, loc. cit., vol. 2, pp. 1551);

3.5.2 sodium alkyl sulfonates, e.g. sodium C_8-C_{18}alkyl sulfonates, e.g. sodium C_{10}-C_{18}alkyl sulfonates;

3.5.3 sodium alkyl aryl sulfonates, e.g. sodium C_8-C_{18}alkyl aryl sulfonates, e.g. sodium C_{10}-C_{18}alkyl aryl sulfonates, wherein aryl is e.g. benzyl, phenyl and the like;

3.5.4 sodium alkyl phosphate e.g. sodium C_8-C_{18}alkyl phosphate, e.g. sodium C_{10}-C_{18}alkyl phosphate, e.g. sodium lauryl phosphate, or e.g. potassium cetyl phosphate, available under the trade name of AMPHISOL K from Hoffmann La Roche Ltd.;

3.5.5. sodium stearoyl lactylate (sodium-O-stearyllactate), e.g. as known and commercially available under the name SSL P55 VEG from Danisco; or

3.5.6 sodium (C_4-C_{12}) fatty acid salts e.g. sodium caprinate (Fiedler, loc. cit., vol. 2, pp. 1051).

3.6 polyoxyethylene(POE)-polyoxypropylene(POP)-polyoxyethylene(POE) surfactants, e.g. poloxamers, e.g. poloxamer 188, as known and commercially available under the tradename of Pluronic® F 68 from BASF or Synperonic® PE/F 68 from Uniqema, or e.g. poloxamer 407 as known and commercially available under tradename Pluronic® F 127 from BASF or Synperonic PE/F 127 from Uniqema.

3.7 vitamin E based surfactants, e.g. as known and commercially available under the name Vitamin E TPGS (polyethoxylated tocopherol succinate) from e.g. Eastman Kodak.

3.8 sucrose esters, e.g. sucrose stearate or sucrose palmitate.

3.9 monoglyceride based food emulsifiers, e.g. as known and commercially available under the trade name Panodan® AM VEG from Danisco (Fiedler, loc. cit.; vol. 2, pp. 1139), or citric acid esters of monoglyceride, e.g. Citrem® LC VEG from Danisco.

3.10 polyethoxylated hydrogenated castor oil, e.g. as known and commercially available under the trade name Cremophor® RH 60 from BASF (Fiedler, loc. cit., vol. 2, pp. 394), which has a saponification value of about 40 to 50, an acid value less than about 1, an iodine value of less than about 1, a water content (Fischer) of about 4.5 to 5.5%, an n_D^{60} of about 1.453 to 1.457 and an HLB of about 15 to 17.

3.11 polyethylene glycol (PEG) sterol ethers having, e.g. from 5 to 35 [CH_2-CH_2-O] units, e.g. 20 to 30 units, also in combination with polyoxethylene alkyl ethers. Preferably the polymer is as known and commercially available under the trade name Solulan® C24 (Choleth 24 (and) Ceteth 24) from Amerchol (Fiedler, loc. cit., vol. 2, pp. 1413), or Forlan® C-24 (Choleth 24 (and) Ceteth 24) from R.I.T.A. Corp. (Fiedler, loc. cit., vol. 2, pp. 647)

Similar products which may also be used are those which are known and commercially available under the trade name Nikkol® BPS-30 (polyethoxylated 30 phytosterol) or Nikkol® BPSH-25 (polyethoxylated 25 phytostanol), from e.g. Nikko Chemicals Co., Ltd.

3.12 lecithins, e.g. soy bean phospholipid, e.g. as known and commercially available under the trade name Lipoid® S75 from Lipoid; or egg phospholipid, e.g. as known and commercially available under the trade name Phospholipon® 90 from Nattermann (Fiedler, loc. cit., vol. 2, pp. 1185)

It is to be appreciated that surfactants may be complex mixtures containing side products or unreacted starting products involved in the preparation thereof, e.g. surfactants made by polyoxyethylation may contain another side product, e.g. polyethylene glycol.

In the compositions of the present invention, a surfactant having a hydrophilic-lipophilic balance (HLB) value of 8 to 40, e.g. 8 to 17, is preferred. The surfactant selected preferably has a hydrophilic-lipophilic balance (HLB) of at least 10. The HLB value is preferably the mean HLB value. Preferably, the surfactant is a polyethylene glycol (PEG) sterol ether having from 5 to 35 [CH_2-CH_2-O] units, e.g. Solulan® C24, a polyethoxylated fatty acid ester, e.g. Myrj® 59, a polyoxyethylene alkyl ether, e.g. Brij® 78P, sodium caprinate, or sodium stearoyl lactylate SSL P55.

In a further alternative embodiment, in the pharmaceutical compositions of the present invention consisting of or consisting essentially of (1) a drug and (3) a surfactant, the constitutional ratio of drug (e.g. cyclosporin) : surfactant may be e.g. from about 1 : 0.1 to 20, preferably from about 1 : 0.1 to 9.

Preferably in the pharmaceutical compositions of the present invention consisting of or consisting essentially of (1) a drug and (3) a surfactant, the surfactant may be selected from the group consisting of surfactants (3.1), (3.2), (3.5) and (3.11). More preferably, the surfactant is a polyethylene glycol (PEG) sterol ether having from 5 to 35 [CH_2-CH_2-O] units, e.g. Solulan® C24, a polyethoxylated fatty acid ester, e.g. Myrj® 59, a polyoxyethylene alkyl ether, e.g. Brij® 78P, sodium caprinate or sodium stearoyl lactate SSL P55. Even more preferably, the surfactant is sodium caprinate or sodium stearoyl lactate SSL P55.

The surfactant may be present in an amount by weight of e.g. 1% up to about 90%, e.g. 10 to 70%, by weight of the composition.

Compositions comprising anionic surfactants, e.g. sodium caprinate or sodium stearoyl lactate SSL P55, preferably are enteric coated. The enteric coating may be applied to tablets and/or to granules, pellets, powders or particles which may be further compressed to tablets.

The term "enteric coating", as used herein, comprises any pharmaceutically acceptable coating preventing the release of the poorly water-soluble drug in the stomach and sufficiently disintegrating in the intestinal tract, e.g. by contact with juices of a pH of about 5, approximately neutral or alkaline intestine juices, to allow the resorption of the active agent through the walls of the intestinal tract. Preferably, the poorly water-soluble drug, e.g. cyclosporin, is released at a pH of about 5. In vitro tests for determining whether or not a coating is classified as an enteric coating is known in the art.

More specifically, the term "enteric coating", as used herein, refers to a coating which remains intact for at least 2 hours, in contact with artificial gastric juices such as HCl of pH 1 at 36 to 38°C and preferably thereafter disintegrates within 30 minutes in artificial intestinal juices such as a KH_2PO_4 buffered solution of pH 6.8.

The enteric coating may be applied as described e.g. in Remington's Pharmaceutical Sciences, 18th Edition, Ed.: Alfonso R. Gennaro, Easton, PA : Mack, 1990, Bauer K., Lehmann K., Osterwald H., Überzogene Arzneiformen, 1988, Wissensch. VG, Stuttgart, the contents of which are incorporated herein.

Preferably, the release of the poorly water-soluble drug is not prolonged by the enteric coating.

In another embodiment, the compositions of the invention, e.g. in form of a tablet, a powder or a capsule, comprise

(1) a poorly water soluble drug, e.g. a cyclosporin,

(2) a polymer which is solid at room temperature, and

(3) a surfactant, e.g. a nonionic or ionic or amphoteric surfactant.

The surfactant may be selected from the group (3.1) to (3.12) mentioned above. Preferably a non-ionic surfactant may be used. More preferably, the surfactant may be selected from the group consisting of surfactants (3.1), (3.2), and (3.11). Even more preferably, the surfactant is a polyethylene glycol (PEG) sterol ether having from 5 to 35 [CH_2-CH_2-O] units, e.g. Solulan® C24, a polyethoxylated fatty acid ester, e.g. Myrj® 59, and a polyoxyethylene alkyl ether, e.g. Brij® 78P.

In a further aspect the present invention provides the compositions of the invention, e.g. in form of a tablet, a powder or a capsule, comprising

(1) a poorly water soluble drug, e.g. a cyclosporin,

(2) a polymer which is solid at room temperature, and

(3) a surfactant, which e.g. is solid at room temperature, e.g. a surfactant which can exist in the form of a, e.g. flowable, powder and having a melting point of e.g. above 40°C.

In the pharmaceutical composition of the present invention comprising (1) a poorly water soluble drug, e.g. a cyclosporin, (2) a polymer which is solid at room temperature, and (3) a surfactant, the amount of the surfactant may be up to about 50%, e.g. up to about 40%, e.g. up to about 20% by weight, e.g. 1 to 15% by weight, preferably from about 2 to 10, in particular about 3 to 7% by weight based on the total weight of the composition comprising the poorly water-soluble drug, e.g. cyclosporin, the polymer and the surfactant. Preferably,

the ratio of surfactant : drug (e.g. cyclosporin) is 1 : 0.5 to 50, e.g. 1 : 1 to 40, e.g. 1 : 2 to 20. Preferably these three components comprise at least 95, or 95% of the composition.

A preferred embodiment comprises cyclosporin compositions comprising a polymer (2) which is solid at room temperature, and a surfactant (3) which is solid at room temperature.

In a further aspect, the invention provides a pharmaceutical composition e.g. in form of a tablet, a powder or a capsule comprising
(1) a poorly water soluble drug, e.g. a cyclosporin,
(2) a polymer,
(3) optionally a surfactant and
(4) a carrier.

In another aspect, the invention provides a pharmaceutical composition e.g. in form of a tablet, a powder or a capsule consisting of or consisting essentially of
(1) a poorly water soluble drug, e.g. a cyclosporin,
(3) a surfactant and
(4) a carrier.

Preferably as a carrier is present e.g.:

4.1 a water-soluble or water-insoluble saccharide such as lactose or mannitol;

4.2 microcrystalline cellulose, e.g. as known and commercially available under the trade name Avicel® from FMC Corporation; or

4.3 colloidal silicon dioxide, e.g. as known and commercially available under the trade name Aerosil®;

4.4 anhydrous calcium phosphate, e.g. as known and commercially available under the trade name Fujicalin®, or anhydrous dicalcium phosphate, e.g. as known and commercially available under the trade name A-TAB® from Rhodia.

A mixture of carriers may be present.

Any carrier, if present, is generally present in an amount of up to about 50%, e.g. 0.5 to 50%, e.g. 10 to 40%, e.g. 15 to 40% by weight, preferably from about 20 to about 30% by

weight based on the total weight of the composition comprising the drug, e.g. cyclosporin, the polymer and/or surfactant and the carrier.

The surfactant is preferably present in an amount of 20 to 50% by weight of the composition, for example about 30% by weight of the composition comprising the drug, e.g. cyclosporin, polymer and/or the surfactant and the carrier.

In another aspect, the invention provides a pharmaceutical composition e.g. in form of a tablet, a powder or a capsule comprising

(1) a poorly water soluble drug, e.g. a cyclosporin, e.g. cyclosporin A,
(2) a polymer,
(3) optionally a surfactant,
(4) optionally a carrier, and
(5) optionally a disintegrant.

In yet another aspect, the invention provides a pharmaceutical composition e.g. in form of a tablet, a powder or a capsule consisting of or consisting essentially of
(i) a poorly water soluble drug (1), e.g. a cyclosporin, e.g. cyclosporin A,
(ii) a surfactant (3),
(iii) a carrier (4), and/or a disintegrant (5).

Suitable disintegrants include e.g.

5.1 natural starches, such as
5.1.1 maize starch, potato starch, and the like,
5.1.2 directly compressible starches, e.g. Sta-rx® 1500, modified starches, e.g. carboxymethyl starches and sodium starch glycolate, available as Primojel®, Explotab®, Explosol®, and
5.1.3 starch derivatives such as amylose;
5.2 crosslinked polyvinylpyrrolidones, e.g. crospovidones, e.g. Polyplasdone® XL and Kollidon® CL;
5.3 alginic acid or sodium alginate;
5.4 methacrylic acid-divinylbenzene copolymer salts, e.g. Amberlite® IRP-88; and
5.5 cross-linked sodium carboxymethylcellulose, available as e.g. Ac-di-sol®, Primellose®, Pharmacel® XL, Explocel®, and Nymcel® ZSX, or

5.6 a mixture of thereof.

The disintegrant or disintegrants may be present in an amount of 1 to 50%, e.g. 5 to 40% by weight based on the total weight of the composition.

In a further aspect, the invention provides a pharmaceutical composition e.g. in form of a tablet, a powder or a capsule comprising
(1) a poorly water soluble drug, e.g. a cyclosporin, e.g. cyclosporin A,
(2) a polymer,
(3) optionally a surfactant,
(4) optionally a carrier,
(5) optionally a disintegrant, and
(6) optionally a lubricant, e.g. magnesium stearate.

In yet another aspect, the invention provides a pharmaceutical composition e.g. in form of a tablet, a powder or a capsule consisting of or consisting essentially of
(i) a poorly water soluble drug (1), e.g. a cyclosporin, e.g. cyclosporin A,
(ii) a surfactant (3),
(iii) a carrier (4), a disintegrant (5) and/or a lubricant (6), e.g. magnesium stearate.

Lubricants may be present in a total amount of up to about 5% by weight, e.g. 2%, e.g. 1% by weight based on the total weight of the composition.

The pharmaceutical composition may also include further additives or ingredients, for example antioxidants, such as ascorbyl palmitate, butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT) and tocopherols, and/or preserving agents. In a further alternative aspect these additives or ingredients may comprise about 0.05 to 1% by weight of the total weight of the composition. The pharmaceutical composition may also include sweetening or flavoring agents in an amount of from e.g. 0.1 to e.g up to about 2.5 or 5% by weight based on the total weight of the composition.

Details of excipients of the invention are described in e.g. Fiedler, H. P., loc cit; "Handbook of Pharmaceutical Excipients", loc cit; or may be obtained from the relevant manufacturers, the contents of which are hereby incorporated by reference.

Preferably the compositions of the present invention do not contain any organic hydrophilic component. Under "organic hydrophilic component" is to be understood any hydrophilic component or any hydrophilic co-component as described in the above mentioned British patent application no. 2 222 770. Such hydrophilic components excluded may comprise no added hydrophilic component such as water soluble components and/or ethanol, propylene glycol or water. Naturally it will be appreciated that small amounts of organic hydrophilic components e.g. which have no significant effect, may be tolerated, e.g. as a result of impurities such as less than 3% by weight of the composition.

Preferably the compositions of the present invention do not contain any lipophilic component. Under "lipophilic component" is to be understood any lipophilic component as described in the above mentioned British patent application no. 2 222 770. Such lipophilic components excluded comprise no added lipophilic component such as glyceryl fatty acid ester. Naturally it will be appreciated that small amounts of lipophilic components e.g. which have no significant effect, may be tolerated, e.g. as a result of impurities such as less than 3% by weight of the composition.

Accordingly, in one aspect the present invention provides a composition as described above which is free, e.g. substantially free, from an organic hydrophilic component and/or a lipophilic component. In one group of compositions of the present invention there is no glyceryl fatty acid present.

The drug, e.g. cyclosporin, may be present in an amount by weight of up to about 50% by weight of the composition. The drug is preferably present in an amount of e.g. 1 to 50%, e.g. 15 to 40% by weight of the composition, for example about 20% by weight of the composition comprising the drug, e.g. cyclosporin, the polymer and/or the surfactant. Yet, the tablets or capsules are of a volume that allows convenient administration, e.g. easy swallowing.

In one aspect, upon dilution with an aqueous medium the compositions of the present invention may form, e.g. to an substantial amount, e.g. to the extent of 60% or more, e.g. 85% or more, e.g. more than 90, 95 or 99%, fine particles of, e.g. substantially amorphous,

poorly water-soluble drug, e.g. cyclosporin. By "substantially amorphous " is meant more than 90%, e.g. more than 95%, preferably about or more than 99% in amorphous form.

Preferably, upon dilution with an aqueous medium, for example water, for example on dilution of 1:1 to 1:300, e.g. 1:5 to 1:100, e.g. 1:10 to 1:100, or in the gastric juices after oral application, the compositions of the present invention, comprising (1) a poorly water soluble drug, e.g. a cyclosporin, (2) a polymer and/or (3) a surfactant, spontaneously substantially form fine particles, e.g. solid particles of substantially amorphous poorly water-soluble drug, e.g. cyclosporin, e.g. of a range of from 50 nm to 20 000 nm, e.g. from 50 nm to 10 000 nm, e.g. from 50 nm to 2000 nm, e.g. as measured by conventional methods, e.g. light diffraction techniques, e.g. based on a Mastersizer. Conveniently, there is a narrow size distribution.

In another aspect, upon dilution with an aqueous medium the compositions of the present invention comprising (1) a poorly water soluble drug, e.g. cyclosporin, (3) a surfactant which is solid at room temperature, may form a system which is a mixture of substantially solubilized drug, e.g. about 10 to 100%, preferably about 10 to 80%, e.g. 30 to 40%, more preferably 40 to 70% of the total drug and particulate drug, e.g. about 0 to 90%, preferably about 20 to 90%, e.g. 60 to 70%, more preferably 30 to 60% of the total drug. The constitutional ratio of drug : surfactant may be preferably 1 : 0.1, or 1 : 0.25, or 1 : 0.5, or 1 : 1, or 1 : 2, or 1 : 4, or 1 : 9. Preferably, the drug is cyclosporin, e.g. cyclosporin A.

In yet a further aspect the present invention provides compositions which upon dilution with an aqueous medium form a system wherein the poorly water-soluble drug, e.g. cyclosporin, e.g. Cyclosporin A, substantially is solubilized, e.g. is solubilized to an extent of about 90% of total drug or more, e.g. more than about 95%. It has been found that surprisingly low drug (e.g. cyclosporin) : nonionic surfactant ratios of e.g. about 1 : 5.3 to 6.6, may be used to completely solubilize the drug, e.g. cyclosporin, when one of the nonionic surfactants as specified above, e.g. Choleth 24 (and) Ceteth 24, e.g. Solulan® C24 or Forlan® C-24; or polyethoxylated (30) phytosterol, e.g. Nikkol® BPS-30; or polyethoxylated (25) phytostanol, e.g. Nikkol® BPSH-25; or polyethoxylated (20) stearyl ether, e.g. Brij® 78P; or polyethoyxlated (20) cetyl ether, e.g. Nikkol® BC-20 TX, is used. Particularly suitable are polyethoxylated (30) phytosterol, e.g. Nikkol® BPS-30; or polyethoxylated (25) phytostanol, e.g. Nikkol® BPSH-25; or polyethoxylated (20) stearyl ether, e.g. Brij® 78P.

The amount of poorly water-soluble drug, e.g. cyclosporin, which can be solubilized may be analyzed by centrifugation followed by HPLC for the distribution of drug, e.g. cyclosporin, between the solubilized and particulate phase.

The state of the particles may be analyzed by X-ray and the particle size distribution may be analyzed e.g. by laser light scattering or electron microscopy.

The compositions of this invention may produce on contact with water stable e.g. particulate systems, e.g. for up to one day or longer, e.g. one day. Preferably the systems remain stable for more than 5 hours.

In one aspect the present invention provides a composition, comprising (1) a poorly water-soluble drug, e.g. cyclosporin, (2) a polymer and/or (3) a surfactant, which is in form of a solid dispersion.

In a further alternative aspect the present invention provides a composition according to the present invention comprising (2) a polymer wherein the poorly water-soluble drug, e.g. cyclosporin, is encapsulated in a polymeric matrix, e.g. in form of microparticles.

The compositions of the invention may be prepared by working up active agent with the excipients. The following processes A to H are contemplated.

A. In one aspect the compositions of the present invention in form of a solid dispersion comprising (1) a poorly water-soluble drug, e.g. cyclosporin, (2) a polymer and/or (3) a surfactant may be obtained by

(i) dissolving, suspending or dispersing the drug, e.g. cyclosporin, and polymer, if present, in a solvent or solvent mixture,

(ii) adding the surfactant, if present, to the drug/solvent or drug/polymer/solvent mixture,

(iii) evaporating the solvent and co-precipitating the drug, e.g. cyclosporin, with the polymer and/or the surfactant,

(iv) drying the resulting residue, e.g. under reduced pressure, milling and sieving the particles.

The solvent of (i) may be a single solvent or a mixture of solvents. Suitable solvents for use according to the present invention may be organic solvents such as an alcohol, e.g. methanol, ethanol, or isopropanol; an ester, e.g. ethylacetate; an ether, e.g. diethylether; a ketone, e.g. acetone; or a halogenated hydrocarbon, e.g. dichloromethane. Preferably a solvent mixture of ethanol/acetone having a weight ratio of ethanol : acetone of between about 1:10 to about 10:1, e.g. 1:5 to 5:1 may be used.

B. In another aspect the compositions of the present invention in form of a solid dispersion comprising (1) a poorly water-soluble drug, e.g. cyclosporin, (2) a polymer and/or (3) a surfactant may be obtained by

(i) dissolving, suspending or dispersing the drug, e.g. cyclosporin, and surfactant, if present, in a solvent or solvent mixture and optionally adding small amounts of water, if necessary,

(ii) adding the polymer, if present, to the drug/solvent or drug/surfactant/solvent mixture,

(iii) evaporating the solvent and co-precipitating the drug, e.g. cyclosporin, with the surfactant and/or the polymer,

(iv) drying the resulting residue, e.g. under reduced pressure, milling and sieving the particles.

The solvent of (i) may be a single solvent or a mixture of solvents. Suitable solvents for use according to the present invention may be organic solvents such as an alcohol, e.g. methanol, ethanol, or isopropanol; an ester, e.g. ethylacetate; an ether, e.g. diethylether; a ketone, e.g. acetone; or a halogenated hydrocarbon, e.g. dichloromethane. Preferably a solvent mixture of ethanol/acetone having a weight ratio of ethanol : acetone of between about 1:10 to about 10:1, e.g. 1:5 to 5:1 may be used.

C. Alternatively, the solid dispersions of the invention, comprising (1) a poorly water-soluble drug, e.g. cyclosporin, (2) a polymer and/or (3) a surfactant, may be prepared by spray-drying techniques. A solution or dispersion as formed above is dispersed through a nozzle at an inlet temperature of about 50 to about 130°C into a chamber. The solvent is evaporated through the nozzle, and finely dispersed particles are collected.

D. In a further alternative embodiment of the present invention the solid dispersion, comprising (1) a poorly water-soluble drug, e.g. cyclosporin, (2) a polymer and/or (3) a

surfactant, may be prepared by spray-drying the solution or dispersion as formed above onto (4) a carrier in the fluid bed.

The particles typically have a mean particle size of less than about 2 mm, e.g. 1 mm, e.g. 0.5 mm, as measured e.g. by light microscopy.

E. The compositions of the present invention wherein the poorly water-soluble drug, e.g. cyclosporin, is encapsulated in a polymeric matrix, e.g. in form of microparticles, may be prepared e.g. according to a process comprising the following steps:

(i) preparation of an internal organic phase comprising

(ia) dissolving the polymer in an organic solvent or solvent mixture. The solvent may be a single solvent or a mixture of solvents. Suitable solvents for use according to the present invention may be organic solvents such as a ketone, e.g. acetone; or a halogenated hydrocarbon, e.g. methylene chloride. Preferably a solvent mixture of methylene chloride/acetone having a weight ratio of methylene chloride : acetone of between about 1:10 to about 10:1, e.g. 1:5 to 5:1, preferably 1:1, may be used,

(ib) adding the poorly water-soluble drug, e.g. cyclosporin, to the polymer solution, and optionally

(ic) adding a surfactant to the solution obtained by step (ib),

(ii) preparation of an external aqueous phase comprising

(iia) preparing a buffer, e.g. acetate buffer,

(iib) dissolving gelatin or polyvinylalcohol (PVA) in water, and

(iic) mixing the solution obtained by step (iib) with the solution obtained by step (iia) to obtain e.g. a 0.5% gelatin solution in the buffer,

(iii) mixing the internal organic phase, e.g. brought at 20 ml/min with a gear pump, with the external aqueous phase, e.g. brought at 400 ml/min with a gear pump, e.g. in a ratio of internal phase to external phase of about 1 : 10 to about 1 : 40, preferably about 1 : 20, with a device creating high shear forces, e.g. with a static mixer, to form e.g. an oil/water emulsion, and

(iv) hardening the microparticles by solvent evaporation, washing for excipients removal and collecting the microparticles.

The microparticles typically have a mean particle size of less than about 350 microns, e.g. about 1 to about 180 microns, as measured e.g. by scanning electron microscopy.

In order to e.g. increase flowability of the final microparticle powder, the obtained microparticles may be further worked up by adding an aqueous solution of a carrier, e.g. lactose, and lyophilization or spray drying of the resulting suspension to obtain a, e.g. flowable, powder.

F. In one embodiment the compositions of the invention, in form of solid dispersions, comprising a surfactant are obtained by

(i) preparation of an organic preconcentrate comprising dissolving the surfactant in an organic solvent or a mixture of solvents, e.g. ethanol, adding the poorly water-soluble drug, e.g. cyclosporin, and stirring until dissolved,

(ii) diluting or delivering the organic preconcentrate obtained in step (i) to a mixer, e.g. a magnetic stirrer or a static mixer, together with an aqueous solution, optionally comprising a carrier, e.g. lactose, and

(iii) spray-drying the mixture or, if no carrier is present in step (ii), spray-drying the diluted preconcentrate obtained in step (ii) onto a carrier, e.g. lactose, e.g. in the fluid bed.

G. In yet a further embodiment of the present invention the compositions of the invention, in form of solid dispersions, comprising a surfactant (3) are prepared by

(i) dissolving the surfactant, e.g. ionic surfactant, the cycloysporin and optionally a carrier e.g. lactose in water, and

(ii) spray-drying the aqueous solution

H. In yet a further alternative embodiment of the present invention the compositions of the invention, in form of solid dispersions, comprising a surfactant (3) are prepared by

(i) dissolving the poorly water-soluble drug, e.g. cyclosporin, in an organic solvent, e.g. propylene glycol, to obtain e.g. a 40% solution of poorly water-soluble drug, e.g. cyclosporin, in propylene glycol,

(ii) mixing the solution obtained in step (i) with a molten surfactant,

(iii) optionally mixing or granulating the mixture obtained in step (ii) with a carrier, e.g. lactose; or microcrystalline cellulose, or colloidal silicon dioxide; or anhydrous calcium phosphate, and

(iv) cooling the mixture obtained in step (ii) or (iii) to obtain a solid composition.

The solid dispersions obtained by processes F to H preferably do not contain any polymer (2).

Other excipients may be added at any stage, preferably however after the powder is formed.

The resulting mixtures of any of the processes F to H described above may be dried, milled and sieved to obtain a fine, e.g. flowable, powder.

The compositions of the invention in powder form, e.g. particles, e.g. solid dispersion particles or microparticles, may be compressed to tablets.

The particles, e.g. solid dispersion particles or microparticles, may be combined with one or more flow enhancers, e.g. colloidal silicon dioxide, and/or one or more solid surfactants as specified above, e.g. sodium lauryl sulfate, e.g. in a total amount of enhancers and/or surfactants of up to about 70% by weight, e.g. 20 to 60% by weight, in particular 40 to 50% by weight based on the total weight of the composition.

If present in the compositions, the filler or a mixture of fillers, the disintegrants or a mixture of disintegrants, the lubricants or a mixture of lubricants, the flow enhancers or a mixture of flow enhancers, the additional surfactant or surfactants may be added to the drug/polymer/solvent mixture, the drug/surfactant/solvent mixture, the drug/polymer/surfactant/solvent mixture or, preferably, to the outer tabletting phase.

In one aspect of the invention the outer tabletting phase may comprise one or more solid surfactants as specified above, e.g. sodium lauryl sulfate, instead or in addition to adding a surfactant to the drug/polymer/solvent mixture in the preparation process of the solid dispersion particles or microparticles, comprising (1) a poorly water-soluble drug, e.g. cyclosporin, (2) a polymer and optionally (3) a surfactant, as hereinabove described.

The outer tabletting phase may comprise e.g. spray-dried lactose/microcrystalline cellulose mixtures, dicalcium phosphate anhydrous or a mixture of α-lactose monohydrate and microcrystalline cellulose, e.g. Microcelac® 100, e.g. to achieve tablet compositions with a suitable average hardness and a short disintegration time.

Microcelac® 100 is a spray-dried compound consisting of 75% α-lactose monohydrate and 25% microcrystalline cellulose produced by Meggle.

Accordingly, in one embodiment, the present invention provides tablet compositions with an average hardness of e.g. from 60 N to 200 N, preferably 80 N to 110 N, and/or a disintegration time of e.g. below about 10 min, preferably below 1 min, wherein the outer tabletting phase comprises e.g. lactose/microcrystalline cellulose mixtures, dicalcium phosphate anhydrous or α-lactose monohydrate/microcrystalline cellulose mixtures.

Preferably, the compositions comprise α-lactose monohydrate/microcrystalline cellulose mixtures, e.g. Microcelac® 100, in an amount of e.g. about 10 to 80%, e.g. about 10 to 60% by weight based on the total weight of the composition or dicalcium phosphate anhydrous in an amount of e.g. about 10 to 80%, e.g. about 10 to 60% by weight based on the total weight of the composition.

Preferably, compositions comprising HPMCP comprise α-lactose monohydrate/microcrystalline cellulose mixtures, e.g. Microcelac®. Preferably, compositons comprising PVP comprise dicalcium phosphate anhydrous.

Applicants have found that surprisingly high drug loadings may be obtained in accordance with the present invention, e.g. drug loadings up to 70%, e.g. from about 20 to about 60%, in particular about 30 to 50% by weight based on the total weight of the particles, e.g. solid dispersion particles or microparticles, or e.g. drug loadings of up to 40%, e.g. about 20% by weight based on total weight of the final composition.

The compositions, e.g. those in the examples hereinafter, show good stability characteristics as indicated by standard stability trials, e.g. no poorly water-soluble drug, e.g. cyclosporin, crystallization (as determined by differential scanning calorimetry) or degradation, having e.g. a shelf life stability of up to one, two or three years, and even longer. The compositions

of this invention may produce stable particulate systems upon dilution with aqueous media, e.g. for up to one day or longer, e.g. one day.

The pharmaceutical compositions of the invention exhibit especially advantageous properties when administered orally; for example in terms of consistency and high level of bioavailability obtained in standard bioavailability trials. These trials are performed in animals e.g. rats or dogs or healthy volunteers using HPLC or a specific or nonspecific monoclonal kit to determine the level of the drug substance, e.g. cyclosporin in the blood. For example, the compositions of Examples 1 to 15 administered p.o. to dogs may give surprisingly high C_{max} and AUC(0-24h) values as detected by a radioimmunoassay (RIA) method using a specific monoclonal antibody and within e.g. 60 to 120%, preferably 90 to 120%, of that of Neoral®.

In one aspect the present invention provides a method of orally administering a pharmaceutical composition, said method comprising orally administering to a patient in need of poorly water-soluble drug, e.g. cyclosporin, therapy a composition according to the present invention.

Pharmacokinetic parameters, for example absorption and blood levels, also become surprisingly more predictable and problems in administration with erratic absorption may be eliminated or reduced. Additionally the pharmaceutical compositions are effective with biosurfactants or tenside materials, for example bile salts, being present in the gastro-intestinal tract. That is, the pharmaceutical compositions of the present invention are fully dispersible in aqueous systems comprising such natural tensides and thus capable of providing particulate systems in situ which are stable. The function of the pharmaceutical compositions upon oral administration remain substantially independent of and/or unimpaired by the relative presence or absence of bile salts at any particular time or for any given individual.

The pharmaceutical compositions of the invention release the poorly water-soluble drug, e.g. cyclosporin, to the extent of e.g. about above 80% over a 60 minute period, e.g. about 75% in a 15 minute period, as measured by standard in vitro dissolution studies, e.g. at pH 6.8 or 1 using the paddle method.

The compositions of this invention show reduced variability in inter- and intra-patient dose response.

In one aspect the present invention provides a method of reducing the variability of bioavailability levels of a poorly water-soluble drug, e.g. cyclosporin, for patients during poorly water-soluble drug, e.g. cyclosporin, therapy, said method comprising orally administering an oral pharmaceutical composition according to the present invention.

The utility of all the pharmaceutical compositions of the present invention may be observed in standard clinical tests in, for example, known indications of drug dosages giving equivalent blood levels of drug; for example using dosages in the range of 2.5 mg to 1000 mg of drug per day for a 75 kilogram mammal, e.g. adult and in standard animal models. The increased bioavailability of the drug provided by the compositions may be observed in standard animal tests and in clinical trials, e.g. as described above.

The optimal dosage of drug to be administered to a particular patient may be considered carefully as individual response to and metabolism of the drug, e.g. cyclosporin, may vary, e.g. by monitoring the blood serum levels of the drug by radioimmunoassay (RIA), enzyme linked immunosorbent assay (ELISA), or other appropriate conventional means. Poorly water-soluble drug, e.g. cyclosporin, dosages may be 25 to 1000 mg per day (preferably 50 mg to 500 mg).

The pharmaceutical composition, e.g. in form of a tablet or a powder suitable for tablet formation, will suitably contain between 10 and 100 mg of the drug, for example 10, 15, 20, 25, 50, or 100 mg. Such unit dosage forms are suitable for administration 1 to 5 times daily depending upon the particular purpose of therapy, the phase of therapy and the like.

The pharmaceutical compositions of the invention are useful for the same indications as the poorly water soluble drugs. The pharmaceutical compositions comprising a cyclosporin are particularly useful for:

a) treatment and/or prevention of organ, cell or tissue transplant rejection, for example for the treatment of the recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants. The pharmaceutical compositions are also indicated for the

prevention of graft-versus-host disease, such as sometimes occurs following bone marrow transplantation;

b) treatment and/or prevention of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronic progrediente and arthritis deformans) and rheumatic diseases; and

c) treatment and/or prevention of psoriasis.

Pharmaceutical compositions of the invention, e.g. comprising cyclosporin, may be used alone or together with other immunosuppressants, immunomodulatory or anti-inflammatory drugs. For example, they may be used in combination with everolimus, sirolimus, tacrolimus, pimecrolimus, mycophenolic acid, mycophenolate sodium, mycophenolate mofetil, an accelerating lymphocyte homing agent, e.g. FTY720, corticosteroids, or the like.

Therefore in a further aspect the present invention provides

i. a pharmaceutical composition, e.g. comprising cyclosporin, as defined above for use in the treatment and/or prevention of organ, cell or tissue transplant rejection, prevention of graft-versus-host disease, treatment and/or prevention of autoimmune disease and of inflammatory conditions, and treatment and/or prevention of psoriasis;

ii. a method of treating and/or preventing organ, cell or tissue transplant rejection, preventing graft-versus-host disease, treating and/or preventing autoimmune disease and inflammatory conditions, and treating and/or preventing psoriasis, comprising administering a composition of the present invention, e.g. comprising cyclosporin, to a patient in the need thereof;

iii. the use of a composition of the present invention, e.g. comprising cyclosporin, in the preparation of a medicament for the treatment and/or prevention of organ, cell or tissue transplant rejection, prevention of graft-versus-host disease, treatment and/or prevention of autoimmune disease and of inflammatory conditions, and treatment and/or prevention of psoriasis; or

iv. a method as defined above comprising co-administering a composition of the present invention, e.g. comprising cyclosporin, and a second drug substance, said second drug substance being e.g. an immunosuppressant, an immunomodulatory or an anti-inflammatory drug.

Following is a description by way of example only of compositions of this invention. Unless otherwise indicated, components are shown in % by weight based on each composition. The examples illustrate compositions useful for example in the prevention of transplant rejection or for the treatment of autoimmune disease, on administration of from 1 to 5 unit dosages/day at a dose of 2 to 5 mg/kg per day. The examples are described with particular reference to Cyclosporin A but equivalent compositions may be obtained employing any cyclosporin or other poorly water-soluble drug.

Example 1 to 7:

Preparation of solid dispersion compositions

Compositions of examples 1 to 7 in amount as indicated in Table 1 are made up by dissolving Cyclosporin A in an ethanol/acetone mixture, adding the polymer, surfactant, if present, and carrier medium, if present, of Table 1, mixing until homogenously dispersed, evaporation of the solvents, and drying, milling and sieving the resulting residue.

Table 1

COMPONENT	Ex 1	Ex 2	Ex 3	Ex 4	Ex 5	Ex 6	Ex 7
Cyclosporin A	21%	30%	30%	40%	20%	25%	30%
PVP K30	-	67%	-	-	-	72%	-
HPMCP HP50	-	-	67%	55%	75%	-	63%
Eudragit® L100-55	50%	-	-	-	-	-	-
Solulan®	-	3%		-	-	3%	-
Myrj® 59	-	-	3%	5%	5%	-	-
Brij® 78P	-	-	-	-	-	-	7%
Lactose	25%	-	-	-	-	-	-
Crospovidone	4%	-	-	-	-	-	-

Example 8 and 9:

Preparation of microparticule compositions

Compositions of example 8 and 9 in amounts as indicated in Table 2 are made up by dissolving HPMCP HP50 in methylene chloride/acetone, adding Cyclosporin A and Brij® 78P or Myrj®59, respectively; delivering the polymer system to a mixer together with a buffered

gelatin solution; evaporation of the solvent, washing for excipients removal and collecting the microparticles.

Table 2

COMPONENT	Ex 8	Ex 9
Cyclosporin A	30%	40%
HPMCP HP50	63%	55%
Brij® 78P	7%	-
Myrj® 59	-	5%

Other examples may be made by replacing Eudragit® L100-55 or HPMCP HP50 by any of the polymers specified above or by replacing Brij® 78P by any of the surfactants specified above.

Example 10:

Compositions of example 10 in amounts as indicated in Table 3 are made up by dissolving the surfactant and the cyclosporin and suspending the carrier in ethanol, stirring to obtain a homogenous suspension, and evaporation of the solvent under reduced pressure.

The resulting powder is milled and sieved. After dilution with water at a ratio of 1+100 at 37°C the distribution of Cyclosporin A between solubilized and particulate phase is analyzed by centrifugation followed by HPLC. The results show a mixture of solubilized (35%) and particulate (65%) cyclosporin A. Particle sizes of up to about 12.5 microns are measured by a light microscope.

Table 3:

quantity given in wt-%

COMPONENTS	Ex. 10	Ex. 11	Ex. 12
Cyclosporin A	25%	30%	25%
Brij® 78P	50%	-	-
Sodium stearyl lactylate P55	-	30%	-
Sodium caprinate	-	-	37%
Lactose	25%	40%	38%

Example 11:

Compositions of example 11 in amounts as indicated in Table 3 are made up by dissolving the surfactant in ethanol, adding the cyclosporin, stirring to obtain a solution, delivering the organic preconcentrate to a mixer together with an aqueous solution of lactose, and spray-drying the mixture to obtain a fine powder.

The resulting powder is diluted with water at a ratio of 1+100 at 37°C and the distribution of Cyclosporin A between solubilized and particulate phase is analyzed by centrifugation followed by HPLC. The results show a mixture of solubilized (29%) and particulate 71% cyclosporin A. Particle sizes of up to about 2.5 microns are measured by a light microscope.

Example 12:

Compositions example 12 in amounts as indicated in Table 3 are made up by dissolving the surfactant, the cyclosporin, and the carrier in water, and spray-drying the aqueous solution to obtain a fine powder.

The resulting powder is diluted with water at a weight ratio of 1+7 at 37°C and the distribution of Cyclosporin A between solubilized and particulate phase is analyzed by centrifugation followed by HPLC. The results show a mixture of solubilized (72%) and particulate (28%) cyclosporin A.

Other examples may be made by replacing Brij® 78P, or sodium stearoyl lactylate P55, or sodium caprinate by any of the surfactants specified above.

Other examples may be made by replacing lactose by any of the carriers specified above.

Example 13 and 14:

Preparation of tablets based on solid dispersion particles

Compositions of examples 13 and 14 in amount as indicated in Table 4 are made up by dissolving Cyclosporin A in an ethanol/acetone mixture, adding the polymer, surfactant, if present, and carrier medium, if present, of Table 4, mixing until homogenously dispersed, evaporation of the solvents, and drying, milling and sieving the resulting residue. The

resulting particles are mixed with the additional excipients and directly compressed to flat tablets.

The tablets have a hardness (compression force), a disintegration time and dissolution rates as indicated in Table 5.

Table 4

COMPONENT	Ex 13	Ex 14	Ex. 15
Cyclosporin A	16.7%	14.3%	20%
PVP K30	-	41.2%	-
HPMCP HP50	22.9%	-	27.5%
Solulan®	-	1.7%	-
Myrj® 59	2.1%	-	2.5%
Crospovidone	20%	30%	20%
Microcelac 100	37.5%	-	29.2%
dicalcium phosphate anhydrous	-	12%	-
magnesium stearate	0.5%	0.5%	0.5%
Aerosil 200	0.3%	0.3%	0.3%

Table 5

	Ex 13	Ex 14	Ex. 15
average hardness in N	91	94	95
disintegration time in minutes	< 1	< 8	< 1
tablet diameter in mm	10	11	9
tablet weight in mg	300	350	250
dissolution rate after 15 min	80%	90%	89%
dissolution rate after 60 min	92%	94%	90%

Example 15

Preparation of tablets based on microparticules

Compositions of example 15 in amounts as indicated in Table 4 are made up by dissolving HPMCP HP50 in methylene chloride/acetone, adding Cyclosporin A and Myrj®59; delivering the polymer system to a mixer together with a buffered gelatin solution; evaporation of the

solvent, washing for excipients removal and collecting the microparticles. The resulting particles are mixed with the additional excipients and directly compressed to flat tablets.
The tablets have a hardness (compression force), a disintegration time and dissolution rates as indicated in Table 5.

Example 16

Single oral doses of 50 mg cyclosporin A per animal of composition of example 1,8, 10, 11 and 12 filled in a hard gelatin capsule size 1, corresponding to about 5 mg/kg were given to fasted dogs (n = 8) using a two-block latin square design with a one-week interval between administrations. The nominal doses of cyclosporin A in mg/kg body weight are listed in Table 6.
Blood (about 1 ml each) was collected from the cephalic or jugular vein at 0 min (= pre-dose), and 10 min, 30 min, 45 min, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours post dose. The EDTA blood samples were stored frozen below -18°C until bioanalysis.
Cyclosporin A blood concentrations were determined by a radioimmunoassay (RIA) method.

The pharmacokinetic parameters C_{max} (highest observed concentration in blood); t_{max} (time to reach C_{max}); and AUC(0-24h) (area under the plasma concentration-time curve from 0 to 24 h, calculated by the linear trapezoidal rule, wherein concentrations below the limit of quantitation (LOQ) were taken as 'zero'), are listed in Table 6.

Table 6:

	Composition of						
	Ex. 1	Ex. 8	Ex. 10	Ex. 11	Ex. 12	Ex. 6	Ex. 13
Actual dose CyA [mg/kg]	4.89	4.93	4.05	4.14	4.07	3.45	4.67
AUC(0-24h) [(ng/ml)·h]	1893	1973	935	894	576	2646	3436
C_{max} [ng/ml]	394	441	223	195	136	428	635
t_{max} [h]	1.69	1.28	1.57	1.86	2.57	1.13	1.53

Example 17

Single oral doses of 50 mg cyclosporin A per animal of composition of example 6 in form of a suspension in water, corresponding to about 2.5 - 4 mg/kgwere given to fasted dogs (n =

10) using a two-block latin square design with a one-week interval between administrations. The nominal doses of cyclosporin A in mg/kg body weight are listed in Table 6.

Blood (about 1 ml each) was collected from the jugular vein at 0 min (= pre-dose), and 10 min, 30 min, 45 min, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours post dose. The EDTA blood samples were stored frozen below -18°C until bioanalysis.

Cyclosporin A blood concentrations were determined by a radioimmunoassay (RIA) method.

The pharmacokinetic parameters C_{max} (highest observed concentration in blood); t_{max} (time to reach C_{max}); and AUC(0-24h) (area under the plasma concentration-time curve from 0 to 24 h, calculated by the linear trapezoidal rule, wherein concentrations below the limit of quantitation (LOQ) were taken as 'zero'), are listed in Table 6.

Example 18

Single oral doses of 50 mg cyclosporin A per animal of tablet compositions of example 13 corresponding to about 5 mg/kg were given to fasted dogs (n = 7) using a two-block latin square design with a one-week interval between administrations. The nominal doses of cyclosporin A in mg/kg body weight are listed in Table 6.

Blood (about 3 ml each) was collected from the cephalic vein at 0 min (= pre-dose), and 10 min, 30 min, 45 min, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours post dose. The EDTA blood samples were stored frozen below -18°C until bioanalysis.

Cyclosporin A blood concentrations were determined by a radioimmunoassay (RIA) method.

The pharmacokinetic parameters C_{max} (highest observed concentration in blood); t_{max} (time to reach C_{max}); and AUC(0-24h) (area under the plasma concentration-time curve from 0 to 24 h, calculated by the linear trapezoidal rule, wherein concentrations below the limit of quantitation (LOQ) were taken as 'zero'), are listed in Table 6.

Claims

1. A solid pharmaceutical composition comprising
   (1) a poorly water soluble drug,
   (2) a polymer which is solid at room temperature, and
   (3) a surfactant which is solid at room temperature and which has a HLB value of between 8 and 17.
2. A composition according to claim 1 wherein the ratio of surfactant : drug is 1 : 1 to 40.
3. A composition according to claim 1 or 2 wherein the surfactant is selected from polyoxyethylene alkyl ethers, polyethoxylated fatty acid esters or polyethylene glycol (PEG) sterol ethers.
4. A composition according to any preceding claim wherein the polymer is selected from polyvinyl pyrrolidone; cellulose derivatives such as hydroxypropylmethylcellulose or such as hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate and cellulose acetate phthalate; and poly(meth)acrylates.
5. A solid pharmaceutical composition comprising
   (1) a poorly water soluble drug,
   (2) a polymer which is solid at room temperature, and
   (3) an anionic surfactant which is solid at room temperature.
6. A composition according to claim 5 wherein the anionic surfactant is sodium caprinate or sodium stearoyl lactate.
7. A composition according to claim 5 or 6 which is enteric coated.
8. A composition according to any preceding claim wherein the composition is in form of a solid dispersion.
9. A composition according to claim 1 to 7 wherein the drug is encapsulated in a polymeric matrix.
10. A composition according to any preceding claim wherein the poorly water soluble drug is cyclosporin A.
11. A composition according to any preceding claim wherein the composition is substantially free of a hydrophilic component.
12. A composition according to any preceding claim wherein the composition is substantially free of a lipophilic component.
13. A composition according to any preceding claim which upon dilution with an aqueous medium forms a system wherein the poorly water-soluble drug substantially is in the form of fine particles.

14. A composition according to any one of claims 1 to 12 which upon dilution with an aqueous medium forms a system which is a mixture of solubilized drug and particulate drug.

15. A composition according to any one of claims 1 to 12 which upon dilution with an aqueous medium forms a system wherein the poorly water-soluble drug substantially is solubilized.

16. Use of a composition as claimed in any one of claims 1 to 15 in the manufacture of a medicament for the treatment of autoimmune diseases or for the use as an immunosuppressant.

17. A process for the production of a composition according to claim 8 which process comprises

(i) dissolving, suspending or dispersing the drug and polymer, if present, in a solvent or solvent mixture,

(ii) adding the surfactant, if present, to the drug/solvent or drug/polymer/solvent mixture,

(iii) evaporating the solvent and co-precipitating the drug with the polymer and/or the surfactant,

(iv) drying the resulting residue, milling and sieving the particles.

18. A process for the production of a composition according to claim 9 which process comprises

(i) preparation of an internal organic phase comprising the drug, the polymer, optionally the surfactant, and an organic solvent,

(ii) preparation of an external aqueous phase comprising a buffered gelatin solution,

(iii) mixing the internal organic phase with the external aqeous phase,

(iv) hardening the microparticles by solvent evaporation.

19. A solid pharmaceutical composition comprising

(1) Cyclosporin A, and

(2) a polymer which is solid at room temperature.

20. A solid pharmaceutical composition comprising

(1) a cyclosporin and

(3) a surfactant which is solid at room temperature.

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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING CYCLOSPORIN

(57) Abstract: A solid pharmaceutical composition, e.g. in form of a tablet, powder or capsule, comprising 1) a poorly water soluble drug, e.g. cyclosporin, 2) a polymer which is solid at room temperature, and 3) a surfactant which is solid at room temperature and which has an HLB value of between 8 and 17.

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 543 393 A (KIM JUNG W ET AL) 6 August 1996 (1996-08-06) * see in particular column 6, lines 9-17; examples 3, 6, 7 and test example *	1-20
X	WO 96 22103 A (CHEIL FOODS & CHEM ;HWANG SUNG JOO (KR); PARK SUN HEE (KR); JEONG) 25 July 1996 (1996-07-25) * see in particular page 5, lines 1-9; examples 1-18 *	1-20
X	WO 90 01329 A (TAKADA KANJI) 22 February 1990 (1990-02-22) * see in particular page 4, lines 2-9; examples 8-13 *	1-20

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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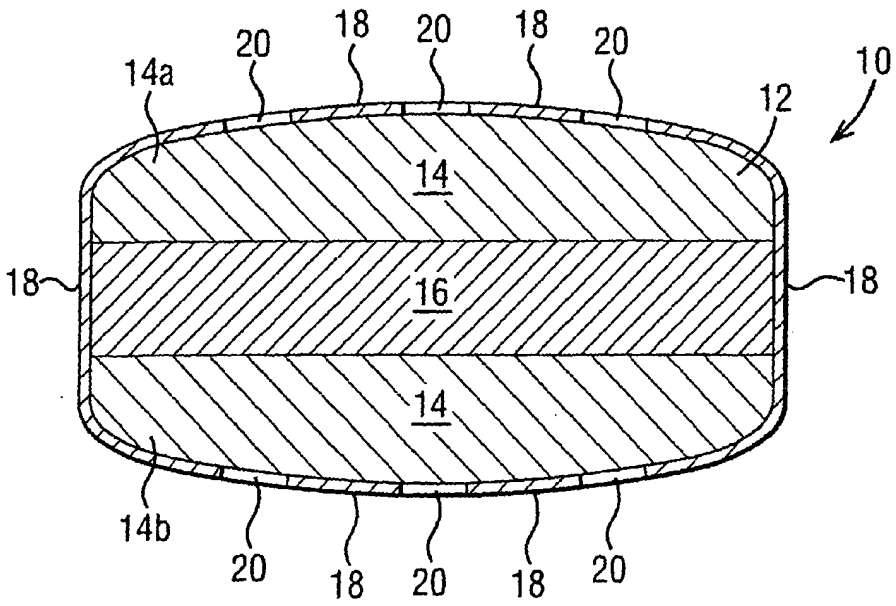
(54) Title: HYDROGEL-DRIVEN DRUG DOSAGE FORM



(57) Abstract: A controlled release dosage form has a coated core with the core comprising a drug-containing composition and a water-swellable composition, each occupying separate regions within the core. The coating around the core is water-permeable, water-insoluble and has at least one delivery port therethrough. A variety of geometric arrangements are disclosed.

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HYDROGEL-DRIVEN DRUG DOSAGE FORM

BACKGROUND OF THE INVENTION

The present invention relates to a dosage form that provides a controlled release of a beneficial agent, or drug, to an environment of use.

Osmotic and hydrogel-driven drug delivery devices for the release of a drug have been known in the art for some time. Exemplary dosage forms have included a tablet comprising a semipermeable wall surrounding a compartment containing the drug and a layer of swellable hydrogel, with the drug being delivered through a passageway in the semipermeable wall by swelling of the hydrogel, as described in U.S. Patent No. 4,327,725; another tablet comprising a wall permeable to an exterior fluid but impermeable to the drug, the wall surrounding a compartment containing two osmotic agents, two expandable polymers and the drug, as described in U.S. Patent No. 4,612,008; drug dispersed in a swellable hydrogel matrix core that releases the drug by diffusion into the environment of use, as described in U.S. Patent No. 4,624,848; a hydrogel reservoir containing a multiplicity of tiny pills wherein each tiny pill consists of a wall surrounding a drug core, as described in U.S. Patent No. 4,851,232; and a two-layered tablet wherein one layer is drug mixed with a hydrogel and the other layer is a hydrogel, as described in U.S. Patent No. 5,516,527.

While the conventional dosage forms described above are functional, nonetheless such dosage forms suffer from a variety of drawbacks. A controlled release dosage form should ideally deliver substantially all of the drug from the dosage form to the environment of use. However, a common problem encountered by osmotic and hydrogel-driven dosage forms, particularly when the drug has low aqueous solubility, is that residual drug is left in the tablet interior after the hydrogel or other swellable material has completely swelled. This residual drug is not available for absorption and, accordingly, such dosage forms require increased amounts of drug to compensate for the failure of the system to release all of the drug into the environment of use.

In addition, the controlled release dosage form must operate within certain size constraints, and yet be capable of delivering most or all of the drug to the environment of use. Dosage forms, particulary for humans, are limited in size, and are usually less than 1 gram, more preferably less than 700 mg in weight. However, for some types of drugs, the dose amount may make up to half or even more of the weight of the dosage form. The water-swellable materials that provide the delivery of the drug must in instances where the dose is high be capable of

providing a highly efficient delivery of the drug, since very little of the dosage form may be available for the swellable material or other excipients.

In addition, it is often desired that the dosage form begin extruding drug relatively quickly upon entering the use environment. However, many delivery systems exhibit a time lag before extruding drug. This can be particularly problematic when the drug has low aqueous solubility or is hydrophobic. Several techniques have been proposed to reduce the time lag, but each has its own drawback. One technique has been to provide high-permeabilitiy coatings by utilizing thin coatings around the dosage form. While this technique provides a quicker uptake of fluid, the thin coating lacks strength and often bursts in use or provides insufficient protection to the dosage form which becomes susceptible to damage during handling. Yet another technique has involved providing pores or one or more passageways that communicate with the water-swellable materials, but this often leads to unacceptable amounts of residual drug. Another technique involves coating the dosage form with an immediate release drug formulation, but this requires additional processing steps and provides a dosage form with two different release rates, which may be undesirable.

Yet another problem encountered with conventional osmotic and hydrogel-driven drug delivery systems is that such dosage forms often require the presence of osmagents. Osmagents are selected such that they generate an osmotic pressure gradient across the barrier of the surrounding coating. The osmotic pressure gradient drives the permeation of water into the tablet and the resulting buildup of sufficient hydrostatic pressure, which forces the drug through the delivery port. These osmagents increase the weight of the dosage form, thus limiting the amount of drug which may be contained in the dosage form. In addition, the presence of additional ingredients in the dosage form, such as osmagents, increases the costs of manufacture due to the need to insure uniform concentrations of the ingredients throughout the dosage form, and may have other drawbacks such as adverse effects on compression properties and on drug stability.

Very little has been done to investigate the delivery of drugs from dosage forms having different arrangements of materials. Dosage forms of the prior art generally fall into one of three arrangements. The first is the conventional bi-layer design, which is characterized by a drug-containing layer and a water-swellable layer. Exemplary of these devices is Wong, et al., U.S. Patent No. 4,612,008.

Yet another arrangement consists of a water-swellable layer surrounded by a drug-containing composition. Such a device is shown in Curatolo, U.S. Patent No. 5,792,471.

Yet another arrangement is shown by McClelland et al., U.S. Patent No. 5,120,548, which discloses a controlled release delivery device containing swelling modulators blended within swellable polymers.

Nevertheless, there is still a need in the art for a controlled release dosage form that results in a highly efficient delivery of drug to an environment of use with very little residual drug, that allows large drug loading so as to minimize the dosage size, that begins releasing drug soon after entering the environment of use, and that limits the number of necessary ingredients. These needs and others which will become apparent to one skilled in the art are met by the present invention, which is summarized and described in detail below.

BRIEF SUMMARY OF THE INVENTION

The various aspects of the invention each provide a controlled release drug dosage form for delivery of at least one drug. A first aspect of the invention provides a controlled release drug dosage form comprising a core and a coating around the core. The core comprises a first drug-containing composition, a second drug containing composition, and a water-swellable composition, each occupying separate regions within the core. The water-swellable composition is located between the first and second drug-containing compositions. The coating is water-permeable, water-insoluble, and has at least one delivery port for communication with the first drug-containing composition and at least one additional delivery port for communication with the second drug-containing composition.

A second aspect of the invention provides a controlled release drug dosage form comprising a core and a coating around said core. The core comprises a drug-containing composition and a water-swellable composition, each occupying separate regions within said core. The drug-containing composition surrounds the water-swellable composition. The drug-containing composition comprises a low-solubility drug and a drug-entraining agent. The water-swellable composition comprises a swelling agent. The coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

A third aspect of the invention provides a controlled release drug dosage form comprising a core and a coating. The core comprises a drug-containing composition and a water-swellable composition, each occupying separate regions within the core. The water-swellable composition comprises a plurality of granules. The drug-containing composition comprises a drug and a drug-entraining agent. The water-swellable composition comprises a swelling agent. The coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

A fourth aspect of the invention provides a controlled release drug dosage form comprising a core and a coating. The core is substantially homogeneous throughout and comprises a mixture of a drug, a drug-entraining agent, a fluidizing agent, and a swelling agent. The coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

This invention further provides a method of treating a disease or condition amenable to treatment with a pharmaceutical agent which is administered in a controlled release (*i.e.*, sustained release or delayed release) dosage form, comprising administering to a person in need of such treatment a controlled release dosage form according to any of the four aspects disclosed above, said dosage form comprising an effective amount of said pharmaceutical agent.

The amount of a particular compound which is administered will necessarily be varied according to principles well known in the art taking into account factors such as the particular compound of interest, the severity of the disease or condition being remediated and the size and age of the patient. In general, the compound will be administered so that an effective dose is received, an "effective dose" being determined from safe and efficacious ranges of administration already known for the particular compound of interest. Alternatively, an effective amount can be determined by the attending physician.

The methods of treatment disclosed above are not limited by or to any particular disease or indication, and the scope of such methods is intended to be broad, such methods of treatment including, but not being limited to, any of the classes of compounds or specific compounds disclosed hereinbelow.

The various aspects of the present invention have one or more of the following advantages. The dosage forms of the present invention are capable of delivering greater amounts of drug to the desired environment of use with greater efficiency using smaller amounts of swelling materials, and also result in lower amounts of residual drug than do conventional compositions. The compositions are also capable of higher drug loading compared with conventional compositions. In addition, the compositions begin delivering drug to the environment of use more quickly than do conventional dosage forms. The dosage forms are capable of rapidly delivering a drug without the coating failing due to rupture as a result of excessive pressure within the core when the dosage form is introduced into an environment of use.

In addition, the various embodiments provide at least one manufacturing advantage relative to the bi-layer design, in that the location of the delivery port is not as important, as discussed below. In addition, for the aspect comprising a homogeneous core, that embodiment eliminates processing associated

with forming separate layers.

The foregoing and other objectives, features, and advantages of the invention will be more readily understood upon consideration of the following detailed description of the invention, taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWING

FIGS. 1-4 are schematic drawings of cross sections of exemplary embodiments of dosage forms of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a controlled release dosage form that is specifically designed to provide controlled release of at least one drug primarily by imbibition of water and extrusion of drug from the dosage form as opposed to primarily by diffusion. Referring now to the figures, wherein like numerals refer to like elements, FIGS. 1-4 depict schematically four exemplary dosage form arrangements. FIG. 1 depicts a "tri-layer" tablet; FIG. 2 depicts a "concentric core" tablet; FIG. 3 depicts a "granular core" tablet; and FIG. 4 depicts a "homogeneous core" tablet. Certain features common to all of the exemplary embodiments may be understood by first considering FIG. 1 which shows an exemplary tri-layer dosage form 10 having a core 12 comprising drug-containing composition(s) 14 and a water-swellable composition 16. The drug-containing composition(s) and the water-swellable composition occupy separate regions in the core. By "separate regions" is meant that the two compositions occupy separate volumes, such that the two are not substantially mixed together. Of course, a small amount of intermixing of the compositions may occur where the compositions come in contact with each other, for example, at the interface between two layers. A coating 18 surrounds the core 12 and is water-permeable, water-insoluble and has one or more delivery ports 20 therethrough. In use, the core 12 imbibes water through the coating 18 from the environment of use such as the gastrointestinal ("GI") tract of a mammal. The imbibed water causes the water-swellable composition 16 to swell, thereby increasing the pressure within the core 12. The imbibed water also increases the fluidity of the drug-containing composition. The pressure difference between the core 12 and the environment of use drives the release of the fluidized drug-containing composition(s) 14. Because the coating 18 remains intact, the drug-containing composition(s) 14 are extruded out of the core 12 through the delivery port(s) 20 into the environment of use. Because the water-swellable composition 16 contains no drug, almost all of the drug is extruded through the delivery port(s) 20, leaving very little residual drug.

The dosage form of the present invention releases the drug to an environment of use primarily by "extrusion" rather than by diffusion. The term "extrusion" as used herein is intended to convey an expulsion or forcing out of some or all of the drug through one or more delivery ports or pores in the coating to the exterior of the dosage form by hydrostatic forces, to be distinguished from delivery by a diffusion mechanism or by erosion of the mass of the device. The drug may be released primarily by extrusion either in the form of a suspension of solids in aqueous solution or the drug may be in solution, to the extent dissolution has taken place in the core 12.

Reference to the "release" of drug as used herein means (1) transport of drug from the interior of the dosage form to its exterior such that it contacts fluid within a mammal (*e.g.*, a mammal's GI tract) following delivery or (2) transport of drug from the interior of the dosage form such that it contacts a test medium for evaluation of the dosage form by an *in vitro* test as described below. Reference to a "use environment" can thus be either to *in vivo* fluids or to an *in vitro* test medium. "Introduction" to a use environment includes either by ingestion or swallowing or use of implants or suppositories, where the use environment is *in vivo,* or being placed in a test medium where the use environment is *in vitro.*

DOSAGE FORM ARRANGEMENT

Four exemplary dosage form arrangements are schematically shown in FIGS. 1-4.

FIG. 1 depicts a "tri-layer" tablet 10 comprising a core 12 that has two drug-containing compositions 14a and 14b on either side of a water-swellable composition 16 and, surrounding the core 12, a coating 18 that has at least one delivery port 20 through the coating connecting each drug layer 14a and 14b with the exterior of the dosage form. The tri-layer dosage form provides several advantages. First, the dosage form may be used to deliver two different drugs. Thus, the drug-containing composition 14a may contain a drug that is different than the drug in drug-containing composition 14b. Second, even when the drug-containing compositions 14a and 14b contain the same drug, the two drug-containing compositions may be formulated differently so as to provide different release rates for the drug. Thus, for example, drug-containing composition 14a could provide a fast release rate for a drug, while drug-containing composition 14b could provide a slow release rate, thus allowing a wide range of drug profiles to be achieved.

Another advantage of the tri-layer design is that the delivery port is located on both sides of the core, rather than on a single side as in the bi-layer arrangement. It is desired that the bi-layer dosage form have at least one delivery

port in communication with the drug-containing composition. A problem when manufacturing bi-layer dosage forms is that for some compositions, providing a delivery port in communication with the water-swellable composition diminishes performance. Thus, care and added expense are required during manufacturing to locate the side of the dosage form facing the drug-containing composition and then provide a delivery port only on that side of the dosage form. In contrast, for the tri-layer design, it is desired to have a delivery port on both sides of the dosage form. Therefore, it is no longer necessary to locate the correct side for providing the delivery port, since a delivery port is provided on both sides of the dosage form.

FIG. 2 depicts a "concentric core" tablet 10' comprising a core 12 that has a drug-containing composition 14 that surrounds a water-swellable composition 16 and surrounding the core, a coating 18 that has at least one delivery port 20 through the coating 18 connecting the drug layer 14 with the exterior of the dosage form. The concentric core dosage form provides at least one processing advantage relative to the bi-layer arrangement in that the location of the delivery port is not critical, since the water-swellable composition is surrounded by the drug-containing composition. Thus any delivery port will be in communication with the drug-containing composition regardless of location. Also, water must pass through the drug-containing composition prior to entering the water-swellable composition ensuring that the drug-containing composition is fluid enough to be delivered prior to pressure being exerted by the water-swellable composition.

FIG. 3 depicts a "granular core" tablet 10" comprising a core 12, a coating 18 and at least one delivery port 20. The core comprises a drug-containing composition 14, and multiple granules of a water-swellable composition 16 mixed throughout the drug-containing composition 14. Like the concentric core embodiment, the location of the delivery port for the granular core is not important, and therefore provides a manufacturing advantage relative to the bi-layer arrangement.

Yet another advantage of the granular core tablet is that it may be formed using conventional single-layer tablet-manufacturing equipment. This avoids the expense of a multi-layer tablet press.

FIG. 4 depicts a "homogeneous core" tablet 100, comprising a core 12, a coating 18 and at least one delivery port 20. The core comprises a homogenous drug-containing composition 15 that contains both the drug and the swelling materials. The homogeneous core provides at least three manufacturing advantages. First, the location of the delivery port is not important, since any delivery port will be in communication with the drug-containing composition. Second, only a single drug-containing composition needs to be prepared, rather than

separate drug-containing compositions and water-swellable compositions. Third, standard single-layer tablet-making equipment can be used to form the core. Accordingly, the cost associated with preparing additional compositions is eliminated.

RELEASE CHARACTERISTICS

An important attribute of the dosage forms of the present invention is the delivery of drug to a use environment in a controlled manner. For some aspects of the present invention, the dosage forms start releasing drug soon after introduction to the use environment. When a rapid onset of delivery is desired, preferably the dosage forms release at least 5 wt% of the drug, and more preferably at least 10 wt% of the drug within 2 hours after introduction to the use environment, where these percentages correspond to the mass of drug released from the core relative to the total mass of drug originally present in the core. By quickly beginning the release of the drug, the dosage form shortens the time required to achieve an effective drug concentration in a use environment such as the upper GI tract. Rapid release can also reduce the time required to achieve an effective drug level in the blood.

It is also desired that the dosage forms release the drug in a controlled manner, preferably at a substantially constant rate. For many drugs, it is preferred that the dosage forms release no more than about 60 wt% of the drug, and more preferably no more than about 50 wt% of the drug, into the use environment within 2 hours after introduction to the use environment. The rate of release of drug from the dosage form should also be sufficiently high to allow release of the drug within a time frame that allows a substantial fraction of the drug delivered to be absorbed into the blood stream. For many drugs the dosage forms preferably release at least 60 wt% of the drug, and more preferably at least 70 wt% of the drug to the use environment within 16 hours after introduction to the use environment. The inclusion of a fluidizing agent in the drug-containing composition is particularly useful when more rapid delivery of drug to the use environment is desired. In particular, when it is desirable to deliver at least 70 wt% of the drug to the use environment within 12 hours after introduction thereto, the invention allows rapid drug release without rupture or otherwise failure of the dosage form coating during operation.

It is also desired that the dosage forms release a substantial amount of the drug contained within the dosage form, leaving a relatively small residual amount of drug after 24 hours. Obtaining low residual amounts of drug is particularly difficult when it is desired to deliver high doses of low-solubility drug. Preferably, the dosage forms of the present invention release at least 80 wt% of drug, more

preferably at least 90 wt%, and even more preferably at least 95 wt% of drug to the use environment within 24 hours after introduction of the dosage form to the use environment.

An *in vitro* test may be used to determine the release profile(s) of the dosage forms of the present invention. *In vitro* tests are well known in the art. An example is a "residual test," which is described below for sertraline HCl. One or more dosage forms is first placed into a stirred USP type 2 dissoette flask containing 900 mL of a buffer solution simulating gastric environment (10 mM HCl, 120 mM NaCl, pH 2.0, 261 mOsm/kg) at 37□C for 2 hours, then removed, rinsed with deionized water, and transferred to a stirred USP type 2 dissoette flask containing 900 mL of a buffer solution simulating the contents of the small intestine (6 mM KH_2PO_4, 64 mM KCl, 35 mM NaCl, pH 7.2, 210 mOsm/kg). In both flasks, the dosage forms are placed in a wire support to keep the dosage forms off of the bottom of the flask, so that all surfaces are exposed to the moving release solution and the solutions are stirred using paddles that rotate at a rate of 50 rpm. At each time interval, a single dosage form is removed from the solution, released material is removed from the surface, and the dosage form cut in half and placed in 100 mL of a recovery solution (1:1 wt/wt ethanol:water, pH adjusted to 3 with 0.1 N HCl), and vigorously stirred overnight at ambient temperature to dissolve the drug remaining in the dosage form. Samples of the recovery solution containing the dissolved drug are filtered using a Gelman Nylon® Acrodisc® 13, 0.45 µm pore size filter, and placed in a vial and capped. Residual drug is analyzed by HPLC. Drug concentration is calculated by comparing UV absorbance of samples to the absorbance of drug standards. The amount remaining in the tablets is subtracted from the total drug present prior to release to obtain the amount released at each time interval.

An alternative *in vitro* test is a direct test, in which samples of the dosage form are placed into a stirred USP type 2 dissoette flask containing 900 mL of a receptor solution such as USP sodium acetate buffer (27 mM acetic acid and 36 mM sodium acetate, pH 4.5) or 88 mM NaCl. Samples are taken at periodic intervals using a VanKel VK8000 autosampling dissoette with automatic receptor solution replacement. Tablets are placed in a wire support as above, paddle height is adjusted, and the dissoette flasks stirred at 50 rpm at 37□C. The autosampler dissoette device is programmed to periodically remove a sample of the receptor solution, and the drug concentration is analyzed by HPLC using the procedure outlined above. Since the drug is usually extruded from the dosage form as a suspension in an entraining polymer, there is often a time lag between when the drug is released and when it is dissolved in the test medium, and thus, measured in the direct test. This time lag depends on the solubility of the drug, the test medium,

and the ingredients of the drug-containing composition, but typically is on the order of 30 to 90 minutes.

While particular buffers or test media in which to conduct *in vitro* tests have been described above, any conventional test media may be used as is well known in the art.

Alternatively, an *in vivo* test may be used. However, due to the inherent difficulties and complexity of the *in vivo* procedure, it is preferred that *in vitro* procedures be used to evaluate dosage forms even though the ultimate use environment is often the human GI tract. Drug dosage forms are dosed orally to a group of mammals, such as humans or dogs and drug release and drug absorption is monitored either by (1) periodically withdrawing blood and measuring the serum or plasma concentration of drug or (2) measuring the amount of drug remaining in the dosage form following its exit from the anus (residual drug) or (3) both (1) and (2). In the second method, residual drug is measured by recovering the tablet upon exit from the anus of the test subject and measuring the amount of drug remaining in the dosage form using the same procedure described above for the *in vitro* residual test. The difference between the amount of drug in the original dosage form and the amount of residual drug is a measure of the amount of drug released during the mouth-to-anus transit time. This test has limited utility since it provides only a single drug release time point but is useful in demonstrating the correlation between *in vitro* and *in vivo* release.

In one *in vivo* method of monitoring drug release and absorption, the serum or plasma drug concentration is plotted along the ordinate (y-axis) against the blood sample time along the abscissa (x-axis). The data may then be analyzed to determine drug release rates using any conventional analysis, such as the Wagner-Nelson or Loo-Riegelman analysis. See also Welling, "Pharmacokinetics: Processes and Mathematics" (ACS Monograph 185, *Amer. Chem. Soc.*, Washington, D.C., 1986). Treatment of the data in this manner yields an apparent *in vivo* drug release profile.

DRUG-CONTAINING COMPOSITION

For the tri-layer, concentric core, and granular core embodiments of the present invention, the drug-containing composition 14 includes at least one drug and preferably additional excipients (the homogeneous core embodiment is discussed below). The drug-containing composition occupies a separate, substantially distinct region from the water-swellable composition. For the granular core embodiment, a substantially distinct region means that the water-swellable composition is present in a plurality of separate granules distributed throughout the drug-containing composition. When it is desired to deliver a relatively large dose of drug (about 100 mg or more) in a single dosage form, the drug-containing composition preferably comprises greater than about 50 wt% of the core. When it is desirable to deliver even greater amounts of drug (*e.g.*, 150 mg or more), the drug-containing composition comprises preferably greater than about 60 wt% of the core, and more preferably greater than about 70 wt% of the core. Preferably, the drug-containing composition 14 is in contact with or in close proximity to the coating 18 which surrounds the dosage form.

The drug-containing composition(s) may contain one or more drugs, and in the case of the tri-layer dosage form, the first drug-containing composition 14a may contain a different drug than the second drug-containing composition 14b. The drug may be virtually any beneficial therapeutic agent and may comprise from 0.1 to 65 wt% of the drug-containing composition 14. In cases where the dose to be delivered is high (*e.g.*, greater than about 100 mg), it is preferred that the drug comprise at least 35 wt% of the drug-containing composition 14. The drug may be in any form, either crystalline or amorphous. The drug may also be in the form of a solid dispersion.

The invention finds particular utility when the drug is a "low-solubility drug," meaning that the drug is either "substantially water-insoluble" (which means that the drug has a minimum aqueous solubility at physiologically relevant pH (e.g., pH 1-8) of less than 0.01 mg/mL), or "sparingly water soluble," that is, has a minimum aqueous solubility at physiologically relevant pH up to about 1 to 2 mg/mL, or has even low to moderate aqueous solubility, having a minimum aqueous solubility at physiologically relevant pH as high as about 10 to 20 mg/mL. In general, it may be said that the drug has a dose-to-aqueous solubility ratio greater than 10 mL, and more typically greater than 100 mL, where the drug solubility is the minimum value in mg/mL observed in any physiologically relevant aqueous solution (e.g., those with pH values between 1 and 8) including USP simulated gastric and intestinal buffers and the dose is in mg. The drug may be employed in its neutral

(e.g., free acid, free base, or zwitterion) form, or in the form of its pharmaceutically acceptable salts as well as in anhydrous, hydrated, or solvated forms, and pro drugs.

Preferred classes of drugs include, but are not limited to, antihypertensives, antidepressants, antianxiety agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, anti-inflammatories, antipsychotic agents, cognitive enhancers, cholesterol-reducing agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, antibiotics, antiviral agents, anti-neoplastics, barbituates, sedatives, nutritional agents, beta blockers, emetics, anti-emetics, diuretics, anticoagulants, cardiotonics, androgens, corticoids, anabolic agents, growth hormone secretagogues, anti-infective agents, coronary vasodilators, carbonic anhydrase inhibitors, antiprotozoals, gastrointestinal agents, serotonin antagonists, anesthetics, hypoglycemic agents, dopaminergic agents, anti-Alzheimer's Disease agents, anti-ulcer agents, platelet inhibitors and glycogen phosphorylase inhibitors.

Specific examples of the above and other classes of drugs and therapeutic agents deliverable by the invention are set forth below, by way of example only. Specific examples of antihypertensives include prazosin, nifedipine, trimazosin, amlodipine, and doxazosin mesylate; a specific example of an antianxiety agent is hydroxyzine; a specific example of a blood glucose lowering agent is glipizide; a specific example of an anti-impotence agent is sildenafil citrate; specific examples of anti-neoplastics include chlorambucil, lomustine and echinomycin; specific examples of anti-inflammatory agents include betamethasone, prednisolone, piroxicam, aspirin, flurbiprofen and (+)-N-{4-[3-(4-fluorophenoxy)phenoxy]-2-cyclopenten-1-yl}-N-hyroxyurea; a specific example of a barbituate is phenobarbital; specific examples of antivirals include acyclovir, nelfinavir, and virazole; specific examples of vitamins/nutritional agents include retinol and vitamin E; specific examples of a -blocker include timolol and nadolol; a specific example of an emetic is apomorphine; specific examples of a diuretic include chlorthalidone and spironolactone; a specific example of an anticoagulant is dicumarol; specific examples of cardiotonics include digoxin and digitoxin; specific examples of an androgen include 17-methyltestosterone and testosterone; a specific example of a mineral corticoid is desoxycorticosterone; a specific example of a steroidal hypnotic/anesthetic is alfaxalone; specific examples of an anabolic agent include fluoxymesterone and methanstenolone; specific examples of antidepression agents include fluoxetine, pyroxidine, venlafaxine, sertraline, paroxetine, sulpiride, [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(lethylpropyl)-amine and

3,5-dimethyl-4-(3'-pentoxy)-2-(2',4',6'-trimethylphenoxy)pyridine; specific examples of an antibiotic include ampicillin and penicillin G; specific examples of an anti-infective include benzalkonium chloride and chlorhexidine; specific examples of a coronary vasodilator include nitroglycerin and mioflazine; a specific example of a hypnotic is etomidate; specific examples of a carbonic anhydrase inhibitor include acetazolamide and chlorzolamide; specific examples of an antifungal include econazole, terconazole, fluconazole, voriconazole and griseofulvin; a specific example of an antiprotozoal is metronidazole; a specific example of an imidazole-type anti-neoplastic is tubulazole; specific examples of an anthelmintic agent include thiabendazole and oxfendazole; specific examples of an antihistamine include astemizole, levocabastine, cetirizine, and cinnarizine; a specific example of a decongestant is pseudoephedrine; specific examples of antipsychotics include fluspirilene, penfluridole, risperidone and ziprasidone; specific examples of a gastrointestinal agent include loperamide and cisapride; specific examples of a serotonin antagonist include ketanserin and mianserin; a specific example of an anesthetic is lidocaine; a specific example of a hypoglycemic agent is acetohexamide; a specific example of an anti-emetic is dimenhydrinate; a specific example of an antibacterial is cotrimoxazole; a specific example of a dopaminergic agent is L-DOPA; specific examples of anti-Alzheimer agents are THA and donepezil; a specific example of an anti-ulcer agent/H2 antagonist is famotidine; specific examples of a sedative/hypnotic include chlordiazepoxide and triazolam; a specific example of a vasodilator is alprostadil; a specific example of a platelet inhibitor is prostacyclin; specific examples of an ACE inhibitor/antihypertensive include enalaprilic acid and lisinopril; specific examples of a tetracycline antibiotic include oxytetracycline and minocycline; specific examples of a macrolide antibiotic include azithromycin, clarithromycin, erythromycin and spiramycin; specific examples of glycogen phosphorylase inhibitors include [R-(R*S*)]-5-chloro-N-[2-hydroxy-3{methoxymethylamino}-3-oxo-l-(phenylmethyl)-propyl]-lH-indole-2-carboxamide and 5-chloro-1-Hindole-2-carboxylic acid [(lS)-benzyl(2R)-hydroxy-3-((3R,4S)dihydroxy-pyrrolidin-1-yl-)-oxypropyl]amide.

Further examples of drugs deliverable by the invention are the glucose-lowering drug chlorpropamide, the anti-fungal fluconazole, the anti-hypercholesterolemic atorvastatin calcium, the antipsychotic thiothixene hydrochloride, the anxiolytics hydroxyzine hydrochloride and doxepin hydrochloride, the anti-hypertensive amlodipine besylate, the antiinflammatories piroxicam and celicoxib and valdicoxib, and the antibiotics

carbenicillin indanyl sodium, bacampicillin hydrochloride, troleandomycin, and doxycycline hyclate.

In an alternative embodiment, the drug is present in the form of a solid, amorphous dispersion. By solid, amorphous dispersion is meant that the drug is dispersed in a polymer so that a major portion of the drug is in a substantially amorphous or non-crystalline state, and its non-crystalline nature is demonstrable by x-ray diffraction analysis or by differential scanning calorimetry. The dispersion may contain from about 5 to 90 wt% drug. The polymer is aqueous-soluble and inert, and, when enhancement of bioavailability is desirable, is preferably concentration-enhancing. Suitable polymers and methods for making solid amorphous dispersions are disclosed in commonly assigned provisional patent applications Serial Nos. 60/119,406 and 60/119,400, the relevant disclosures of which are incorporated by reference. Suitable dispersion polymers include ionizable and non-ionizable cellulosic polymers, such as cellulose esters, cellulose ethers, and cellulose esters/ethers; and vinyl polymers and copolymers having substituents selected from the group consisting of hydroxyl, alkylacyloxy, and cyclicamido, such as polyvinyl pyrrolidone, polyvinyl alcohol, copolymers of polyvinyl pyrrolidone and polyvinyl acetate. Particularly preferred polymers include hydroxypropylmethyl cellulose acetate succinate (HPMCAS), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl methyl cellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), and polyvinyl pyrrolidone (PVP). Most preferred are HPMCAS, HPMCP, CAP and CAT.

When the drug has a low solubility (less than about 20 mg/ml) it is preferable that the drug-containing composition also comprise an entraining agent. The use of an entraining agent is necessitated by the low-solubility drug, which due to its low-solubility does not dissolve sufficiently within the core 12 to be extruded in the absence of an entraining agent. The entraining agent suspends or entrains the drug so as to aid in the delivery of the drug through the delivery port(s) 20 to the environment of use. While not wishing to be bound by any particular theory, it is believed that upon imbibing water into the dosage form, the entraining agent imparts sufficient viscosity to the drug-containing composition to allow it to suspend or entrain the drug, while at the same time remaining sufficiently fluid to allow the entraining agent to pass through the delivery port(s) 20 along with the drug. It has been found that there is a good correlation between the usefulness of a material as an entraining agent and the viscosity of an aqueous solution of the material. The entraining agent generally is a material that has high water solubility and in operation forms aqueous solutions with viscosities of at least 50 centipoise (cp) and preferably aqueous solutions with viscosities of 200 cp or greater.

The amount of the entraining agent present in the drug-containing composition may range from about 5 wt% to about 98 wt% of the drug-containing composition, preferably 10 wt% to 50 wt% more preferably 10 wt% to 40 wt%. The entraining agent may be a single material or a mixture of materials. Examples of such materials include polyols, and oligomers of polyethers, such as ethylene glycol oligomers or propylene glycol oligomers. In addition, mixtures of polyfunctional organic acids and cationic materials such as amino acids or multivalent salts, such as calcium salts may be used. Of particular utility are polymers such as polyethylene oxide (PEO), polyvinyl alcohol, PVP, cellulosics such as hydroxyethyl cellulose (HEC), hydroxypropylcellulose (HPC), HPMC, methyl cellulose (MC), carboxy methyl cellulose (CMC), carboxyethylcellulose (CEC), gelatin, xanthan gum or any other water-soluble polymer that forms an aqueous solution with a viscosity similar to that of the polymers listed above. An especially preferred entraining agent is non-crosslinked PEO or mixtures of PEO with the other materials listed above.

When the drug and a polymeric entraining agent make up about 80 wt% or more of the drug-containing composition, then the entraining agent should have a sufficiently low molecular weight that it becomes sufficiently fluid so that both the drug and entraining agent can be rapidly extruded from the dosage form, instead of swelling and rupturing the water-permeable coating that surrounds the dosage form. Thus, for example, when PEO is the drug-entraining agent, it is generally preferred that it have a molecular weight of from about 100,000 to about 300,000 daltons. (References to molecular weights of polymers herein and in the claims are to average molecular weights.)

When the drug and the entraining agent make up less than about 80 wt% of the drug-containing composition, a smaller portion of a more viscous entraining agent is preferred. For example, when the entraining agent is PEO, a lower fraction of a higher molecular weight of PEO from about 500,000 to 800,000 daltons may be used. Thus, there is an inverse relationship between the preferred PEO molecular weight and the weight fraction of the drug-containing composition that is drug and entraining agent. Thus, as the weight fraction decreases from about 0.9 to about 0.8, to about 0.7, to about 0.6, the preferred PEO molecular weight increases from about 200,000 daltons to about 400,000 daltons, to about 600,000 daltons, to about 800,000 daltons, respectively, and the weight fraction of entraining agent correspondingly decreases (the weight fraction of drug being relatively constant). It should be noted that for a particular formulation, the optimum PEO molecular weight for the entraining agent may vary higher or lower than those values by 20% to 50%. Likewise, when selecting an appropriate molecular weight of other polymeric entraining agents such as HEC, HPC, HPMC, or MC, as the weight

fraction of entraining agent in the drug-containing composition is reduced, a higher molecular weight for the entraining agent is generally preferred.

In one embodiment of the invention, the drug-containing composition further comprises a swelling agent. The swelling agent is generally a water-swellable polymer that substantially expands in the presence of water. Inclusion of even a small amount of such a swellable polymer can significantly enhance the onset, rate, and completeness of drug delivery. The degree of swelling of a swelling agent can be assessed by compressing particles of the swelling agent in a press to form a compact of the material having a "strength" ranging from 3 to 16 Kp/cm^2, where strength is the hardness of the compact in Kp as measured with a Schleuniger Tablet Hardness Tester, model 6D, divided by its maximum cross-sectional area normal to the direction of force in cm^2. For example, about 500 mg of a swelling agent can be compressed in a 13/32-inch die using an "f press." The swelling of a compact is measured by placing it between two porous glass frits in a glass cylinder and contacting it with a physiologically relevant test medium, such as simulated gastric or intestinal buffer, or water. The volume of the water-swollen compact after 16 to 24 hours contact with the test medium divided by its initial volume is termed the "swelling ratio" of the swelling agent. Generally, swelling agents suitable for inclusion in the drug layer are those water-swellable polymers that have swelling ratios, when water is the test medium, of at least 3.5, preferably greater than 5.

A preferred class of swelling agents comprises ionic polymers. Ionic polymers are generally polymers that have a significant number of functional groups that are substantially ionized in an aqueous solution over at least a portion of the physiologically relevant pH range 1 to 8. Such ionizable functional groups include carboxylic acids and their salts, sulfonic acids and their salts, amines and their salts, and pyridine salts. To be considered an ionic polymer, the polymer should have at least 0.5 milli-equivalents of ionizable functional groups per gram of polymer. Such ionic polymer swelling agents include sodium starch glycolate, sold under the trade name EXPLOTAB, and croscarmellose sodium, sold under the trade name AC-DI-SOL.

In one embodiment of the invention in which the drug-containing composition comprises a drug, a drug-entraining agent, and a swelling agent, the swelling agent is present in an amount ranging from about 2 to about 20 wt% of the drug-containing composition 14. In other embodiments of the invention, the swelling agent is optionally present in an amount ranging from 0 to about 20 wt%.

In another embodiment of the present invention, the drug-containing composition further comprises a fluidizing agent. As used herein, a "fluidizing agent" is a water-soluble compound that allows the drug-containing composition to rapidly

become fluid upon imbibing water when the dosage form is introduced into a use environment. Rapid fluidization of the drug-containing composition allows the composition to be extruded from the dosage form without a build-up of excessive pressure. This results in a relatively short time lag. That is, the time between introduction of the dosage form into the environment of use and the onset of drug delivery is relatively short. In addition, the inclusion of a fluidizing agent reduces the pressure within the core and thus reduces the risk of failure of the coating that surrounds the core of the dosage form. This is particularly important when a relatively rapid rate of drug release is desired, necessitating the use of a highly water-permeable coating that conventionally is relatively thin and weak. (By a rapid rate of release is generally meant that greater than 70 wt% of the drug originally present in the dosage form is released within 12 hours of the time the dosage form is introduced into the use environment.)

The fluidizing agent can be essentially any water-soluble compound that rapidly increases the fluidity of the drug-containing composition when water is imbibed into the core. Such compounds generally have aqueous solubilities of at least 30 mg/mL and generally have a relatively low molecular weight (less than about 10,000 daltons) such that upon imbibing a given quantity of water, the drug-containing composition rapidly becomes more fluid relative to a similar drug-containing composition that does not include the fluidizing agent. By more fluid is meant that the pressure required to extrude the drug through the delivery port(s) is lower than a similar composition without the fluidizing agent. This increased fluidity can be temporary, meaning that the increased fluidity occurs for only a short time after introduction of the dosage form to a use environment (*e.g.*, 2 hours), or the increased fluidity can occur over the entire time the dosage form is in the use environment. Exemplary fluidizing agents are sugars, organic acids, amino acids, polyols, salts, and low-molecular weight oligomers of water-soluble polymers. Exemplary sugars are glucose, sucrose, xylitol, fructose, lactose, mannitol, sorbitol, maltitol, and the like. Exemplary organic acids are citric acid, lactic acid, ascorbic acid, tartaric acid, malic acid, fumaric, and succinic acid. Exemplary amino acids are alanine and glycine. Exemplary polyols are propylene glycol and sorbitol. Exemplary oligomers of low-molecular weight polymers are polyethylene glycols with molecular weights of 10,000 daltons or less. Particularly preferred fluidizing agents are sugars and organic acids. Such fluidizing agents are preferred as they often improve tableting and compression properties of the drug-containing composition relative to other fluidizing agents such as inorganic salts or low-molecular weight polymers.

In order for the fluidizing agent to rapidly increase the fluidity of the drug-containing composition at low water levels in the core 12 of the dosage form, the fluidizing agent must generally be present in an amount such that it makes up at least about 10 wt% of the drug-containing composition 14. To ensure that the drug-containing composition 14 does not become so fluid such that the drug-entraining agent cannot properly entrain or suspend the drug, particularly long after (12 hours or longer) introduction of the dosage form into the use environment, the amount of fluidizing agent generally should not exceed about 60 wt% of the drug-containing composition. In addition, as mentioned above, when a fluidizing agent is included, a drug-entraining agent with a higher molecular weight and correspondingly higher viscosity is generally included in the drug-containing composition, but at a lower level. Thus, for example, when the drug-containing composition comprises about 20 to 30 wt% of the low-solubility drug and about 30 wt% of a fluidizing agent such as a sugar, about 20 to 50 wt% of a high molecular weight polymer such as PEO with a molecular weight of about 500,000 to 800,000 daltons is preferable to a lower molecular weight PEO.

The drug-containing composition 14 may further include solubilizing agents that promote the aqueous solubility of the drug, present in an amount ranging from about 0 to about 30 wt% of the drug-containing composition 14. Examples of suitable solubilizing agents include surfactants; pH control agents such as buffers, organic acids and organic acid salts and organic and inorganic bases; glycerides; partial glycerides; glyceride derivatives; polyhydric alcohol esters; PEG and PPG esters; polyoxyethylene and polyoxypropylene ethers and their copolymers; sorbitan esters; polyoxyethylene sorbitan esters; carbonate salts; and cyclodextrins.

There are a variety of factors to consider when choosing an appropriate solubilizing agent for a drug. The solubilizing agent should not interact adversely with the drug. In addition, the solubilizing agent should be highly efficient, requiring minimal amounts to effect the improved solubility. It is also desired that the solubilizing agent have a high solubility in the use environment. For acidic, basic, and zwitterionic drugs, organic acids, organic acid salts, and organic and inorganic bases and base salts are known to be useful solubilizing agents. It is desired that these compounds have a high number of equivalents of acid or base per gram. The selection of solubilizing agent will therefore be highly dependent on the properties of the drug.

A preferred class of solubilizing agents for basic drugs is organic acids. Since basic drugs are solubilized by protonation, and since the solubility of basic drugs in an aqueous environment of pH 5 or higher is reduced and often may reach an extremely low value by pH 7.5 (as in the colon), it is believed that addition

of an organic acid to the dosage form for delivery to the use environment with such drugs assists in solubilization and hence absorption of the drug. An exemplary basic drug is sertraline, which has moderate solubility at low pH, low solubility at pH values above 5 and extremely low solubility at pH of about 7.5. Even a slight decrease in the pH of the aqueous solution at high pH may result in dramatic increases in the solubility of basic drugs. In addition to simply lowering the pH, the presence of organic acids and their conjugate bases also raises the solubility at a given pH if the conjugate base salt of the basic drug has a higher solubility than the neutral form or the chloride salt of the drug.

It has been found that a preferred subset of organic acids meeting such criteria consists of citric, succinic, fumaric, adipic, malic and tartaric acids. The table below gives properties of these organic acids. Of these, fumaric and succinic are especially preferred when a high ratio of equivalents of acid per gram is desired. In addition, citric, malic, and tartaric acid have the advantage of extremely high water solubility. Succinic acid offers a combination of both moderate solubility and a high acid equivalent per gram value. Thus, the use of a highly soluble organic acid serves multiple purposes: it improves the solubility of the basic drug, particularly when the use environment is at a pH above about 5 to 6; it makes the drug-containing composition more hydrophilic so that it readily wets; and it dissolves, lowering the viscosity of the layer rapidly, thus acting as a fluidizing agent. Thus, by accomplishing multiple functions with a single ingredient, additional space is available for the low-solubility drug within the drug-containing composition.

Properties of Organic Acid Solubilizing Agents

Organic Acid	Equivalents Value (mEq/g)	Water Solubility (mg/mL)
Fumaric	17.2	11
Succinic	16.9	110
Citric	15.6	>2000
Malic	14.9	1750
Adipic	13.7	45
Tartaric	13.3	1560

For acidic drugs, solubility is increased as pH increases. Exemplary classes of solubilizing agents for acidic drugs include alkalinizing or buffering agents and organic bases. It is believed that addition of an alkylating agent or organic base

to the dosage form assists in solubilization and hence absorption of the drug. Examples of alkylating or buffering agents include potassium citrate, sodium bicarbonate, sodium citrate, dibasic sodium phosphate, and monobasic sodium phosphate. Examples of organic bases include meglumine, eglumine, monoethanol amine, diethanol amine, and triethanol amine.

The drug-containing composition 14 may optionally include a concentration-enhancing polymer that enhances the concentration of the drug in a use environment relative to control compositions that are free from the concentration-enhancing polymer. The concentration-enhancing polymer should be inert, in the sense that it does not chemically react with the drug in an adverse manner, and should have at least some solubility in aqueous solution at physiologically relevant pHs (e.g. 1-8). Almost any neutral or ionizable polymer that has an aqueous solubility of at least 0.1 mg/mL over at least a portion of the pH range of 1-8 may be suitable. Especially useful polymers are those discussed above for forming solid-amorphous dispersions of the drug with a polymer. Preferred polymers include HPMCAS, HPMC, HPMCP, CAP, CAT, and PVP. More preferred polymers included HPMCAS, HPMCP, CAP and CAT. Without being bound by any particular theory or mechanism of action, it is believed that the concentration–enhancing polymer prevents or retards the rate at which a drug, delivered from the dosage form and present in the use environment at a concentration greater than its equilibrium value, approaches its equilibrium concentration. Thus, when the dosage form is compared to a control dosage form that is identical except for the absence of the concentration-enhancing polymer, the concentration-enhancing polymer-containing dosage form provides, at least for a short time period, a greater concentration of dissolved drug in the use environment. Appropriate drug forms and concentration-enhancing polymers are discussed in commonly assigned pending patent application "Pharmaceutical Compositions Providing Enhanced Drug Concentrations" filed December 23, 1999, U.S. provisional patent application No. 60/171,841, the relevant portions of which are herein incorporated by reference.

The drug-containing composition 14 may optionally include excipients that promote drug stability. Examples of such stability agents include pH control agents such as buffers, organic acids and organic acid salts and organic and inorganic bases and base salts. These excipients can be the same materials listed above for use as solubility-enhancing agents or fluidizing agents. Another class of stability agents is antioxidants, such as butylated hydroxy toluene (BHT), butylated hydroxyanisole (BHA), vitamin E, and ascorbyl palmitate. The amount of stability agent used in the drug-containing composition should be sufficient to stabilize the low-solubility drug. For pH control agents such as organic acids, the stability agent,

when present, may range from 0.1 to 20 wt% of the drug-containing composition. Note that in some formulations, antioxidants such as BHT can lead to discoloration of the dosage form. In these cases, the amount of antioxidant used should be minimized so as to prevent discoloration. The amount of antioxidant used in the drug-containing composition generally ranges from 0 to 1 wt% of the drug-containing composition.

Finally, the drug-containing composition 14 may also include other conventional excipients, such as those that promote performance, tableting or processing of the dosage form. Such excipients include tableting aids, surfactants, water-soluble polymers, pH modifiers, fillers, binders, pigments, osmagents, disintegrants and lubricants. Exemplary excipients include microcrystalline cellulose; metallic salts of acids such as aluminum stearate, calcium stearate, magnesium stearate, sodium stearate, and zinc stearate; fatty acids, hydrocarbons and fatty alcohols such as stearic acid, palmitic acid, liquid paraffin, stearyl alcohol, and palmitol; fatty acid esters such as glyceryl (mono- and di-) stearates, triglycerides, glyceryl (palmitic stearic) ester, sorbitan monostearate, saccharose monostearate, saccharose monopalmitate, and sodium stearyl fumarate; alkyl sulfates such as sodium lauryl sulfate and magnesium lauryl sulfate; polymers such as polyethylene glycols, polyoxyethylene glycols, and polytetrafluoroethylene; and inorganic materials such as talc and dicalcium phosphate. In a preferred embodiment, the drug-containing composition 14 contains a lubricant such as magnesium stearate.

WATER-SWELLABLE COMPOSITION

Referring again to FIGS. 1-3, the tri-layer, concentric core, and granular core dosage forms further comprise a water-swellable composition 16. The water-swellable composition greatly expands as it imbibes water through the coating 18 from the use environment. As it expands, the water-swellable composition increases the pressure within the core 12, causing extrusion of the fluidized drug-containing composition through the port(s) 20 into the environment of use. To maximize the amount of drug present in the dosage form and to ensure that the maximum amount of drug is released from the dosage form so as to minimize residual drug, the water-swellable composition should have a swelling ratio of at least about 2, preferably 3.5, and more preferably 5.

The water-swellable composition 16 comprises a swelling agent in an amount ranging from about 30 to 100 wt% of the water-swellable composition 16. The swelling agent is generally a water-swellable polymer that greatly expands in the presence of water. As discussed above in connection with the swelling agent of the

drug-containing composition, the degree of swelling of a swelling agent, or the water-swellable composition itself, can be assessed by measuring its swelling ratio.

Suitable swelling agents for the water-swellable composition are generally hydrophilic polymers that have swelling ratios of about 2.0 or greater. Exemplary hydrophilic polymers include polyoxomers such as PEO, cellulosics such as HPMC and HEC, and ionic polymers. In general, the molecular weight of water swellable polymers chosen for the swelling agent is higher than that of similar polymers used as entraining agents such that, at a given time during drug release, the water-swellable composition 16 after imbibing water tends to be more viscous, less fluid, and more elastic relative to the drug-containing composition 14. In some cases the swelling agent may be even substantially or almost entirely water insoluble such that when partially water swollen during operation, it may constitute a mass of water-swollen elastic particles. Generally, the swelling agent is chosen such that, during operation, the water-swellable composition 16 generally does not substantially intermix with the drug-containing composition 14, at least prior to extruding a majority of the drug-containing composition 14. Thus, for example, when PEO is the swelling agent used in the water-swellable composition 16, a molecular weight of about 800,000 daltons or more is preferred and more preferably a molecular weight of 3,000,000 to 8,000,000 daltons.

A preferred class of swelling agents is ionic polymers, described above for use in various embodiments of the drug-containing composition 14. Exemplary ionic polymer swelling agents include sodium starch glycolate, sold under the trade name EXPLOTAB, croscarmellose sodium, sold under the trade name AC-DI-SOL, polyacrylic acid, sold under the trade name CARBOBOL, and sodium alginate sold under the trade name KELTONE.

The water-swellable composition may optionally further comprise osmotically effective agents, often referred to as "osmogens" or "osmagents." The amount of osmagent present in the water-swellable composition may range from about 0 to about 40 wt% of the water-swellable composition. Typical classes of suitable osmagents are water-soluble salts and sugars that are capable of imbibing water to thereby effect an osmotic pressure gradient across the barrier of the surrounding coating. The osmotic pressure of a material can be calculated using the van't Hoff equation. (See, e.g., *Thermodynamics*, by Lewis and Randall). By "osmotically effective agent" is meant the inclusion of a material with low enough molecular weight, high enough solubility, and sufficient mass in the water-swellable composition that upon imbibing water from the use environment it forms an aqueous solution within the interior of the tablet such that its osmotic pressure exceeds that of the use environment, thereby providing an osmotic pressure driving force for

permeation of water from the use environment into the tablet core. Typical useful osmagents include magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, sodium sulfate, d-mannitol, urea, sorbitol, inositol, raffinose, sucrose, glucose, fructose, lactose, and mixtures thereof.

In one embodiment of the invention, the water-swellable composition 16 is substantially free from an osmotically effective agent, meaning that there is either a sufficiently small amount of osmagent or that any osmagent present has sufficiently low solubility so as not to increase the osmotic pressure of the water-swellable composition 16 substantially beyond that of the use environment. In order for the dosage form to provide satisfactory release of drug in the absence of an osmagent in the water-swellable composition 16, and when the water-swellable polymer is not an ionic polymer, the dosage form should have a coating that is highly permeable to water. Such high-permeability coatings are described below. When the water-swellable composition 16 is substantially free of an osmotically effective agent, the water swellable composition preferably contains a substantial quantity, typically at least 10 wt% and preferably at least 50 wt%, of a highly swelling polymer such as sodium starch glycolate or sodium croscarmellose. As described earlier, highly swelling materials can be identified by measuring the "swelling ratio" of the material formed into a compact using the method described previously. When the water-soluble composition is substantially free of an osmotically effective solute, it is preferred that the swelling polymer have a swelling ratio of at least 3.5, preferably at least 5. The dosage form should also have a high strength coating to prevent rupture when highly swelling materials are used. Such coatings are described below.

The release of a drug relatively quickly without the inclusion of an osmagent in the water-swellable composition is a surprising result, since conventional wisdom in the art has held that osmagents should be included in the water-swellable composition to achieve good performance. Circumventing the need for inclusion of an osmagent provides several advantages. One advantage is that the space and weight which would otherwise be occupied by osmagent may be devoted to drug, thus permitting an increase in the amount of drug within the dosage form. Alternatively, the overall size of the dosage form may be decreased. In addition, eliminating the osmagent simplifies the process for manufacture of the dosage form, since the water-swellable composition 16 may omit the step of including an osmagent.

In one embodiment of the invention, the water swellable composition 16 comprises a swelling agent and a tableting aid. The preferred swelling agents

(e.g., those that are highly swelling) are difficult to compress to a hardness suitable for use in the dosage form. However, it has been found that adding a tableting aid to the water-swellable composition in the amount of 5 to 50 wt% of the water-swellable composition 16 results in a material that compresses to a hardness suitable for use in the dosage form. At the same time inclusion of a tableting aid can adversely affect the swelling ratio of the water-swellable composition 16. Thus, the quantity and type of tableting aid used must be carefully selected. In general, hydrophilic materials with good compression properties should be used. Exemplary tableting aids include sugars such as lactose, in particular spray-dried versions sold under the trade name FASTFLOW LACTOSE, or xylitol, polymers such as microcrystalline cellulose, HPC, MC or HPMC. Preferred tableting aids are microcrystalline cellulose, both standard grades sold under the trade name AVICEL and silicified versions sold under the trade name PROSOLV and HPC. The amount of tableting aid is chosen to be sufficiently high so that the core 12 compresses well yet sufficiently low so that the water-swellable composition 16 still has a swelling ratio of at least 2, preferably 3.5, more preferably greater than 5. Typically, the amount is at least 20 but less than 60 wt%.

It is further desired that the mixture of swelling agent and tableting aid result in a material that has a "strength" of at least 3 Kiloponds (Kp)/cm^2, and preferably at least 5 Kp/cm^2. Here, "strength" is the fracture force, also known as the core "hardness," required to fracture a core 12 formed from the material, divided by the maximum cross-sectional area of the core 12 normal to that force. In this test, the fracture force is measured using a Schleuniger Tablet Hardness Tester, model 6D. Both the compressed water-swellable composition 16 and resulting core 12 should have a strength of at least 3 Kp/cm^2, and preferably at least 5 Kp/cm^2.

In a preferred embodiment, the water-swellable composition 16 comprises a mixture of swelling agents in addition to a tableting aid. For example, the swelling agent croscarmellose sodium can be compressed into a compact with higher strength than the swelling agent sodium starch glycolate. However, the swelling ratio of croscarmellose sodium is lower than that of sodium starch glycolate.

The water-swellable composition 16 may also include solubility-enhancing agents or excipients that promote stability, tableting or processing of the dosage form of the same types mentioned above in connection with the drug-containing composition. However, it is generally preferred that such excipients comprise a minor portion of the water-swellable composition 16. In one preferred embodiment, the water-swellable composition 16 contains a lubricant such as magnesium stearate.

THE HOMOGENEOUS CORE

The preceding discussion of drug-containing composition 14 and water-swellable composition 16 applies to the tri-layer, concentric core, and granular core embodiments. However, for the homogeneous core, the drug-containing composition 15 contains both the drug and swelling materials. In general, the drug-containing composition will simply be a mixture of materials suitable for use in the drug-containing composition 14 and the water-swellable composition 16 of the other embodiment described above. Thus, at a minimum, the drug-containing composition 15 comprises at least a drug, an entraining agent, and a swelling agent. The drug-containing composition 15 may optionally include a fluidizing agent, a solubility-enhancing agent, a concentration-enhancing polymer, a stability promoting agent, and/or conventional excipients discussed above in connection with the drug-containing composition. Likewise, the drug-containing composition may optionally also include osmogens, and/or tableting aids as discussed above in connection with the water-swellable composition.

The amounts of the respective materials will in general fall within the ranges described above in the discussion of the drug-containing composition and the water-swellable composition. In particular, preferred compositions for the homogeneous core embodiment are those that contain from 2 to about 30% of a swelling agent that has a swelling ratio of at least about 2 and preferably at least about 3.5, and more preferably at least about 5. Preferred swelling agents are ionic polymers such as carboxymethyl cellulose, sodium starch glycolate, crosscarmelose sodium, polyacrylic acid and sodium alginate. In addition, preferred homogeneous core compositions will also contain an entraining agent such as HEC, HPC, HPMC, or PEO in an amount from about 5 to about 80% of the core contents. Preferably, in addition to the drug, swelling agent, and entraining agent, the core also contains a fluidizing agent.

The various novel combinations of these agents in the core of the homogeneous core embodiment yield numerous advantages, including more rapid onset and more complete release of drug, relative to homogeneous core dosage forms previously known.

THE CORE

The core 12 may be any known tablet that can be formed by an extrusion or compression process and be subsequently coated and utilized for delivery of drug to a mammal. The tablet can generally range in size from about 1 mm to about 10 cm for its longest dimension. The maximum size of the tablet will be different for different mammalian species. It can have essentially any shape such that its aspect ratio, defined as the tablet's longest dimension divided by the tablet's shortest dimension, ranges from about 1 to about 5. In addition, the dosage form may comprise two or more relatively small tablets contained in a relatively large container such as a capsule.

Exemplary core 12 shapes are spheres, ellipsoids, cylinders, capsule or caplet shapes and any other known shape. The core 12, following coating, can comprise the entire or a portion of the dosage form. The final dosage form can be for oral, rectal, vaginal, subcutaneous, or other known method of delivery into the environment of use. When the dosage form 10 is intended for oral administration to a human, the core 12 generally has an aspect ratio of about 3 or less, a longest dimension of about 2 cm or less and a total weight of about 1.5 g or less and preferably a total weight of about 1.0 g or less.

To form the dosage form, the ingredients comprising the drug-containing composition 14 and the water-swellable composition 16 are first mixed or blended using processes known in the art. See for example, Lachman, et al., "The Theory and Practice of Industrial Pharmacy" (Lea & Febiger, 1986). For example, a portion of the ingredients of the drug-containing composition 14 can first be blended, then wet granulated, dried, milled, and then blended with additional excipients prior to tableting. Similar processes can be used to form the water-swellable composition.

Once the materials are properly mixed, the core 12 is formed using procedures known in the art, such as compression or extrusion.

For tri-layer dosage forms, the method used to make the core depends on whether the two drug-containing compositions 14a and 14b are the same. Where they are the same, a single drug-containing composition is prepared. A portion of the drug-containing composition mixture is placed in a tablet press and leveled by lightly tamping with the press. The desired amount of water-swellable composition 16 is then added. A second portion of the drug-containing composition is then added on top of the water-swellable composition. The tablet is then compressed.

Where the two drug-containing compositions 14a and 14b differ, then each drug-containing composition 14a and 14b are separately prepared. The tablet is prepared by placing first the drug-containing composition 14a in a tablet press and

leveling by lightly tamping with the press. The desired amount of water-swellable composition 16 is then added. The desired amount of the drug-containing composition 14b is then added on top of the water-swellable composition 16. The tablet is then compressed.

For the concentric core dosage form, the core 12 is first prepared by placing the desired amount of the water-swellable composition 16 in a press and compressing to form a small initial core. A first portion of the drug-containing composition is placed in a larger press, gently leveled and lightly compressed. The small initial core of water-swellable composition 16 is then placed on top of the first portion of the drug-containing composition and centered. The remaining amount of the drug-containing composition 14 is then added to the press. The tablet is compressed to the desired hardness.

For the granular dosage form, the water-swellable composition 16 is prepared and formed into granules using any conventional method, such as wet or dry granulation. The granules may vary in size from very small particulates less than 0.1 mm in diameter to large particles (up to 2 mm) that are each a significant fraction of the total volume of the dosage form. A preferred size range is an average diameter of between 0.1 mm and 2 mm, and more preferred is an average diameter of between 0.5 and 1.5 mm. In use, the size of the granules should be chosen so that upon swelling the granules are larger than the delivery ports in the coating. The granules will therefore be retained within the coating and displace the drug-containing composition, which is extruded through the delivery ports. The tablet core is prepared by adding the prepared granules of water-swellable composition 16 to the drug-containing composition 14, so that the granules are distributed throughout the drug-containing composition. The resulting composition is then placed into a tablet press, and then compressed.

Finally, for the homogeneous core dosage form, the drug-containing composition 15 is formed by mixing all of the ingredients using any conventional method to form a relatively homogeneous mixture. The mixture is then added to a tablet press, and then compressed. In contrast to the granular core embodiment, the swelling agent is present in particles having a small enough size (*e.g.*, less than 0.1 mm) so that even when swollen the swelling agent particles are extruded through the delivery port along with the other ingredients in the core.

The amount of force used to compress the tablet core will depend on the size of the dosage form, as well as the compressibility and flow characteristics of the compositions. Typically, a pressure is used that results in a tablet with a strength of 3 to 20 Kp/cm^2.

THE COATING:

Following formation of the core 12, coating 18 is applied. Coating 18 should have both a sufficiently high water permeability that the drug can be delivered within the desired time frame, and high strength, while at the same time be easily manufactured. A water permeability is chosen to control the rate at which water enters the core, thus controlling the rate at which drug is delivered to the use environment. Where a high dose of a low-solubility drug is required, the low solubility and high dose combine to make it necessary to use a high permeability coating to achieve the desired drug release profile while keeping the tablet acceptably small. High strength is required to ensure the coating does not burst when the core swells as it imbibes water, leading to an uncontrolled delivery of the core contents to the use environment. The coating must be easily applied to the dosage form with high reproducibility and yield. Furthermore, the coating must be non-dissolving and non-eroding during release of the drug-containing composition, generally meaning that it be sufficiently water-insoluble that drug is substantially entirely delivered through the delivery port(s) 20, in contrast to delivery via permeation through coating 18.

As described above, the coating 18 is highly water-permeable to allow rapid imbibition of water into core 12 and as a result a rapid release of the drug-containing composition 14. A relative measure of the water permeability of the coating can be made by conducting the following experiment. Finished dosage forms are placed in an open container which is in turn placed in an environmental chamber held at a constant temperature of 40□C and a constant relative humidity of 75%. The initial rate of weight gain of the dry dosage forms, determined by plotting the weight of the dosage form versus time, divided by the surface area of the dosage form yields a value termed "water flux (40/75)." The water flux (40/75) for a dosage form has been found to be a useful relative measure of the water permeabilities of coatings. When a rapid release of the drug is desired, the coating should have a water flux (40/75) value of at least 1.0×10^{-3} gm/hr·cm², and preferably at least 1.3×10^{-3} gm/hr·cm².

As mentioned, the coating should also have a high strength to ensure the coating 18 does not burst when the core swells due to imbibition of water from the use environment. A relative measure of coating strength can be made by conducting the following experiment that measures the "durability" of the coating. Finished tablets are placed into an aqueous medium for 10 to 24 hours, allowing the core to imbibe water, swell, and release drug to the media. The swollen dosage form can then be tested in a hardness tester, such as a Model 6D Tablet Tester manufactured by Schleuniger Pharmatron, Inc. When the delivery port(s) located on

the face(s) of the dosage form, the dosage form is placed into the tester so that its delivery port(s) (20) faces one side of the compression plates such that the delivery port(s) is blocked by the compression plate. The force, in Kp, required to rupture the coating is then measured. The durability of the coating is then calculated by dividing the measured rupture force by the maximum cross-sectional area of the dosage form normal to the applied force. Preferably, the coating has a durability of at least 1 Kp/cm^2, more preferably at least 2 Kp/cm^2, and even more preferably at least 3 Kp/cm^2. Coatings with this or greater durability ensure virtually no burst tablets when the dosage forms are tested *in vivo*.

Coatings with these characteristics can be obtained using hydrophilic polymers such as plasticized and unplasticized cellulose esters, ethers, and ester-ethers. Particularly suitable polymers include cellulose acetate ("CA"), cellulose acetate butyrate, and ethyl cellulose. A particularly preferred set of polymers are cellulose acetates having acetyl contents of 25 to 42%. A preferred polymer is CA having an acetyl content of 39.8%, and specifically, CA 398-10 manufactured by Eastman of Kingsport, Tennessee, having an average molecular weight of about 40,000 daltons. Another preferred CA having an acetyl content of 39.8% is high molecular weight CA having an average molecular weight greater than about 45,000, and specifically, CA 398-30 (Eastman) reported to have an average molecular weight of 50,000 daltons. The high molecular weight CA provides superior coating strength, which allows thinner coatings and thus higher permeability.

Coating is conducted in conventional fashion by first forming a coating solution and then coating by dipping, fluidized bed coating, or preferably by pan coating. To accomplish this, a coating solution is formed comprising the coating polymer and a solvent. Typical solvents useful with the cellulosic polymers noted above include acetone, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, nitroethane, nitropropane, tetrachloroethane, 1,4-dioxane, tetrahydrofuran, diglyme, and mixtures thereof. A particularly preferred solvent is acetone. The coating solution typically will contain 3 to 15 wt% of the polymer, preferably 5 to 10 wt%, most preferably 7 to 10 wt%.

The coating solution may also comprise pore-formers, non-solvents, or plasticizers in any amount so long as the polymer remains substantially soluble at the conditions used to form the coating and so long as the coating remains water-permeable and has sufficient strength. Pore-formers and their use in fabricating coatings are described in U.S. Patent Nos. 5,612,059 and 5,698,220, the pertinent disclosures of which are incorporated herein. The term "pore former," as used

herein, refers to a material added to the coating solution that has low or no volatility relative to the solvent such that it remains as part of the coating following the coating process but that is sufficiently water swellable or water soluble such that, in the aqueous use environment it provides a water-filled or water-swollen channel or "pore" to allow the passage of water thereby enhancing the water permeability of the coating. Suitable pore-formers include polyethylene glycol (PEG), PVP, PEO, HEC, HPMC and other aqueous-soluble cellulosics, water-soluble acrylate or methacrylate esters, polyacrylic acid and various copolymers and mixtures of these water soluble or water swellable polymers. Enteric polymers such as cellulose acetate phthalate (CAP) and HPMCAS are included in this class of polymers. The pore former can also be a water soluble, pharmaceutically acceptable material, such as a sugar, organic acid, or salt. Examples of suitable sugars include sucrose and lactose; examples of organic acids include citric acid and succinic acid; examples of salts include sodium chloride and sodium acetate. Mixtures of such compounds may also be used. The pore former may be soluble in the solvent used in the coating solution, or it may be insoluble, such that the coating solution is a slurry or suspension. A particularly preferred pore former is PEG having an average molecular weight from 1000 to 8000 daltons. A particularly preferred PEG is one having a molecular weight of 3350 daltons. The inventors have found that to obtain a combination of high water permeability and high strength when PEG is used as a pore former, the weight ratio of CA:PEG should range from about 6.5:3.5 to about 9:1.

The addition of a non-solvent to the coating solution results in exceptional performance. By "non-solvent" is meant any material added to the coating solution that substantially dissolves in the coating solution and reduces the solubility of the coating polymer or polymers in the solvent. In general, the function of the non-solvent is to impart porosity to the resulting coating. As described below, porous coatings have higher water permeability than an equivalent weight of a coating of the same composition that is not porous and this porosity, when the pores are gas filled, as is typical when the non-solvent is volatile, is indicated by a reduction in the density of the coating (mass/volume). Although not wishing to be bound by any particular mechanism of pore formation, it is generally believed that addition of a non-solvent imparts porosity to the coating during evaporation of solvent by causing the coating solution to undergo liquid-liquid phase separation prior to solidification. As described below for the case of using water as the non-solvent in an acetone solution of cellulose acetate, the suitability and amount of a particular candidate material can be evaluated for use as a non-solvent by progressively adding the candidate non-solvent to the coating solution until it becomes cloudy. If this does not occur at any addition level up to about 50 wt% of

the coating solution, it generally is not appropriate for use as a non-solvent. When clouding is observed, termed the "cloud point," an appropriate level of non-solvent for maximum porosity is the amount just below the cloud point. When lower porosities are desired, the amount of non-solvent can be reduced as low as desired. It has been found that suitable coatings can be obtained when the concentration of non-solvent in the coating solution is greater than about 20% of the non-solvent concentration that results in the cloud point.

Suitable non-solvents are any materials that have appreciable solubility in the solvent and that lower the coating polymer solubility in the solvent. The preferred non-solvent depends on the solvent and the coating polymer chosen. In the case of using a volatile polar coating solvent such as acetone or methyl ethyl ketone, suitable non-solvents include water, glycerol, ethylene glycol and its low molecular-weight oligomers (e.g., less than about 1,000 daltons), propylene glycol and its low molecular weight oligomers (e.g., less than about 1,000 daltons), C_1 to C_4 alcohols such as methanol or ethanol, ethylacetate, acetonitrile and the like.

In general, to maximize its effect, (*e.g.*, formation of pores), the non-solvent should have similar or less volatility than the coating solution solvent such that, during initial evaporation of the solvent during the coating process, sufficient non-solvent remains to cause phase separation to occur. In many cases, where a coating solution solvent such as acetone is used, water is a suitable non-solvent. For acetone solutions comprising 7 wt% CA and 3 wt% PEG, the cloud point at room temperature is at about 23 wt% water. Thus the porosity and in turn the water permeability (which increases with increasing porosity) can be controlled by varying the water concentration up to near the cloud point. For acetone solutions comprising CA and PEG with a total concentration of about 10 wt%, it is desired that the coating solution contain at least 4 wt% water to obtain a suitable coating. When a higher porosity, and thus a higher water permeability is desired (to obtain a faster release rate), the coating solution should contain at least about 15 wt% water.

In one embodiment of the invention, the coating solution is homogeneous, in that when the polymer, solvent, and any pore formers or non-solvents are mixed, the solution comprises a single phase. Typically, a homogenous solution will be clear, and not be cloudy as discussed above.

When using CA 398-10, exemplary coating solution weight ratios of CA:PEG 3350:water are 7:3:5, 8:2:5, and 9:1:5, with the remainder of the solution comprising a solvent such as acetone. Thus, for example, in a solution having a weight ratio of CA:PEG 3350:water of 7:3:5, CA comprises 7 wt% of the solution, PEG 3350 comprises 3 wt% of the solution, water comprises 5 wt% of the solution, and acetone comprises the remaining 85 wt%. Preferred coatings are

generally porous even in the dry state (prior to delivery to the aqueous use environment). By "porous" is meant that the coating has a dry-state density less than the density of the nonporous coating material. By "nonporous coating material" is meant a coating material formed by using a coating solution containing no non-solvent, or the minimum amount of non-solvent required to produce a homogeneous coating solution. The coating in the dry state has a density that is less than 0.9 times, and more preferably less than 0.75 times that of the nonporous coating material. The dry-state density of the coating can be calculated by dividing the coating weight (determined from the weight gain of the tablets before and after coating) by the coating volume (calculated by multiplying the coating thickness, as determined by optical or scanning electron microscopy, by the tablet surface area). The porous nature of the coating is one of the factors that leads to the combination of high water permeability and high strength of the coating.

The coatings may also be asymmetric, meaning that there is a gradient of density throughout the coating thickness. Generally, the outside surface of the coating will have a higher density than the coating nearest the core.

The coating can optionally include a plasticizer. A plasticizer generally swells the coating polymer such that the polymer's glass transition temperature is lowered, its flexibility and toughness increased and its permeability altered. When the plasticizer is hydrophilic, such as polyethylene glycol, the water permeability of the coating is generally increased. When the plasticizer is hydrophobic, such as diethyl phthalate or dibutyl sebacate, the water permeability of the coating is generally decreased.

It should be noted that additives can function in more than one way when added to the coating solution. For example, PEG can function as a plasticizer at low levels while at higher levels it can form a separate phase and act as a pore former. In addition, when a non-solvent is added, PEG can also facilitate pore formation by partitioning into the non-solvent-rich phase once liquid-liquid phase separation occurs.

The weight of the coating around the core depends on the composition and porosity of the coating, the surface to volume ratio of the dosage form, and the desired drug release rate, but generally should be present in an amount ranging from about 3 to 30 wt%, preferably from 8 to 25 wt%, based on the weight of the uncoated core. However, a coating weight of at least about 8 wt% is generally preferred so as to assure sufficient strength for reliable performance, and more preferably a coating greater than about 13 wt%.

While porous coatings based on CA, PEG, and water yield excellent results, other pharmaceutically acceptable materials may be used so long as the

coating has the requisite combination of high water permeability, high strength, and ease of manufacture. Further, such coatings may be dense, or asymmetric, having one or more dense layers and one or more porous layers, as described in U.S. Patent Nos. 5,612,059 and 5,698,220.

The coating 18 must also contain at least one delivery port 20 in communication with the interior and exterior of the coating to allow for release of the drug-containing composition to the exterior of the dosage form. The delivery port can range in size from about the size of the drug particles, and thus could be as small as 1 to 100 microns in diameter and may be termed pores, up to about 5000 microns in diameter. The shape of the port may be substantially circular, in the form of a slit, or other convenient shape to ease manufacturing and processing. The port(s) may be formed by post-coating mechanical or thermal means or with a beam of light (*e.g.*, a laser), a beam of particles, or other high-energy source, may be formed by drilling completely through the dosage form, or may be formed *in situ* by rupture of a small portion of the coating. Such rupture may be controlled by intentionally incorporating a relatively small weak portion into the coating. Delivery ports may also be formed *in situ* by erosion of a plug of water-soluble material or by rupture of a thinner portion of the coating over an indentation in the core. Delivery ports may be formed by coating the core such that one or more small regions remains uncoated. In addition, the delivery port can be a large number of holes or pores that may be formed during coating, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Patent Nos. 5,612,059 and 5,698,220, the disclosures of which are incorporated by reference. When the delivery pathways are pores there can be a multitude of such pores that range in size from about 1 □m to greater than about 100 □m. During operation, one or more of such pores may enlarge under the influence of the hydrostatic pressure generated during operation. The number of delivery ports 20 may vary from 1 to 10 or more. In aggregate, the total surface area of core exposed by delivery ports is less than about 5%, and more typically less than about 1%.

At least one delivery port is formed through the coating so that the drug-containing composition will be extruded out of the delivery port by the swelling action of the water-swellable composition. For the tri-layer embodiment, it is desired to have at least one delivery port located on each of the respective faces of the tablet opposite each of the drug-containing compositions 14a and 14b. For the remaining embodiments, the location of the delivery ports is not critical, since any location will provide a delivery port in communication with either the drug-containing composition 14, in the case of the concentric core and granular core embodiments, or the drug-containing composition 15 in the case of the homogeneous core embodiment. Thus,

for these embodiments the delivery port may be located at any location on the coating.

Other features and embodiments of the invention will become apparent from the following examples which are given for illustration of the invention rather than for limiting its intended scope.

Example 1

Exemplary dosage forms of the present invention were made with a tri-layer geometry of the type depicted in Fig. 1. The tri-layer core consisted of a drug containing composition distributed evenly between the top and bottom tablet layers and a water-swellable composition comprising the middle layer.

To form the drug-containing composition the following materials were wet granulated (see Table A): 35 wt% of the citrate salt of 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenylsulphony]-4-methylpiperazine, also known as sildenafil citrate (hereinafter referred to as Drug 1) having a solubility of about 20 □g/mL at pH 6, 30 wt% xylitol (trade name XYLITAB 200), 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% sodium starch glycolate (trade name EXPLOTAB), and 1 wt% magnesium stearate. The drug-containing composition ingredients were first combined with 26% of the total PEO, and without the magnesium stearate, in a twinshell mixer and blended for 10 minutes. Next, the ingredients were milled using a hammer mill and passed through a 0.065-inch screen. This material was blended again for 10 minutes in a twinshell mixer. An intensifier bar was inserted into the twinshell mixer and the material was granulated using deionized water. The granules were tray-dried in a 40□C oven overnight, then milled the following morning using a hammer mill and passed through a 0.065-inch screen. The drug-containing composition ingredients were again placed in a twinshell mixer and the remaining 74% of the total PEO was added to the mixer. The drug-containing composition ingredients were blended for 10 minutes, the magnesium stearate was added, and the mixture was blended again for 4 minutes.

To form the water-swellable composition (see Table B), the following materials were blended: 74.5 wt% EXPLOTAB, 24.5 wt% of the tableting aid silicified microcrystalline cellulose (trade name PROSOLV 90), and 1.0 wt% magnesium stearate. The water-swellable composition ingredients were first combined without the magnesium stearate in a twinshell mixer and blended for 20 minutes. An intensifier bar was inserted into the twinshell mixer and the material was granulated using deionized water. The granules were tray-dried in a 40□C oven overnight, then milled the following morning using a hammer mill and passed through a 0.065-inch

screen. The water-swellable composition ingredients were again placed in a twinshell mixer, the magnesium stearate was added, and the mixture was blended for 4 minutes.

Tablet cores were formed by placing 200 mg of drug-containing composition in a standard 13/32 inch die and gently leveling with the press. Then, 100 mg water-swellable composition was placed in the die on top of the drug-containing composition and leveled. The second half of the drug-containing composition (200 mg) was added and the tablet core compressed to a hardness of about 11 Kp. The resulting tri-layer tablet core had a total weight of 500 mg and contained a total of 28.3 wt% Drug 1 (141.5 mg), 24.3 wt% XYLITAB 200, 22.3 wt% PEO 600,000 daltons, 19.0 wt% EXPLOTAB, 4.9 wt% PROSOLV 90, and 1.2 wt% magnesium stearate.

Coatings were applied by a Vector LDCS-20 pan coater. The coating solution contained cellulose acetate (CA 398-10 from Eastman Fine Chemical, Kingsport, Tennessee), polyethylene glycol having a molecular weight of 3350 daltons (PEG 3350, Union Carbide), water, and acetone in a weight ratio of 7/3/5/85 (wt%). The flow rate of the inlet heated drying air of the pan coater was set at 40 ft^3/min with the outlet temperature set at 25□C. Nitrogen at 20 psi was used to atomize the coating solution from the spray nozzle, with a nozzle-to-bed distance of 2 inches. The pan rotation was set to 20 rpm. The so-coated tablets were dried at 50□C in a convection oven. The final dry coating weight amounted to 47.5 mg or 9.5 wt% of the tablet core. Five 900 μm diameter holes were then laser-drilled in the coating on each drug-containing composition side of the tablet to provide 10 delivery ports per tablet. Table C summarizes the characteristics of the dosage form.

To simulate *in vivo* drug dissolution, tablets were placed in 900 mL of a simulated gastric solution (10 mM HCl, 100 mM NaCl, pH 2.0, 261 mOsm/kg) in a USP type 2 dissoette flask. Samples were taken at periodic intervals using a VanKel VK8000 autosampling dissoette with automatic receptor solution replacement. Tablets were placed in a wire support, the paddle height was adjusted, and the dissoette flasks were stirred at 100 rpm at 37□C. The autosampler dissoette device was programmed to periodically remove a sample of the receptor solution, and the drug concentration was analyzed by HPLC using a Waters Symmetry C_{18} column. The mobile phase consisted of 0.05 M triethanolamine (pH 3)/ methanol/ acetonitrile in a volume ratio of 58/25/17. Drug concentration was calculated by comparing UV absorbance at 290 nm to the absorbance of Drug 1 standards. Results are shown in Table 1 and summarized in Table F.

Table 1

Time (hours)	Drug (wt% released)
0	0
1	5
2	19
3	32
6	63
9	83
12	94
15	95
18	96
21	99
24	100

The data show that 19 wt% of the drug was released within 2 hours, 83 wt% within 9 hours, and 100 wt% of the drug was released within 24 hours. Thus, the present invention provided a rapid release of over 80 wt% within 9 hours and no residual value at 24 hours, of a relatively high dose (97 mgA) of a low-solubility drug in a relatively low mass (547.5 mg) dosage form.

Examples 2A–2D

These examples demonstrate the inventive delivery of various drugs from tri-layer tablets. For the tablets of Example 2A, the drug-containing composition consisted of 28 wt% sertraline HCl (Drug 2) having a solubility of 0.2 mg/mL at pH 7, 37 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. The ingredients were milled using a hammer mill and passed through a 0.065-inch screen, then blended again for 20 minutes in the TURBULA mixer. Next, magnesium stearate was added and the drug-containing composition was blended again for 4 minutes in the same mixer.

To form the water-swellable composition, the following materials were blended: 72.5 wt% EXPLOTAB, 25 wt% microcrystalline cellulose (AVICEL PH 102), and 2.5 wt% magnesium stearate. The water-swellable composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. Next, magnesium stearate was added and the water-swellable composition was blended again for 4 minutes in the same mixer.

Tablet cores were formed by placing 200 mg of drug-containing composition in a standard 13/32 inch die and gently leveling with the press. Then, 100 mg water-swellable composition was placed in the die on top of the drug-containing composition and leveled. The second half of the drug-containing composition (200 mg) was added and the tablet core compressed to a hardness of about 11 Kp. The resulting tri-layer tablet core had a total weight of 500 mg and contained a total of 22.5 wt% Drug 2 (112.5 mg), 29.5 wt% XYLITAB 200, 23 wt% PEO 600,000 daltons, 18.5 wt% EXPLOTAB, 5 wt% AVICEL, and 1.5 wt% magnesium stearate.

Coatings were applied as described in Example 1. The final dry coating weight amounted to 50.5 mg or 10.1 wt% of the tablet core. Five 900 µm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet. Table C summarizes the characteristics of the dosage form.

Dissolution tests were performed by placing the tablets in 900 mL of a simulated gastric solution (10 mM HCl, 100 mM NaCl, pH 2.0, 261 mOsm/kg) for 2 hours, then transferring the tablets to 900 mL of a simulated intestinal environment solution (6 mM KH_2PO_4, 64 mM KCl, 35 mM NaCl, pH 7.2, 210 mOsm/kg), both solutions being stirred at 100 rpm. A residual dissolution test was performed as described in the Detailed Description section. Residual drug was analyzed by HPLC using a Phenomenex Ultracarb 5 ODS 20 column. The mobile phase consisted of 35 vol% TEA-acetate buffer (3.48 mL triethanolamine and 2.86 mL glacial acetic acid in 1L HPLC H_2O) in acetonitrile. Drug concentration was calculated by comparing UV absorbance at 230 nm to the absorbance of sertraline standards. The amount of drug remaining in the tablets was subtracted from the total initial amount of drug in the tablet to obtain the amount released at each time interval. The results are presented in Table 2 and summarized in Table F.

For the tablets of Example 2B, the drug-containing composition consisted of 33 wt% of the mesylate salt of the drug 4-[3-[4-(2-methylimidazol-1-yl) phenylthio] phenyl]-3,4,5,6-tetrahydro-2H-pyran-4-carboxamide hemifumarate (Drug 3) having a solubility of 3.7 mgA/mL at pH 4, 31 wt% XYLITAB 200, 30 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate (see Table A). The drug-containing composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. The ingredients were milled using a hammer mill and passed through a 0.065-inch screen, then blended again for 20 minutes in the TURBULA mixer. Next, magnesium stearate was added and the drug-containing composition was blended again for 4 minutes in the same mixer.

The water-swellable composition consisted of 74.5 wt% EXPLOTAB, 24.5 wt% PROSOLV 90, and 1 wt% magnesium stearate. The water-swellable composition ingredients were first combined without the magnesium stearate in a twinshell mixer and blended for 20 minutes. An intensifier bar was inserted into the twinshell mixer and the material was granulated using deionized water. The granules were tray-dried in a 40□C oven overnight, then milled the following morning using a hammer mill and passed through a 0.065-inch screen. The water-swellable composition ingredients were again placed in a twinshell mixer, the magnesium stearate was added, and the mixture was blended for 4 minutes.

Tablets for Example 2B were compressed and coated as described in Example 1. The resulting tri-layer tablet cores had a total weight of 500 mg and contained a total of 25.9 wt% Drug 3 (129.5 mg), 25.0 wt% XYLITAB 200, 23.9 wt% PEO 600,000 daltons, 19.1 wt% EXPLOTAB, 4.9 wt% PROSOLV 90, and 1.2 wt% magnesium stearate. The final dry coating weight amounted to 46.5 mg or 9.3 wt% of the tablet core. Five 900 µm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed on these tablets in accordance with the procedure described for Example 2A above, with the following exceptions: dissoette stir speed was 50 rpm, and residual drug was analyzed by dissolving tablets in 0.1 N HCl and measuring UV absorbance at 258 nm. Results are shown in Table 2 and summarized in Table F.

For the tablets of Example 2C, the drug-containing composition consisted of 35 wt% of nifedipine (Drug 4) having a solubility of 26 µg/mL in phosphate-buffered saline at pH 6.5, 30 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate (see Table A). The drug-containing composition was processed as described in Examples 2A and 2B above.

The water-swellable composition consisted of 74.5 wt% EXPLOTAB, 25 wt% AVICEL PH200, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. Next, magnesium stearate was added and the water-swellable composition was blended again for 4 minutes in the same mixer.

Tablets for Example 2C were compressed and coated as described in Example 1, with all weighing and tabletting procedures performed under low-light conditions (nifedipine is light-sensitive). The resulting tri-layer tablet cores had a total weight of 500 mg and contained a total of 28 wt% Drug 4 (140 mg), 24 wt% XYLITAB 200, 23 wt% PEO 600,000, 18.9 wt% EXPLOTAB, 5 wt% AVICEL, and 1.1

wt% magnesium stearate. The final dry coating weight amounted to 45.5 mg or 9.1 wt% of the tablet core. Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed on these tablets in accordance with the procedure described for Example 2A above, with the following exceptions: residual drug was analyzed by HPLC using a C_{18} column with a mobile phase of 50% water/ 25% methanol/ 25% acetonitrile (vol. %) and UV detection at 235 nm. Results are shown in Table 2 and summarized in Table F.

For the tablets of Example 2D, the drug-containing composition consisted of 40 wt% of the drug 4-amino-5-(4-fluorophenyl)-6,7-dimethoxy-2-[4-(morpholinocarbonyl) perhydro-1,4-diazepin-1-yl]quinoline, (Drug 5) having a solubility of 0.4 mg/mL at pH 7.6, 28 wt% XYLITAB 200, 26 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate (see Table A). The drug-containing composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. The ingredients were milled using a hammer mill and passed through a 0.065-inch screen, then blended again for 20 minutes in the TURBULA mixer. Next, magnesium stearate was added and the drug-containing composition was blended again for 4 minutes in the same mixer.

The water-swellable composition consisted of 74.2 wt% EXPLOTAB, 25.0 wt% PROSOLV 90, 0.3 wt% Red Lake #40, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were first combined without the magnesium stearate in a twinshell mixer and blended for 20 minutes. An intensifier bar was inserted into the twinshell mixer and the material was granulated using deionized water. The granules were tray-dried in a 40□C oven overnight, then milled the following morning using a hammer mill and passed through a 0.065-inch screen. The water-swellable composition ingredients were again placed in a twinshell mixer, the magnesium stearate was added, and the mixture was blended for 4 minutes.

Tablets for Example 2D were compressed and coated as described in Example 1. The resulting tri-layer tablet cores had a total weight of 534 mg and contained a total of 32.58 wt% Drug 6 (174 mg), 22.49 wt% XYLITAB 200, 21.49 wt% PEO 600,000, 17.69 wt% EXPLOTAB, 4.70 wt% PROSOLV 90, 0.06 wt% Red Lake #40, and 0.99 wt% magnesium stearate. The final dry coating weight amounted to 61 mg or 11.4 wt% of the tablet core. Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed on these tablets in accordance with the procedure described for Example 2A above, with the following exceptions:

dissoette stir speed was 50 rpm, and residual drug was analyzed by HPLC using a Phenomenex Luna C_{18} column with a mobile phase of 60% water/ 40% acetonitrile/ 0.1% diethylamine (vol. %) and UV detection at 255 nm. Results are shown in Table 2 and summarized in Table F.

Table 2

Example	Time (hours)	Drug (% released)
2A	0	0
	2	23
	4	46
	8	85
	14	92
	20	90
2B	0	0
	2	27
	4	48
	8	72
	12	81
	18	86
	24	83
2C	0	0
	2	33
	4	50
	8	69
	14	83
	20	85
2D	0	0
	2	17
	4	41
	8	67
	14	86
	20	90

Examples 2A through 2D show greater than 80% drug delivered after 20 hours with virtually no lag time. Along with Example 1, these examples show that different low-solubility drugs can be successfully delivered from dosage forms of this invention.

Example 3

This example demonstrates that the ionic swelling agent can be blended with a high percentage of tableting aid to form a tri-layer dosage form with the desired release profile.

For the tablets of Example 3, the drug-containing composition consisted of 35 wt% Drug 1, 30 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. The ingredients were milled using a hammer mill and passed through a 0.065-inch screen, then blended again for 20 minutes in the TURBULA mixer. Next, magnesium stearate was added and the drug-containing composition was blended again for 4 minutes in the same mixer. The drug-containing composition was then wet-granulated using deionized water and dried overnight in a 40□ C oven.

The water-swellable composition consisted of 25 wt% EXPLOTAB, 74.5 wt% PROSOLV 90, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. Next, magnesium stearate was added and the water-swellable composition was blended again for 4 minutes in the same mixer.

Tablets were compressed and coated as described in Example 1. The final dry coating weight was 48.5 mg (9.7 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet. Table C summarizes the characteristics of the dosage form.

Dissolution tests were performed on these tablets in accordance with the procedure described for Example 2A, except residual drug was analyzed using the HPLC method described in Example 1. The results are presented in Table 3 and summarized in Table F.

Table 3

Example	Time (hours)	Drug (wt% released)
3 EXPLOTAB/ PROSOLV 90 = 25/75*	0	0
	2	27
	4	43
	8	65
	12	77
	19	82
	24	93

* approximate

The data show that the weight ratio of swelling agent to tableting aid of about 75/25 can be used to achieve a desired drug release profile.

Example 4

This example demonstrates delivery of Drug 1 with the desired release profile from a tri-layer dosage form containing sodium croscarmellose as the ionic swelling agent in the water-swellable composition.

For the tablets of Example 4, the drug-containing composition consisted of 35 wt% Drug 1, 30 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. The ingredients were milled using a hammer mill and passed through a 0.065-inch screen, then blended again for 20 minutes in the TURBULA mixer. Next, magnesium stearate was added and the drug-containing composition was blended again for 4 minutes in the same mixer.

For tablets of Example 4, the water-swellable composition consisted of 74.5 wt% sodium croscarmellose (AC-DI-SOL), 25 wt% PROSOLV 90, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. Next, magnesium stearate was added and the water-swellable composition was blended again for 4 minutes in the same mixer.

Tablets for Example 4 were compressed and coated as described in Example 1. The final dry coating weight was 52 mg (10.4 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed as described in Example 3 (using the gastric-to-intestinal transfer test of Example 2A with the HPLC method of Example 1). The results are presented in Table 4 and summarized in Table F.

Table 4

Time (hours)	Drug (wt% released)
0	0
2	21
4	48
8	81
14	90
20	89

The data show that 21 wt% of the drug was released within 2 hours, 81 wt% within 8 hours, and 89 wt% of the drug was released within 20 hours. Thus,

the present invention provided delivery of low-solubility Drug 1 using sodium croscarmellose as the ionic swelling agent.

Example 5

This example demonstrates that high drug loadings may be delivered from tri-layer dosage forms of the invention.

For the tablets of Example 5, the drug-containing composition consisted of 56 wt% Drug 1, 20 wt% XYLITAB 200, 19 wt% PEO with an average molecular weight of 600,000 daltons, 4 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were processed as described in Example 4.

The water-swellable composition consisted of 74.5 wt% EXPLOTAB, 25 wt% PROSOLV 90, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were processed as described in Example 4.

Tablet cores were formed by placing 250 mg of drug-containing composition in a standard 13/32 inch die and gently leveling with the press. Then, 200 mg water-swellable composition was placed in the die on top of the drug-containing composition and leveled. The second half of the drug-containing composition (250 mg) was added and the tablet core compressed to a hardness of about 11 Kp. The resulting tri-layer tablet core had a total weight of 700 mg and contained a total of 40.0 wt% Drug 1 (280 mg), 14.3 wt% XYLITAB 200, 13.6 wt% PEO 600,000 daltons, 24.0 wt% EXPLOTAB, 7.1 wt% PROSOLV 90, and 1.0 wt% magnesium stearate.

Tablets for Example 5 were coated as described in Example 1. The final dry coating weight was 77 mg (11.0 wt%). Five 900 µm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed as described in Example 3. The results are presented in Table 5 and summarized in Table F.

Table 5

Time (hours)	Drug (wt% released)
0	0
2	13
4	34
8	63
14	85
20	85

The data show that 13 wt% of the drug was released within 2 hours, 63 wt% within 8 hours, and 85 wt% of the drug was released within 20 hours. Thus, the present invention provided delivery of a high dose of low-solubility Drug 1.

Examples 6A–6D

These examples demonstrate the relationship between the drug release profile and the water permeability of the coating. For the tri-layer tablets of Examples 6A, 6B, 6C, and 6D, the drug-containing composition consisted of 35 wt% Drug 1, 30 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were processed as described in Example 4.

The water-swellable compositions consisted of 74.5 wt% EXPLOTAB, 25 wt% AVICEL PH102, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were processed as described in Example 4.

Tablets for Examples 6A–6D were compressed and coated as described in Example 1. For the tablets of Example 6A, the coating had a final dry weight of 26 mg (5.2 wt%). For the tablets of Example 6B, the coating had a final dry weight of 49.5 mg (9.9 wt%). For the tablets of Example 6C, the coating had a final dry weight of 78 mg (15.6 wt%). For the tablets of Example 6D, the coating had a final dry weight of 107 mg (21.4 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet. Table C summarizes the characteristics of the dosage forms.

Generally, the thicker the coating, the lower the expected water permeability. Dissolution tests were performed on these tablets as described in Example 3. Results are shown in Table 6 and are summarized in Table F.

Table 6

Example	Time (hours)	Drug (wt% released)
6A	0	0
	2	32
	4	58
	8	90
	14	95
	20	94
6B	0	0
	2	25
	4	40
	8	73
	14	92
	20	92
6C	0	0
	2	11
	4	36
	8	66
	14	85
	20	92
6D	0	0
	2	4
	4	27
	8	54
	14	86
	20	90

Examples 6A–6D show that as the water permeability decreased, i.e., as the coating weight increased, the rate of drug release decreased. The data show that as the coating thickness increased, the fraction of drug delivered between 0 and 8 hours decreased, while the fraction of drug delivered from 8 to 20 hours increased.

Example 7

Exemplary dosage forms of the present invention were made with a tri-layer core geometry of the type depicted in FIG. 1. This example illustrates dosage forms of this invention which release drug over a short duration, utilizing a durable, high permeability coating.

For the tablets of Example 7, the drug-containing composition consisted of 35 wt% Drug 1, 30 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were processed as described in Example 4.

The water-swellable composition consisted of 74.5 wt% EXPLOTAB, 25 wt% PROSOLV 90, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were processed as described in Example 4.

Tablets were compressed and coated as described in Example 1, except that the coating solution contained CA, PEG 3350, water, and acetone in a weight ratio of 7/3/23/67 (wt%). The amount of water in the coating solution was increased to increase the porosity. The coating had a final dry weight of 56.5 mg (11.3 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed as described in Example 3, except that the flasks were stirred at 50 rpm. The results are presented in Table 7 and summarized in Table F.

Table 7

Time (hours)	Drug (wt% released)
0	0
2	31
4	66
8	90
14	94
20	94

The data show that 31 wt% of Drug 1 was released within 2 hours, 90 wt% within 8 hours, and 94 wt% of the drug was released within 20 hours. Thus, for coatings with increased water permeability, the rate of drug release increased.

Example 8

This example illustrates the delivery of 5-(2-(4-(3-benzisothiazolyl)-piperazinyl)ethyl-6-chlorooxindole (Drug 6) having a solubility of 3 □g/mL in model fasted duodenal solution, from a tri-layer dosage form of the invention. The drug was in the form of a solid amorphous dispersion comprising 10 wt% of Drug 6 and 90 wt% hydroxy propylmethyl cellulose acetate succinate, HF grade (HPMCAS -HF), a concentration-enhancing polymer.

Amorphous solid dispersions of Drug 6 in HPMCAS were prepared by spray-drying a solution containing 0.30 wt% Drug 6, 2.7 wt% HPMCAS -HF, and 97 wt% methanol. The solution was spray-dried using a two-fluid external mix spray nozzle at 1.8 bar at a feed rate of 140 g/min into the stainless steel chamber of a Niro spray-dryer, maintained at a temperature of 264□C at the inlet and 62□C at the outlet.

To form the drug-containing composition, the following materials were blended: 35 wt% Drug 6 dispersion (1:9 Drug 1:HPMCAS), 29 wt% PEO having an average molecular weight of 600,000 daltons, 30 wt% XYLITAB 200, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. Next, half of the magnesium stearate was added and the drug-containing composition was blended again for 4 minutes. The second half of the magnesium stearate was added and the mixture was blended for 5 minutes.

To form the water-swellable composition, the following materials were blended: 74.8 wt% EXPLOTAB, 24.8 wt% PROSOLV 90, and 0.4 wt% magnesium stearate. The water-swellable composition ingredients were processed as described in Example 4.

Tablets for Example 8 were compressed and coated as described in Example 1. Assays of these tablets confirmed 15 mg of active Drug 6 (mgA). The coating had a final dry weight of 43 mg (8.6 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet. Table C summarizes the characteristics of the dosage form.

Release of the Drug 6 dispersion from the tri-layer tablets into simulated intestinal buffer was measured. The dissoette flasks were stirred at 50 rpm at 37□C. For each sampling interval, a tablet was removed from the test solution, placed in 200 mL of recovery solution consisting of 75% methanol/ 25% water, and stirred overnight to dissolve the remaining drug in the tablet. Residual drug was analyzed by HPLC using a Phenomenex ODS 20 column. The mobile phase consisted of 60% 0.02 M KH_2PO_4, pH 3/ 40% acetonitrile. Drug concentration was calculated by comparing UV absorbance at 254 nm to the absorbance of Drug 6 standards. The amount of drug remaining in the tablets was subtracted from the total initial amount of drug in the tablet to obtain the amount released at each time interval. The results are presented in Table 8 and summarized in Table F.

Table 8

Time (hours)	Drug (wt% released)
0	0
1	10
2	23
4	48
8	77
12	88
18	85
24	89

The data demonstrate satisfactory delivery of a dispersion of Drug 6 from tri-layer dosage forms of this invention.

Example 9 This example describes the results of tests to determine the swelling volume of swelling agents that may be used in the formulation of the water-swellable composition.

The following experiment was used to determine the swelling ratio of materials. The materials were first blended and then 500 mg of the material was compressed into a tablet using a 13/32-inch die, the tablet having a strength ranging from 3 to 16 Kp/cm^2. This compressed material was then placed into a glass cylinder of approximately the same inside diameter as the tablet. The height of the tablet was then measured. Using this height and the diameter of the tablet, the volume of the dry material was determined. Next, the glass cylinder was filled with test media of either deionized water, simulated intestinal buffer, or simulated gastric buffer. The glass cylinder and test media were all equilibrated at a constant temperature of 37□C. As the materials in the tablet absorbed water, the height of the tablet increased. At each time interval, the height of the tablet was measured, from which the volume of the swollen tablet was determined. The ratio of the volume of the tablet after reaching a constant height to that of the volume of the dry tablet is the swelling ratio of the material. The results of these tests are shown in Table 9.

Table 9

Water-Swellable Composition			Swelling Ratio (v/v)		
Swelling Agent	Tableting Aid/ Additive	Swelling Agent/ Tableting Aid (w/w)	Gastric Buffer	Intestinal Buffer	Water
PEO 5,000,000	NONE	100/0	2.4	2.4	2.4
PEO 5,000,000	Microcrystal-line cellulose[1]	85/15	2.2	2.1	2.4
PEO 5,000,000	Microcrystal-line cellulose	70/30	2.0	2.1	2.4
PEO 5,000,000	Microcrystal-line cellulose	50/50	2.0	1.9	1.9
PEO 5,000,000	NaCl	70/30	2.6	2.6	2.8
PEO 2,000,000	Microcrystal-line cellulose	85/15	2.8	2.8	3.0
Polyacrylic acid[2]	Silicified microcrystal-line cellulose[3]	70/30	1.9	1.5	-
Polyacrylic acid	Microcrystal-line cellulose	50/50	1.8	1.7	-
Sodium cros-carmelose[4]	None	100/0	7.0	5.4	7.1
Sodium cros-carmellose	Microcrystal-line cellulose	85/15	7.1	5.9	7.2
Sodium cros-carmellose	Microcrystal-line cellulose	70/30	5.5	6.3	5.5
Sodium cros-carmellose	Microcrystal-line cellulose	50/50	4.6	5.3	5.7
Sodium starch glycolate[5]	Microcrystal-line cellulose	50/50	7.1	7.7	25.2
Sodium starch glycolate	Microcrystal-line cellulose	70/30	9.0	9.6	26.8
Sodium starch glycolate	Microcrystal-line cellulose	85/15	10.9	11.9	34.7
Sodium starch glycolate	Silicified Microcrystal-line cellulose	50/50	7.9	8.7	-
Sodium starch glycolate	Silicified Microcrystal-line cellulose	75/25	7.4	9.1	14.4
Sodium starch glycolate	Silicified Microcrystal-line cellulose	70/30	10.6	11.2	-
Sodium starch glycolate	Hydroxypropyl cellulose[6]	98/2	-	17.2	-
Sodium starch glycolate	Hydroxypropyl cellulose	95/5	5.6	8.4	-

Sodium starch glycolate	Hydroxypropyl cellulose	90/10	7.2	6.9	-
Sodium starch glycolate	Hydroxypropyl cellulose	85/15	-	3.8	3.8
Sodium starch glycolate	Hydroxypropyl cellulose	70/30	3.7	3.9	3.3
Sodium starch glycolate	Hydroxypropyl cellulose	50/50	2.4	2.5	2.4
Sodium alginate[7]	Silicified microcrystal-line cellulose	50/50	2.7	2.9	-
Hydroxyethyl cellulose[8]	NONE	100/0	2.8	2.8	2.7
Hydroxyethyl cellulose	Microcrystal-line cellulose	50/50	2.4	2.1	2.5
1 = AVICEL 2 = CARBOPOL 974PNF 3 = PROSOLV 90 4 = AC-DI-SOL 5 = EXPLOTAB 6 = Klucel 7 = Keltone LVCR 8 = Natrosol					

Examples 10A–10C These examples demonstrate that various osmogens can be used in the drug-containing composition to form tri-layer dosage forms with the desired release profile. For the tablets of Example 10A, the drug-containing composition consisted of 35 wt% Drug 1, 29 wt% PEO having an average molecular weight of 600,000 daltons, 30 wt% sorbitol, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. For the tablets of Example 10B, the drug-containing composition consisted of 35 wt% Drug 1, 29 wt% PEO having an average molecular weight of 600,000 daltons, 30 wt% FAST FLO Lactose, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. For the tablets of Example 10C, the drug-containing composition consisted of 35 wt% Drug 1, 19 wt% PEO having an average molecular weight of 600,000 daltons, 40 wt% XYLITAB 200, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were processed as described in Example 4.

For the tablets of Examples 10A-10C, the water-swellable compositions consisted of 74.5 wt% EXPLOTAB, 25.0 wt% PROSOLV 90, and 0.5 wt% magnesium stearate. For the tablets of Example 10C, the water-swellable composition ingredients were processed as described in Example 4. For the tablets of Examples 10A and 10B, the water-swellable composition ingredients were processed as described in Example 1.

Tablets for Examples 10A–10B were compressed and coated as described in Example 1. The final dry coating weights for each example were 58 mg (11.6 wt%) for 10A, 35 mg (7.0 wt%) for 10B, and 48.5 mg (9.7 wt%) for 10C respectively. For all of these examples, five 900 μm diameter holes were then laser-

drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet. Table C summarizes the characteristics of the dosage forms.

Dissolution tests were performed as described in Example 3, except that the flasks for Examples 10A–10C were stirred at 50 rpm. The results are presented in Table 13 and summarized in Table F.

Table 10

Example	Time (hours)	Drug (wt% released)
10A	0	0
	1	4
30% Sorbitol	2	20
	4	40
	6	53
	8	68
	14	86
	20	90
10B	0	0
	2	11
30% Lactose	4	35
	8	60
	12	90
	18	89
	20	90
	24	90
10C	0	0
	1	12
40% XYLITAB	2	30
	4	48
	6	77
	8	81
	14	89
	20	89

The data show that a variety of materials may be used as the osmogen in the drug-containing composition without any adverse effect on the desired drug release profile.

Example 11

This example illustrates delivery of two different drugs from a tri-layer dosage form of the invention. Tri-layer tablets for Example 11 were made with two different drug layers.

For the tablets of Example 11, the top drug-containing composition consisted of 17 wt% cetirizine dihydrochloride (Drug 7), 25 wt% PROSOLV 90,

40 wt% XYLITAB 200, 17 wt% EXPLOTAB, and 1 wt% magnesium stearate. The top layer did not contain a drug entraining agent (e.g., PEO), which reduced the viscosity of the solvated layer and allowed faster release of Drug 7. The bottom drug-containing composition consisted of 60 wt% pseudoephedrine hydrochloride (Drug 8), 34 wt% PEO having an average molecular weight of 600,000, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. Each mixture of drug-containing composition ingredients was processed as described in Example 4. The water-swellable composition consisted of 74.5 wt% EXPLOTAB, 25 wt% PROSOLV 90, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were processed as described in Example 1.

Tablets for Example 11 were compressed as described in Example 1, except that 400 mg of the bottom layer containing pseudoephedrine was placed in the f-press and leveled, 100 mg of the sweller layer was added and leveled, and 60 mg of the top layer containing cetirizine was added and the tablet compressed. Tablets were coated as described in Example 1. The final dry coating weight for Example 11 was 125.5 mg (22.4 wt%). Five 900 µm diameter holes were then laser-drilled in the coating on the pseudoephedrine side of the tablet, and five 2000 µm diameter holes were laser-drilled in the coating on the cetirizine side of the tablet, to provide 10 delivery ports per tablet.

Dissolution tests were performed as described in Example 3, except that the flasks for Example 11 were stirred at 50 rpm, and the recovery solution for dissolution of residual drug was 50% acetonitrile/ 50% water for Example 11. The HPLC method for analysis of pseudoephedrine and cetirizine uses a Zorbax Stablebond® CN column with a mobile phase of 50% 0.1M KH_2PO_4, pH 6.5/ 50% methanol containing 1 g/L sodium octanesulfonate, and UV detection at 214 nm. The results are presented in Table 11 and summarized in Table F.

Table 11

Example	Time (hours)	Drug (wt% released)
11 Drug 7	0	0
	0.5	23
	1	47
	2	52
	4	56
	8	97
	12	97
	18	97
	24	97
11 Drug 8	0	0
	0.5	0
	1	5
	2	17
	4	32
	8	64
	12	74
	18	97
	24	98

The data show that two different drugs can be successfully delivered from tri-layer dosage forms of the invention, and that the rate of delivery for each drug can be independently modified.

Examples 12A–12C

Examples 12A–12C illustrate the delivery of a low solubility drug (Drug 1) using three different dosage form geometries, each comprising a drug-containing composition and a water-swellable composition.

Tablets for Example 12A were tri-layer dosage forms, with the drug-containing composition consisting of 35 wt% Drug 1, 30 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were processed as described in Example 4. The water-swellable composition consisted of 74.5 wt% EXPLOTAB, 25 wt% AVICEL PH200, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were processed as described in Example 4. Tablets were compressed and coated as described in Example 1. The coating had a final dry weight of 52.5 mg (10.5 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Tablets for Example 12B were concentric core dosage forms, with the same drug-containing composition and water-swellable composition as Example 12A, blended using the same processes. To form the tablets, 100 mg of the water-swellable composition was compressed with 1/4-inch tooling to a hardness of 6 Kp. Next, 200 mg of the drug-containing composition was placed in the f-press and gently leveled and compressed with a spatula. The sweller core was placed on top of this and centered. The remaining drug-containing composition (200 mg) was added and the tablet compressed with 9/16-inch tooling to a hardness of about 11 Kp. Tablets were coated as described in Example 1. The coating had a final dry weight of 55 mg (11.0 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Tablets for Example 12C were homogeneous core dosage forms (as in FIG. 4). The tablet cores contained 28 wt% Drug 1, 21 wt% XYLITAB 200, 20 wt% PEO with an average molecular weight of 600,000 daltons, 30 wt% EXPLOTAB, and 1 wt% magnesium stearate. The homogeneous core ingredients were first combined without the magnesium stearate and blended for 20 minutes in a TURBULA mixer. The ingredients were milled using a hammer mill and passed through a 0.065-inch screen, then blended again for 20 minutes in the TURBULA mixer. Next, magnesium stearate was added and the composition was blended again for 4 minutes in the same mixer. Tablets contained 500 mg each. Tablets were coated as described in Example 1. The coating had a final dry weight of 47.5 mg (9.5 wt%). Five 900 μm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests for Examples 12A–12C were performed as described in Example 3. The results are presented in Table 12 and summarized in Table F.

Table 12

Example	Time (hours)	Drug (wt% released)
12A	0	0
	2	25
	4	53
	8	75
	14	95
	20	95
12B	0	0
	2	27
	4	49
	8	69
	14	87
	20	88
12C	0	0
	2	11
	4	40
	8	65
	14	81
	20	85

The data show that drug can be delivered from dosage forms of the invention in various geometries, with no time lag and low residual drug.

Example 13

This example demonstrates delivery of Drug 1 with the desired release profile from a concentric core dosage form containing sodium croscarmellose as the ionic swelling agent.

For the tablets of Example 13, the drug-containing composition consisted of 35 wt% Drug 1, 30 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate. The drug-containing composition ingredients were processed as described in Example 4.

For tablets of Example 13, the water-swellable composition consisted of 74.5 wt% sodium croscarmellose, 25 wt% PROSOLV 90, and 0.5 wt% magnesium stearate. The water-swellable composition ingredients were processed as described in Example 4.

To form the tablets, 100 mg of the water-swellable composition was compressed with 1/4-inch tooling to a hardness of 5 Kp. Next, 200 mg of the drug-containing composition was placed in the f-press and gently leveled and compressed with a spatula. The sweller core was placed on top of this and centered. The

remaining drug-containing composition (200 mg) was added and the tablet compressed with 9/16-inch tooling to a hardness of about 11 Kp. Tablets were coated as described in Example 1. The coating had a final dry weight of 50 mg (10.0 wt%). Five 900 µm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed as described in Example 3. The results are presented in Table 13 and summarized in Table F.

Table 13

Time (hours)	Drug (wt% released)
0	0
2	21
4	54
8	75
14	85
20	84

The data show that 21 wt% of the drug was released within 2 hours, 75 wt% within 8 hours, and 84 wt% of the drug was released within 20 hours.

Example 14 This example demonstrates delivery of Drug 1 with the desired release profile from a granular core dosage form containing a granular swelling agent.

The tablets contained 28 wt% Drug 1, 24 wt% XYLITAB 200, 23 wt% PEO with an average molecular weight of 600,000 daltons, 24 wt% EXPLOTAB (granular, 0.85-1.18 mm), and 1 wt% magnesium stearate. The mixture was processed using the same procedures used to process the drug-containing composition of Example 4. Tablets contained 500 mg each. Tablets were coated as described in Example 1. The coating had a final dry weight of 47.5 mg (9.5 wt%). Five 900 µm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

Dissolution tests were performed as described in Example 3. The results are presented in Table 14 and summarized in Table F.

Table 14

Time (hours)	Drug (wt% released)
0	0
2	20
4	45
8	69
14	81
20	85

The data show that 20 wt% of the drug was released within 2 hours, 69 wt% within 8 hours, and 85 wt% of the drug was released within 20 hours. Thus, the present invention provided delivery of a low-solubility drug from a granular core dosage form using granular EXPLOTAB as the swelling agent.

Example 15

This example demonstrates the in vivo release of Drug 2 from a granular core dosage form. The tablets of Example 15 contained 22.5 wt% Drug 2, 30 wt% XYLITAB 200, 26.5 wt% PEO with an average molecular weight of 600,000 daltons, 20 wt% EXPLOTAB (granular, 0.85-1.18 mm), and 1 wt% magnesium stearate. The mixture was processed using the same procedures used to process the drug-containing composition of Example 4. Tablets contained 500 mg each. Tablets were coated as described in Example 1. The coating had a final dry weight of 55.5 mg (11.1 wt%). Eight 1000 µm diameter slits were then laser-drilled in the coating on the band of the tablet to provide delivery ports.

In vivo residual tests were performed in 5 dogs as follows: Each of five dogs were dosed with tablets (which were marked for later identification) over a six-hour period (i.e., one tablet every two hours) with oral gavage of 50 mL water. The bowel movement was screened for tablets and the recovery time noted. All tablets were recovered intact, i.e., there were no splits in the coatings. The amount of undelivered drug was determined by extracting the unreleased drug from the tablets and the drug released was determined by subtracting the unreleased amount from the known initial amount of drug present in the tablets. Results are shown in Table 15.

Table 15.1

Dog No.	Time (hours)	Drug (wt% released)
1	7.75	51
	5.75	27
	3.75	15
2	24	75
	22	66
	20	71
3	7.5	47
	5.5	30
	3.5	28
4	7.5	48
	5.5	33
	3.5	25
5	28	68
	26	74
	24	68

These tablets were also tested in vitro using a residual dissolution test. These tests were performed in a USP type 2 dissoette using the conditions described in Example 2A. Results are shown in Table 15.2.

Table 15.2

Time (hours)	Drug (wt% released)
0	0
2	22
4.5	52
8.3	61
14	65
20	71

The data show satisfactory in vivo drug delivery with dosage forms of the invention. Good correlation is observed between in vitro and in vivo data.

Example 16

This example demonstrates the in vivo delivery of Drug 2 from tri-layer tablets. For the tablets of Example 16, the drug-containing composition consisted of 28 wt% Drug 2, 37 wt% XYLITAB 200, 29 wt% PEO with an average molecular weight of 600,000 daltons, 5 wt% EXPLOTAB, and 1 wt% magnesium stearate; and the water-swellable composition consisted of 72.5 wt% EXPLOTAB, 25 wt% AVICEL PH102, and 2.5 wt% magnesium stearate. The drug-containing compositions and water-swellable composition were processed as described in Example 4. Tablets were compressed and coated as described in Example 1. The coating had a final dry weight of 50.5 mg (10.1 wt%). Five 900 µm diameter holes were then laser-drilled in the coating on each side of the tablet to provide 10 delivery ports per tablet.

In vivo residual tests were performed in dogs as follows: Each of five dogs were dosed with tablets (which were marked for later identification) over a six-hour period (i.e., one tablet every two hours) with oral gavage of 50 mL water. The bowel movement was screened for tablets and the recovery time noted. All tablets were recovered intact, i.e., there were no splits in the coatings. The amount of undelivered drug was determined by extracting the unreleased drug from the tablets and the drug released was determined by subtracting the unreleased amount from the known initial amount of drug present in the tablets. Results are shown in Table 16.1.

Table 16.1

Dog No.	Time (hours)	Drug (wt% released)
1	24	86
	22	86
	20	84
2	26.5	87
	24.5	87
	22.5	86
3	26.5	86
	24.5	86
	22.5	85
4	33 - 48	87
	31 - 46	90
	29 - 44	87
5	26.5	88
	24.5	85
	22.5	82

These tablets were also tested in vitro using a residual dissolution test. These tests were performed in a USP type 2 dissoette using the conditions described in Example 2A. Results are shown in Table 16.2.

Table 16.2

Time (hours)	Drug (wt% released)
0	0
2	23
4	46
8	85
14	92
20	90

The data show satisfactory in vivo drug delivery with dosage forms of the invention. Good correlation is observed between in vitro and in vivo data.

The terms and expressions which have been employed in the foregoing specification are used therein as terms of description and not of limitation, and there is no intention, in the use of such terms and expressions, of excluding equivalents of the features shown and described or portions thereof, it being recognized that the scope of the invention is defined and limited only by the claims which follow.

Table A. Composition of the Drug-containing Layer for "Trilayer" and Concentric Core Examples

		Drug-containing Layer Composition								
Example	Drug	Drug Conc. (wt%)	PEO Type	PEO Conc. (wt%)	Explotab Conc. (wt%)	Xylitab 200 Conc. (wt%)	Mg Stearate Conc. (wt%)	Other Ingredients	Conc. (wt%)	Processing Method
1	1	35	600K	29	5	30	1	-	-	Wet Granulated
2A	2	28	600K	29	5	37	1	-	-	Dry Blended
2B	3	33	600K	30	5	31	1	-	-	Dry Blended
2C	4	35	600K	29	5	30	1	-	-	Dry Blended
2D	5	40	600K	26	5	28	1	-	-	Dry Blended
3	1	35	600K	29	5	30	1	-	-	Wet Granulated
4	1	35	600K	29	5	30	1	-	-	Dry Blended
5	1	56	600K	19	4	20	1	-	-	Dry Blended
6A	1	35	600K	29	5	30	1	-	-	Dry Blended
6B	1	35	600K	29	5	30	1	-	-	Dry Blended
6C	1	35	600K	29	5	30	1	-	-	Dry Blended
6D	1	35	600K	29	5	30	1	-	-	Dry Blended
7	1	35	600K	29	5	30	1	-	-	Dry Blended
8	6	3.5 Dispersion	600K	29	5	30	1	HPMCAS-HF	31.5	Dry Blended
10A	1	35	600K	29	5	30 sorbitol	1	-	-	Dry Blended
10B	1	35	600K	29	5	30 lactose	1	-	-	Dry Blended

10C	1	35	600K	19	5	40	1	-	-	Dry Blended
11(1)	7	17	-	0	17	40	1	PROSOLV	25	Dry Blended
11(2)	8	60	600K	34	5	0	1	-	-	Dry Blended
12A	1	35	600K	29	5	30	1	-	-	Dry Blended
12B	1	35	600K	29	5	30	1	-	-	Dry Blended
13	1	35	600K	29	5	30	1	-	-	Dry Blended
16	2	28	600K	29		37	1	-	-	Dry Blended

Table B. Composition of the Water-swellable Composition for Trilayer and Concentric Core Examples

Example	Sweller Type	Sweller Conc. (wt%)	Tabletting Aid Type	Tabletting Aid Conc. (wt%)	Mg Stearate Conc. (wt%)	Other Ingredients	Conc. (wt%)	Processing Method
1	Explotab	74.5	Prosolv 90	24.5	1.0	-	-	Wet Granulated
2A	Explotab	72.5	Avicel	25	2.5	-	-	Dry Blended
2B	Explotab	74.5	Prosolv 90	24.5	1.0	-	-	Wet Granulated
2C	Explotab	74.5	Avicel	25	0.5	-	-	Dry Blended
2D	Explotab	74.2	Prosolv 90	25	0.5	Red Lake #40	0.3	Wet Granulated
3	Explotab	25	Prosolv 90	74.5	0.5	-	-	Dry Blended
4	sodium croscar-mellose	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
5	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
6A	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
6B	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
6C	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
6D	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
7	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
8	Explotab	74.8	Prosolv 90	24.8	0.4	-	-	Dry Blended
10A	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended
10B	Explotab	74.5	Prosolv 90	25	0.5	-	-	Dry Blended

10C	Explotab	74.5	Prosolv 90	25	0.5	-	Dry Blended
11	Explotab	74.5	Prosolv 90	25	0.5	-	Dry Blended
12A	Explotab	74.5	Prosolv 90	25	0.5	-	Dry Blended
12B	Explotab	74.5	Avicel	25	0.5	-	Dry Blended
13	sodium croscar-mellose	74.5	Prosolv 90	25	0.5	-	Dry Blended
16	Explotab	72.5	Avicel	25	2.5	-	Dry Blended

Table C. Details of Tablet Formulations for Trilayer and Concentric Core Examples

Example	Core Weight (mg)	Ratio of Total Drug Layers to Sweller Layer (w/w)	CA Conc. (wt%)	PEG Cont. (wt%)	H_2O Conc. (wt%)	Coating Amount (wt% of uncoated tablet)	Number of Holes	Hole Size (µm)
1	500	4:1	7	3	5	9.5	10	900
2A	500	4:1	7	3	5	10.1	10	900
2B	500	4:1	7	3	5	9.3	10	900
2C	500	4:1	7	3	5	9.1	10	900
2D	534	4:1	7	3	5	11.4	10	900
3	500	4:1	7	3	5	9.7	10	900
4	500	4:1	7	3	5	10.4	10	900
5	500	2.5:1	7	3	5	11.0	10	900
6A	500	4:1	7	3	5	5.2	10	900
6B	500	4:1	7	3	5	9.9	10	900
6C	500	4:1	7	3	5	15.6	10	900
6D	500	4:1	7	3	5	21.4	10	900
7	500	4:1	7	3	23	11.3	10	900
8	500	4:1	7	3	5	8.6	10	900
10A	500	4:1	7	3	5	11.6	10	900
10B	500	4:1	7	3	5	7.0	10	900
10C	500	4:1	7	3	5	9.7	10	900

11	500	4.6:1	7	3	5	22.4	10	2000, 900
12A	500	4:1	7	3	5	10.5	10	900
12B	500	4:1	7	3	5	11.0	10	900
13	500	4:1	7	3	5	10.0	10	900
16	500	4:1	7	3	5	10.1	10	900

Table D. Composition of the Core for "Granular Core" and Homogeneous Core Examples

		Drug-containing Layer Composition						
Example	Drug	Drug Conc. (wt%)	PEO Type	PEO Conc. (wt%)	Explotab Conc. (wt%)	Xylitab 200 Conc. (wt%)	Mg Stearate Conc. (wt%)	Processing Method
12C	1	28	600K	29	20	22	1	Dry Blended
14	1	28	600K	23	24 granular	24	1	Dry Blended
15	2	22.5	600K	26.5	20 granular	30	1	Dry Blended

Table E. Details of Tablet Formulations for "Granular Core" and Homogeneous Core Examples

Example	Core Weight (mg)	Sweller (wt% of core)	CA Conc. (wt%)	PEG Cont. (wt%)	H2O Conc. (wt%)	Coating Amount (wt% of uncoated tablet)	Number of Holes	Hole Size (□m)
12C	500	20	7	3	5	9.5	10	900
14	500	24	7	3	5	9.5	10	900
15	500	20	7	3	5	11.1	8	1000 slits

Table F. Summary of Release Rates For All Examples

Example	2-hr Release (%)	8-hr Release (%)	12-hr Release (%)	16-hr Release (%)	20-hr Release (%)	Release Rate 2-12 hr (%/hr)
1	19	76*	94	95*	100 (24 hr)	7.5
2A	23	85	90*	91*	90	6.7
2B	27	72	81	84*	83 (24 hr)	5.4
2C	33	69	78*	84*	85	4.5
2D	17	67	80*	87*	90	6.3
3	27	65	77	80*	93 (24 hr)	5.0
4	21	81	87*	90*	89	6.6
5	13	63	78*	85*	85	6.5
6A	32	90	93*	95*	94	6.1
6B	25	73	86*	92*	92	6.1
6C	11	66	79*	87*	92	6.8
6D	4	54	75*	87*	90	7.1
7	31	90	93*	94*	94	6.2
8	23	77	88	88*	89 (24 hr)	6.5
10A	20	68	80*	87*	90	6.0
10B	11	60	90	89*	90 (24 hr)	7.9
10C	30	81	86*	89*	89	5.6
11 Drug 7	23	97	97	97*	97 (24 hr)	7.4

11 Drug 8	17	64	74	89*	98 (24 hr)	5.7
12A	25	75	88*	95*	95	6.3
12B	27	69	81*	87*	88	5.4
12C	11	65	76*	82*	85	6.5
13	21	75	88*	85*	84	6.7
14	20	69	77*	82*	85	5.7
15	22	61	64*	67*	71	4.2
16	23	85	90*	92*	90	6.7

* Interpolated from data.

CLAIMS

1. A controlled release drug dosage form comprising a core and a coating around said core wherein:

(a) said core comprises a drug-containing composition, another drug-containing composition, and a water-swellable composition, each occupying separate regions within said core, said water-swellable composition being located between said drug-containing composition and said another drug-containing composition; and

(b) said coating is water-permeable, water-insoluble, and has at least one delivery port for communication with said drug-containing composition and another delivery port for communication with said another drug-containing composition.

2. A controlled release drug dosage form comprising a core and a coating around said core wherein:

(a) said core comprises a drug-containing composition and a water-swellable composition, each occupying separate regions within said core, said drug-containing composition surrounding said water-swellable composition;

(b) said drug-containing composition comprises a low-solubility drug and a drug-entraining agent;

(c) said water-swellable composition comprises a swelling agent; and

(d) said coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

3. A controlled release drug dosage form comprising a core and a coating around said core wherein:

(a) said core comprises a drug-containing composition and a water-swellable composition, each occupying separate regions within said core, said water-swellable composition comprising a plurality of granules;

(b) said drug-containing composition comprises a low-solubility drug and a drug-entraining agent;

(c) said water-swellable composition comprises a swelling agent; and

(d) said coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

4. A controlled release drug dosage form comprising a core and a coating around said core wherein:

(a) said core is substantially homogeneous throughout and comprises a mixture of a low-solubility drug, a drug-entraining agent, and a swelling agent; and

(b) said coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

5. The dosage form of claim 1 wherein said drug-containing composition has a different formulation than said another drug-containing composition.

6. The dosage form of claim 1 wherein said drug-containing composition comprises a low-solubility drug, and said first drug-containing composition comprises a drug-entraining agent.

7. The dosage form of any one of claims 2-4 and 6 wherein said drug-entraining agent is selected from the group consisting of polyols, oligomers of polyethers, mixtures of polyfunctional organic acids, cationic materials, polyethylene oxide, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, carboxyethylcellulose, gelatin, and xanthan gum.

8. The dosage form of any one of claims 1-3 wherein said drug-containing composition further comprises a swelling agent.

9. The dosage form of any one of claims 1-4 wherein said core further comprises a solubilizing agent.

10. The dosage form of any one of claims 1-3 wherein said drug-containing composition further comprises a fluidizing agent having a solubility of at least 30 mg/mL and said fluidizing agent comprises at least 10 wt% of said drug-containing composition, and said fluidizing agent is selected from the group

consisting of an organic acid, a salt, a sugar, an amino acid, a polyol, and a low-molecular weight oligomer of a water-soluble polymer.

11. The dosage form of any one of claims 1-4 comprising an ionic swelling agent.

12. The dosage form of any one of claims 1-3 wherein said water-swellable composition has a swelling ratio of at least 2.

13. The dosage form of any one of claims 2-4 and 6 wherein said low-solubility drug is selected from the group consisting of sildenafil and pharmaceutically acceptable salts of sildenafil, sertraline and pharmaceutically acceptable salts of sertraline, the mesylate salt of the drug 4-[3-[4-(2-methylimidazol-1-yl) phenylthio] phenyl]-3,4,5,6-tetrahydro-2H-pyran-4-carboxamide hemifumarate, nifedipine, (+)-2-(3-benzyl-4hydroxy-chroman-7-yl)-4-trifluoromethyl-benzoic acid, 4-amino-5-(4-fluorophenyl)-6,7-dimethoxy-2-[4-(morpholinocarbonyl) perhydro-1,4-diazepin-1-yl]quinoline, and 5-(2-(4-(3-benzisothiazolyl)-piperazinyl)ethyl-6-chlorooxindole.

14. The dosage form of any one of claims 1-4 wherein said coating has a water flux (40/75) of at least 1.0 x 10^{-3} gm/cm^2-hr.

15. The dosage form of any one of claims 1-4 and 14 wherein said coating has a durability of at least 1 Kp/cm^2.

16. The dosage form of any one of claims 1-4 wherein said coating is formed from a solution having a weight ratio of cellulose acetate to polyethylene glycol of from 9:1 to 6.5:3.5.

17. The dosage form of any one of claims 1-4 wherein said coating comprises a polymeric asymmetric membrane comprising a thick, porous region and a dense thin region.

18. The dosage form of any one of claims 2-4 and 6 wherein, following introduction of said dosage form to a use environment, no more than 50 wt% of said low-solubility drug is released to said use environment within 2 hours and at least 60 wt% to said use environment is released within 12 hours.

19. The dosage form of any one of claims 2-4 and 6 wherein, following introduction of said dosage form to a use environment, at least about 80 wt% of said low-solubility drug is released to said use environment within about 24 hours.

20. The dosage form of any one of claims 1-4 wherein said core further comprises a concentration-enhancing polymer.

FIG. 1

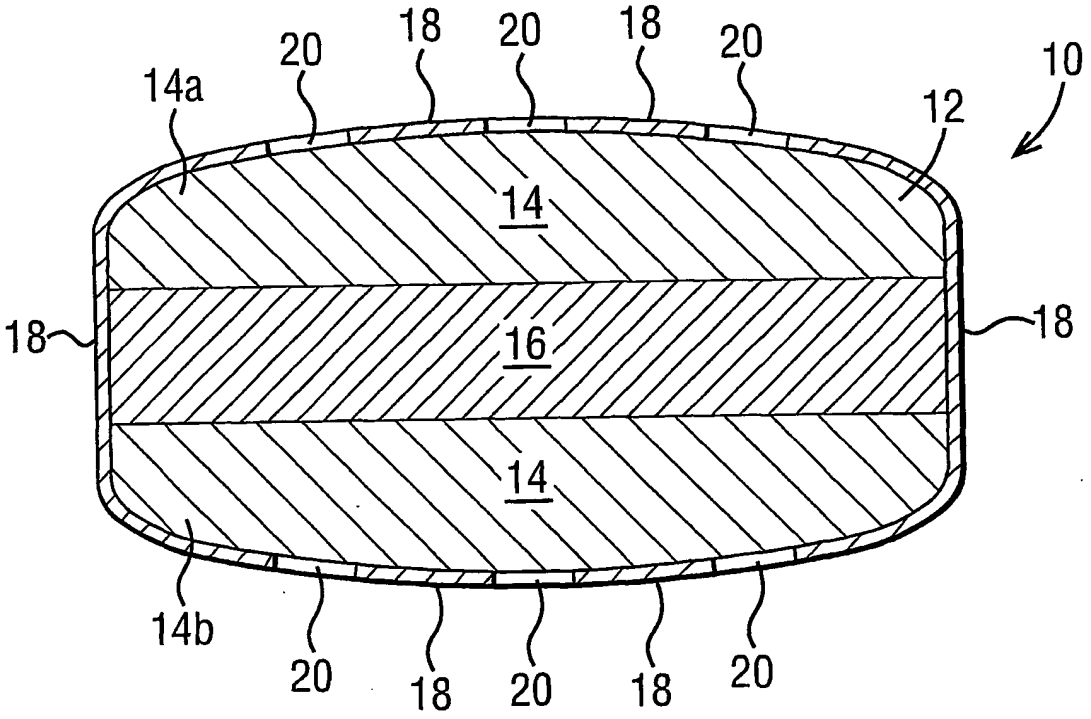

FIG. 2

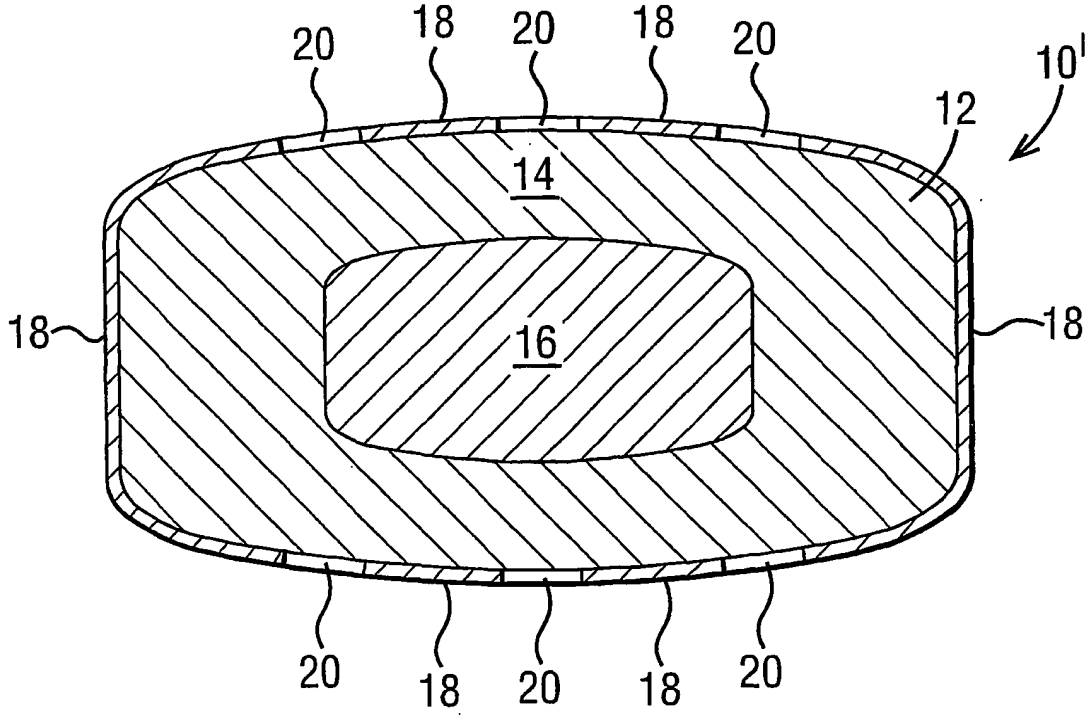

FIG. 3

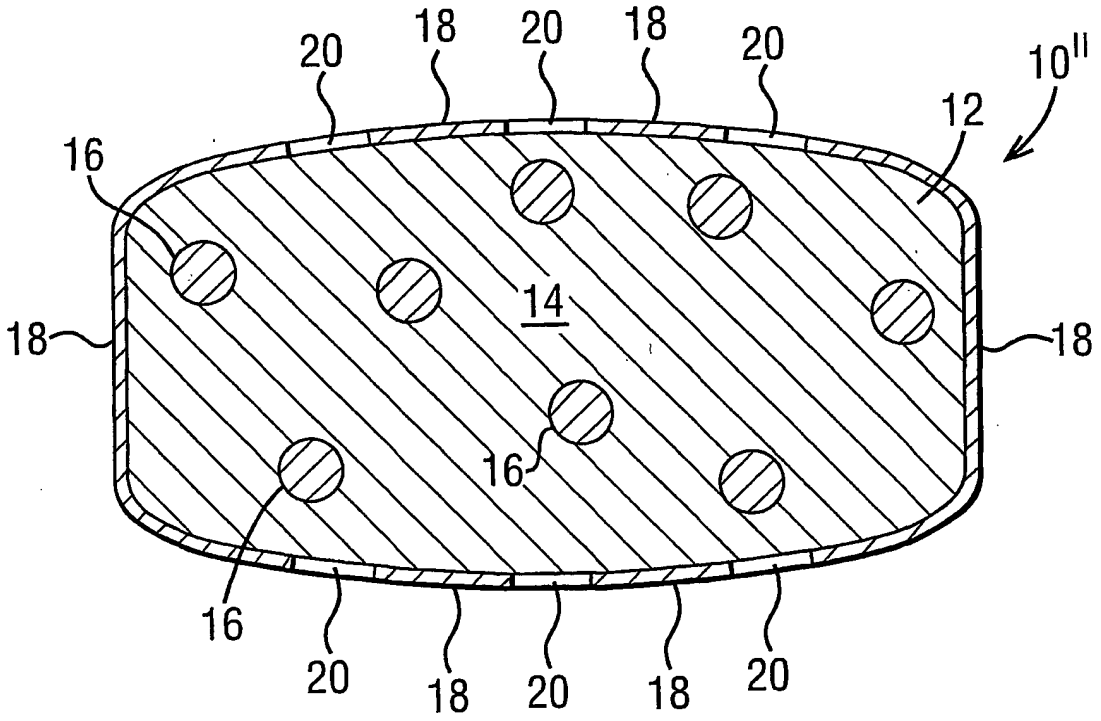
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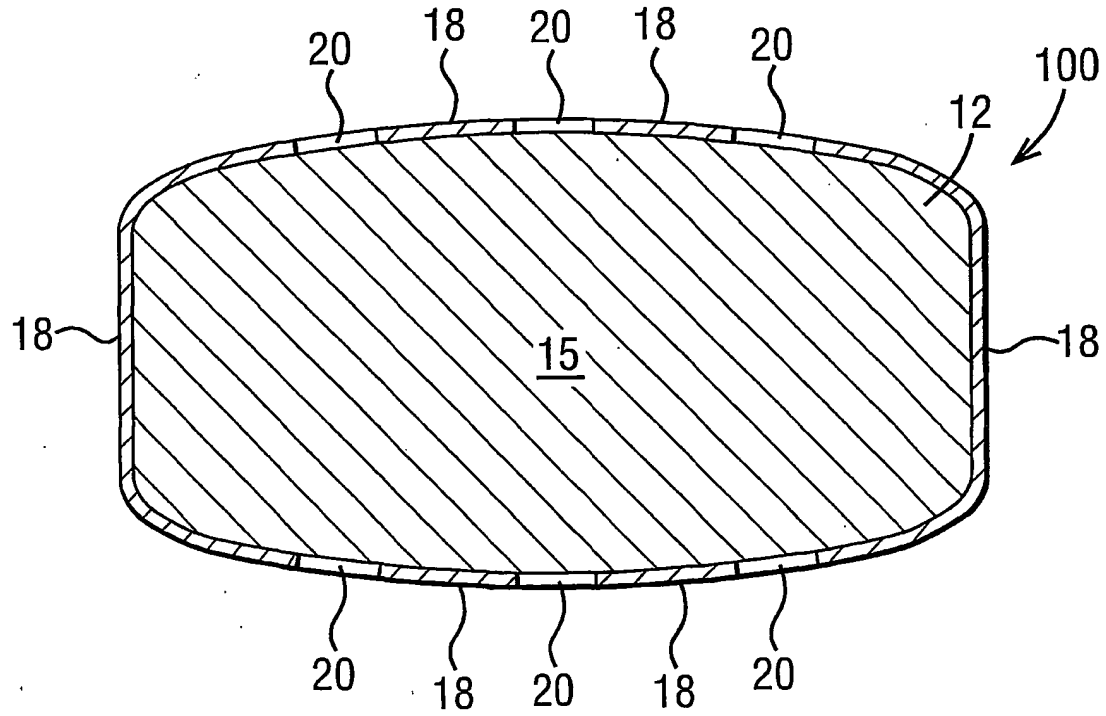
FIG. 4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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(25) Filing Language: English

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(30) Priority Data:
60/224,199 9 August 2000 (09.08.2000) US

(71) Applicant *(for all designated States except US)*: **PFIZER PRODUCTS INC.** [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventors; and

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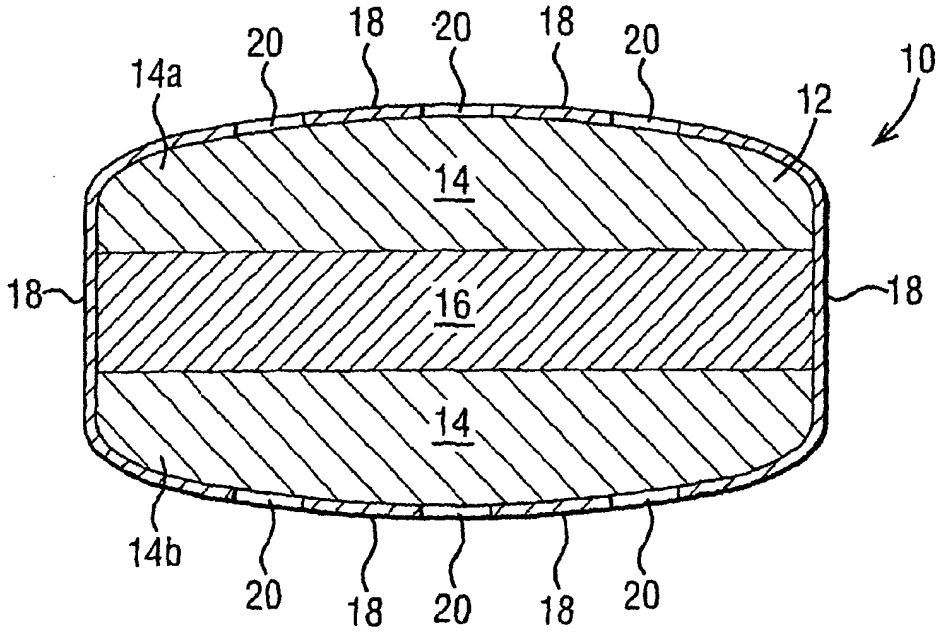
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian

[Continued on next page]

(54) Title: HYDROGEL-DRIVEN DRUG DOSAGE FORM



(57) Abstract: A controlled release dosage form has a coated core with the core comprising a drug-containing composition and a water-swellable composition, each occupying separate regions within the core. The coating around the core is water-permeable, water-insoluble and has at least one delivery port therethrough. A variety of geometric arrangements are disclosed.

WO 02/011702 A3

patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
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(88) Date of publication of the international search report:
28 November 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/01390

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 116 842 A (ALZA CORP) 5 October 1983 (1983-10-05) page 2, line 2 - line 18 page 2, line 43 -page 3, line 48; figures 1-3 page 5, line 58 -page 6, line 12 figures 7,8; examples 1-5 claims ---	1,5-12, 14,15, 18-20
P,X	EP 1 027 888 A (PFIZER PROD INC) 16 August 2000 (2000-08-16) cited in the application paragraph [0008] figure 4; examples 3,6 --- -/--	1,6-12, 14-16, 18-20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2002	06. 09. 02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Epskamp, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/01390

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 197 47 261 A (BAYER AG) 29 April 1999 (1999-04-29) page 2, line 38 - line 47 page 2, line 54 - line 60 examples 1-4 ---	
A	WO 99 01120 A (PFIZER PROD INC) 14 January 1999 (1999-01-14) page 2, line 17 - line 24 page 14, line 25 - line 30 example 7 -----	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 01/01390

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

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

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

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

see additional sheet

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

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

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

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

1,5,6,7-20(partially)

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1, 5, 6, 7-20 (partially)

A controlled release dosage form comprising a core and a coating around said core wherein: (a) said core comprises a drug-containing composition, another drug-containing composition, and a water-swellable composition, each occupying separate regions within said core, said water-swellable composition being located between said drug-containing composition and said another drug-containing composition; and (b) said coating is water-permeable, water-insoluble, and has at least one delivery port for communication with said drug-containing composition and another delivery port for communication with said another drug-containing composition.

2. Claims: 2, 7-20 (partially)

A controlled release dosage form comprising a core and a coating around said core wherein: (a) said core comprises a drug-containing composition and a water-swellable composition, each occupying separate regions within said core, said drug-containing composition surrounding said water-swellable composition; (b) said drug-containing composition comprises a low-solubility drug and a drug-entraining agent; (c) said water-swellable composition comprises a swelling agent; and (d) said coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

3. Claims: 3, 7-20 (partially)

A controlled release dosage form comprising a core and a coating around said core wherein: (a) said core comprises a drug-containing composition and a water-swellable composition, each occupying separate regions within said core, said water-swellable composition comprising a plurality of granules; (b) said drug-containing composition comprises a low-solubility drug and a drug-entraining agent; (c) said water-swellable composition comprises a swelling agent; and (d) said coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

4. Claims: 4, 7-20 (partially)

A controlled release dosage form comprising a core and a coating around said core wherein: (a) said core is substantially homogeneous throughout and comprises a mixture of a low-solubility drug, a drug-entraining agent, and a

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

swelling agent; and (b) said coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 01/01390

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		SK 181099 A3	11-07-2000
		TR 9903297 T2	21-07-2000
		ZA 9805708 A	10-01-2000

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(19) World Intellectual Property Organization
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PCT

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(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/US02/20257

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/895,463 29 June 2001 (29.06.2001) US

(71) Applicant: **BRIDGE PHARMA, INC.** [US/US]; 902 Contento Street, Sarasota, FL 34242 (US).

(72) Inventor: **ABERG, A., K., Gunnar**; 902 Contento Street, Sarasota, FL 34242 (US).

(74) Agents: **LEMACK, Kevin, S.** et al.; Nields & Lemack, 176 E. Main Street, Westboro, MA 01581 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

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WO 03/002059 A2

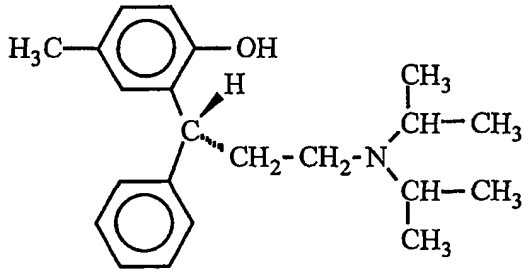
(54) Title: TOLTERODINE METABOLITES

(57) Abstract: Methods for treating smooth muscle hyperactivity, including urinary incontinence, while avoiding concomitant liability of adverse effects associated with tolterodine and the racemic version thereof are disclosed. The methods comprise administering a therapeutically effective amount of a mono-isopropyl metabolite or a parahydroxymethyl metabolite or a parahydroxymethyl mono-isopropyl metabolite of tolterodine or racemic versions thereof or a pharmaceutically acceptable salt of either metabolite. Pharmaceutical compositions in the form of tablets and transdermal devices comprising said compounds and acceptable carriers are also disclosed.

TOLTERODINE METABOLITES

FIELD OF THE INVENTION

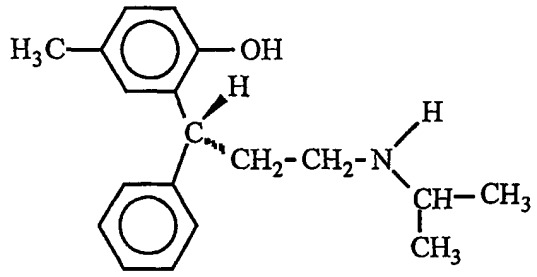
This invention relates to a compound named tolterodine and having the formula:



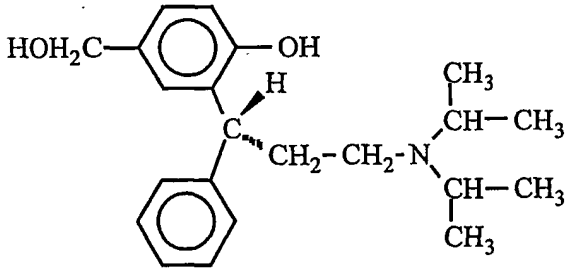
Tolterodine

The generic name TOLTERODINE (CAS-124937-51-5; INN) refers to the R-enantiomer of the drug. In this document, the racemate of this drug is referred to as RS-tolterodine (or RS-TOLT). The R-isomer (tolterodine) is here referred to as TOLT. The chemical name of tolterodine is R(+)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine and the chemical name of RS-TOLT is RS-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine. Des-isopropyl-tolterodine is a metabolite of TOLT and is here referred to as DES-TOLT and the racemate thereof is referred to as RS-DES-TOLT. The chemical name for RS-DES-TOLT is RS-*N*-Isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine and the chemical name of DES-TOLT is R(+)-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine. The compound 5-hydroxymethyl-tolterodine is a metabolite of TOLT and is here referred to as 5-HM and the racemate thereof is referred to as RS-5-HM. The chemical name for RS-5-HM and 5-HM are RS-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine and R(+)-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine, respectively. The compounds DES-TOLT can undergo hepatic oxidation of the paramethyl substituent, whereby the compound 5-HM-DES-TOLT is formed. The chemical name for 5-HM-DES-TOLT is R(+)-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine and this compound exists in the racemic form as well as. The 5-

hydroxylated compound 5-HM-DES-TOLT can undergo further oxidative metabolism and via the aldehyde, the 5-carboxylic acid metabolite is formed in the liver.



R(+)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine
DES-TOLT)



R(+)-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-
3-phenylpropylamine **5-HM)**

Specifically, the invention relates to processes for preparing certain metabolites of tolterodine and to methods for treating smooth muscle hyperactivity disorders using such metabolites. Smooth muscle hyperactivity disorders of the urinary bladder cause urinary disorders, including urinary incontinence and pollakiuria. Smooth muscle hyperactivity disorders of the gastrointestinal tract cause gastrointestinal disorders, including irritable bowel syndrome and diarrhea. Other smooth muscle hyperactivity disorders occur also in conjunction with asthma, urolithiasis, choledocholithiasis and cholelithiasis. The present invention describes the use of the anticholinergic compounds DES-TOLT, RS-DES-TOLT, 5-HM, RS-5-HM, 5-HM-DES-TOLT and RS-5-HM-DES-TOLT and pharmaceutical compositions containing at least one of said compounds, while avoiding side effects of the parent compounds, said parent compounds being TOLT and RS-TOLT.

BACKGROUND OF THE INVENTION.

TOLT has been shown to reduce urinary bladder hyperactivity in patients suffering from urinary incontinence and the drug exerts a spasmolytic effect on bladder smooth muscle by inhibiting the action of acetylcholine. TOLT has selectivity for muscarinic receptors over nicotinic receptors and as a result, no blocking effects are observed at skeletal neuromuscular junctions. Like TOLT and RS-TOLT, the active metabolites thereof exert antimuscarinic activities that account for their therapeutic activities.

The compounds DES-TOLT and 5-HM have been described as major metabolites of TOLT by several investigators, such as for example Nilvebrant et al. 1997 (Antimuscarinic potency and bladder selectivity of PNU-200577, a major metabolite of tolterodine. Pharmacol Toxicol 81:169-172), Brynne et al. 1997 (Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity. Int J Clin Pharmacol Ther 35: 287-295), Andersson et al. 1998 (Biotransformation of tolterodine, a new muscarinic antagonist, in mice, rats, and dogs. Drug Metab Dispos. 26:528-535) and Postlind et al 1998 (Tolterodine, a new muscarinic receptor antagonist, is metabolized by cytochromes P450 2D6 and 3A in human liver microsomes. Drug Metab Dispos 26: 289-293). It is not known to us if the compound 5-HM-DES-TOLT, or any of the further oxidized metabolites thereof have previously been synthesized. The medicinal use of the tolterodine metabolite 5-HM has been described by Johansson et al. in US Pat. 5,559,269 (1996) and US 5,686,464 (1997), both with foreign application priority date November 06, 1992 (SE 9203318). The medicinal use of RS- DES-TOLT or DES-TOLT or any of the paramethyl-oxidized metabolites thereof have to our knowledge not been described.

SUMMARY OF THE INVENTION

Methods for treating smooth muscle hyperactivity, including urinary incontinence, while avoiding concomitant liability of adverse effects associated with tolterodine and the racemic version thereof are disclosed. The methods comprise administering a therapeutically effective amount of a mono-isopropyl metabolite or a parahydroxymethyl metabolite or a parahydroxymethyl mono-isopropyl metabolite of tolterodine or racemic versions thereof or a pharmaceutically acceptable salt of either

metabolite. Pharmaceutical compositions in the form of tablets and transdermal devices comprising said compounds and acceptable carriers are also disclosed.

DETAILED DESCRIPTION OF THE INVENTION

Pharmacological studies of the metabolites of tolterodine and the corresponding racemates have now been performed in comparison with tolterodine. These studies demonstrate that DES-TOLT, as well as 5-HM-DES-TOLT and the further oxidized metabolites thereof have potent antimuscarinic activities.

It has been found that TOLT and RS-TOLT cause a prolongation of the QTc-interval of the EKG. Prolongation of the QTc interval is indicative of risk for a type of fatal cardiac arrhythmias that is called torsades des Pointes, as described for terfenadine by Woosley et al. 1993 (Mechanism of the cardiotoxic actions of terfenadine. JAMA 269: 1532-1536). The risk for cardiac arrhythmias with TOLT and RS-TOLT in patients may be particularly high when one of said compounds is combined with other drugs that utilize the same metabolic enzyme as said compounds or when said compound is given to patients who are "poor metabolizers" as described by Stahl et al., 1995. However, it was surprisingly found that DES-TOLT and 5-HM as well as RS-DES-TOLT and RS-5-HM did not cause a prolongation of the QTc interval of the EKG. It is therefore concluded that DES-TOLT, 5-HM, RS-DES-TOLT, RS-5-HM, 5-HM-DES-TOLT and RS-5-HM-DES-TOLT offer anticholinergic treatment for smooth muscle hyperactivity disorders, while being devoid of electrophysiological cardiac side effects that reside in the parent compounds, said parent compounds being TOLT and RS-TOLT.

Synthesis of DES-TOLT and RS-DES-TOLT.

Synthetic methods of making of DES-TOLT and RS-DES-TOLT were described by Jönsson et al. in European Patent Application 89850017.8 and are hereby incorporated by reference.

Synthesis of 5-HM and RS-5-HM.

Synthetic methods of making of 5-HM and RS-5-HM were described by Johansson et al. in US Pat 5,559,269 and are hereby incorporated by reference.

Synthesis of 5-HM-DES-TOLT.

The synthesis of 5-HM-DES-TOLT was performed by using a combination of the methods for making 5-HM and DES-TOLT as described in the above mentioned references by Jönsson et al. (European Patent Application 89850017.8) and Johansson et al. (US Pat 5,559,269), and as known to those skilled in the art of synthetic chemistry.

Therapeutic doses.

The magnitude of a prophylactic or therapeutic dose of a compound of the present invention in the acute or chronic management of disease will vary with the severity and nature of the condition to be treated and the route of administration. The dose and the frequency of the dosing will also vary according to the age, body weight and response of the individual patient. In general, the total daily oral dose range for DES-TOLT or 5-HM or 5-HM-DES-TOLT for the conditions described herein is from about 0.5 mg to about 100 mg in single or divided doses, preferably in divided doses or in single dose using a controlled release oral formulation. In managing the patient, the therapy should be initiated at a low dose, perhaps at 1 or 2 mg to about 10 mg orally, and may be increased up to about 50 mg depending on the patient's global response. It is further recommended that patients over 65 years and those with impaired renal or hepatic function initially receive low doses and that they be titrated based on individual response(s) and plasma drug level(s). It may be necessary to use dosages outside these ranges in some cases, particularly if the drug is administered by routes other than the oral route, as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response. The terms "a therapeutically effective amount" and "an amount sufficient to treat the disorder but insufficient to cause adverse effects" are encompassed by the above-described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the compounds of the present invention. For example, oral, sublingual, parental (i.e. subcutaneous, intramuscular, intravenous, etc.), transdermal, vaginal, aerosol and like forms of administration may be employed. Additionally, the drug may be administered directly into the bladder, as described for oxybutynin by Massad et al.

[J. Urol. 148, 595-597 (1992)] or rectally directly into the gastrointestinal canal as known in the art. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, suppositories, microencapsulated systems, slow-release and controlled release systems, transdermal delivery systems, and the like.

The pharmaceutical compositions of the present invention comprise of DES-TOLT, 5-HM, RS-DES-TOLT, RS-5-HM, 5-HM-DES-TOLT or RS-5-HM-DES-TOLT as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

The terms "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic acids. Suitable pharmaceutically acceptable acid addition salts for the compound of the present invention include acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pathothenic, phosphoric, p-toluenesulfonic, succinic, sulfuric, tartaric, and the like. The hydrochloride is particularly preferred.

The compositions of the present invention include suspensions, solutions, elixirs or solid dosage forms. Carriers such as starches, sugars, and microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like are suitable in the case of oral solid preparations (such as powders, capsules, and tablets), and oral solid preparations are preferred over the oral liquid preparations.

Because of their ease of administration, tablets and capsules represent the more advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release means and by means of various delivery devices as known by those skilled in the art. Controlled release means transdermal delivery and delivery devices include patches, ionophoretic systems and the like, as well as slow release or controlled release oral formulations.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete unit dosage forms such as capsules,

cachets, suppositories, or tablets, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation, just as is known for the racemic mixture. Carriers such as starches, sugars, and microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like are suitable in the case of oral solid preparations (such as powders, capsules, and tablets), and oral solid preparations are preferred over the oral liquid preparations.

For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. All of the foregoing techniques are well know to persons of skill in the pharmaceutical art. Each tablet may contain from about 0.5 mg to about 25 mg of the active ingredient.

Example 1

ORAL UNIT DOSAGE FORMULATION

Tablets:

Ingredients	per tablet	per batch of 10,000 tablets
DES-TOLT	5 mg	50 g
Microcrystalline cellulose	30 mg	300 g
Lactose	70 mg	700 g

Calcium stearate	2 mg	20 g
FD&C Blue #1 Lake	0.03 mg	300 mg

The DES-TOLT is blended with lactose and cellulose until a uniform blend is formed. The lake is added and further blended. Finally, the calcium stearate is blended in, and the resulting mixture is compressed into tablets using a 9/32 inch (7 mm) shallow concave punch. Tablets of other strengths may be prepared by altering the ration of active ingredient to the excipients or to the final weight of the tablet.

Pharmacological studies of tolterodine and metabolites thereof.

1. Ligand binding studies: Affinity for muscarinic receptors.

The experiments are carried out on membranes prepared from SF9 cells infected with baculovirus to express human recombinant muscarinic receptor subtypes. After incubation with the test article and the proper radioligand (^{3}H pirenzepine) and washing, bound radioactivity is determined with a liquid scintillation counter, using a commercial scintillation cocktail. The specific radioligand binding to a muscarinic receptor is defined as the difference between total binding and nonspecific binding determined in the presence of an excess of unlabelled ligand. IC_{50} values (concentrations required to inhibit 50% of specific binding) are determined by non-linear regression analysis of the competition curves. These parameters are obtained by curve fitting using Sigmaplot™ software.

2. Functional Characterization of Antimuscarinic Activities on Smooth Muscle Strips.

Experiments are performed using methods similar to those described by Kachur et al, 1988 (R and S enantiomers of oxybutynin: Pharmacological effects in guinea pig bladder and intestine. J Pharmacol Exp Ther 247: 867-872) and Noronha-Blob and Kachur, 1991 (Enantiomers of Oxybutynin: In vitro pharmacological characterization at M1, M2 and M3 muscarinic receptors and in vivo effects on urinary bladder contraction, mydriasis and salivary secretion in guinea pigs. J Pharmacol Exp Ther 256: 562-567). Strips of tissue (approximately 10 mm long and 1.5 mm wide) are removed from the body of the urinary bladder of male guinea pigs weighing 400-600 g. Preparations of the longitudinal smooth muscle of the colon of guinea pigs are prepared as known from the prior art (Acta Physiol

Scand 64: 15-27, 1965). This method is also modified and used for the testing of the drugs on smooth muscle from the kidney, the gall bladder and the airways. The tissues are suspended in an oxygenated buffer of the following composition, in mM: NaCl 133; KCl 4.7; $CaCl_2$ 2.5; $MgSO_4$ 0.6; NaH_2PO_4 1.3; $NaHCO_3$ 16.3; and glucose 7.7, or of a similar composition. The smooth muscle strips are maintained at or about 37.5 C. In each experiment up to seven strips are removed from a single animal, suspended in tissue chambers and allowed to equilibrate with the bathing solution for one hour before proceeding with the experiment. Contractions are recorded with transducers on a polygraph.

The present series of experiments focuses on the anticholinergic actions of DES-TOLT, and RS-DES-TOLT and their metabolites. In these experiments, in order to assess the viability of each tissue and to serve as a frame of reference, contractions of each strip of tissue are recorded initially in response to exposure to tissue medium in which NaCl is replaced by KCl to yield a concentration of 137.7 mM KCl in the medium. This is followed by return to the standard medium, and then by exposures to progressively in creasing concentrations of carbachol, with separate exposures to each concentration only until the peak response has been recorded. Then, leaving one strip untreated and/or one strip exposed to the test solution to serve as control tissue(s), the remaining strips each are exposed for one hour to one concentration of an antagonist. Finally, the responses to increasing concentrations of carbachol are recorded a second time.

4. Cardiac side effects.

Male guinea pigs (450-600 g) are anesthetized with freshly prepared dialurethane sodium. The jugular vein is catheterized for iv administration of test drugs and the trachea is exposed and cannulated. Subdermal electrodes are positioned for Lead II electrocardiogram recording, monitored on a Grass Polygraph recorder, set at a paper speed of 50 mm/sec. The animals are allowed to stabilize for 30 minute after completion of surgery, and three baseline EKG recordings are then made at 10-minute intervals. The animals are then given a dose of the test compound or vehicle as an intravenous infusion over 30 min. EKG recordings are used to determine QT intervals and heart rates. To compensate for variations in heart rates, QTc intervals are calculated from QT- and RR-intervals as known to those skilled in the art. Prolongation of QTc is indicative of a prolonged action potential, caused by an inhibition of

the delayed rectifier potassium channel. Prolongation of QTc is the known cause of Torsades de Pointes ventricular fibrillation by drugs such as terfenadine, astemizole and terodiline (now withdrawn from the market).

Other methods for studying cardiac side effects are also used.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents include numerous pharmaceutically acceptable salt forms e.g. sulfate, fumarate, hydrobromide, hydrochloride, dihydrochloride, methanesulphonate, hydroxynaphthoate, or where appropriate one or other of the hydrate forms thereof, see Merck Index 11th edition (1989) items 9089, 209, 3927, 4628, 8223, 5053, 5836, 8142, 2347, 7765, 1840, 9720, 7461, 1317,4159, and 963 and references cited therein and Am. Rev. Resp. Dis. 1988, 137: (4;2/2) 32. Such equivalents also include the co-administration of at least one compound of the present invention with any other drug that is used to combat diseases in mammals, mentioned in this document. Such equivalents also include the co-administration of at least one compound of the present invention with any other compound or drug that may be used in combination with medication for urinary incontinence or other forms of smooth muscle hyperactivity. Those skilled in the art of pharmacology will realize that the pharmacologically active compounds of the present invention may also be combined with in different concentrations with cholinergically inert compounds, such as S-tolterodine or a metabolite thereof. Those skilled in the art of medicine will also realize that higher or lower doses than those indicated here may be preferred and the doses may be given more or less frequently than suggested here.

Those skilled in the art of drug metabolism will realize that 5-hydroxymethyl metabolites of TOLT or RS-TOLT can and will undergo further oxidative metabolism as described in this document. All such further oxidized metabolites, including aldehydes and the carboxylic acids are included in the present invention.

Those skilled in the art of drug metabolism will realize that DES-TOLT can and will undergo additional dealkylation, whereby a di-des-isopropyl metabolite is formed. This pharmacologically active antimuscarinic metabolite and the paramethyl-oxidized forms thereof are included in the present invention.

Those skilled in the art, will realize that smooth muscle hyperactivity disorders comprise such disorders of the urinary bladder, the gastrointestinal tract, the urinary ducts ("kidney stone pain") the gall fluid ducts ("gall stone pains") and the smooth muscles of the airways.

Those skilled in the art of pharmacology, will realize that the compounds of the invention, having certain pharmacological properties such as antihistaminic activity and anticholinergic activity may be useful for other indications than those listed here. Such indications include but are not limited to cardiovascular indications such as heart failure, myocardial infarction, stroke, and allergic disorders and are equivalents to the specific embodiments of the invention described herein.

Those skilled in the art know that transdermal delivery systems often contain one or more permeation enhancer(s) that dramatically may improve the transdermal absorption of a drug of this invention.

All equivalents are intended to be included in this present invention.

What is claimed is:

1. A method for treating cholinergically induced smooth muscle hyperactivity disorders, comprising the administration to a mammal in need of such treatment a therapeutically effective amount of a compound selected from the group consisting of R,S-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, R(+)-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl amine, RS-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or R(+)-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein said compound is R,S-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

3. The method of claim 1, wherein said compound is R(+)-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl amine, or a pharmaceutically acceptable salt thereof.

4. The method of claim 1, wherein said compound is RS-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

5. The method of claim 1, wherein said compound is R(+)-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

6. A method for treating cholinergically induced smooth muscle hyperactivity disorders, comprising the administration to a mammal in need of such treatment a therapeutically effective amount of a compound selected from the group consisting of R,S-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, R(+)-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, RS-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine, R(+)-*N*-Isopropyl-3-

(2-hydroxy-5-(hydroxymethyl) phenyl)-3-phenylpropylamine, RS-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or R(+)-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl) phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof, while reducing or eliminating concomitant liability of adverse side effects associated with the corresponding parent compounds, those parent compounds being RS-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine and R(+)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine.

7. The method of claim 6, wherein said compound is R,S-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

8. The method of claim 6, wherein said compound is R(+)-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

9. The method of claim 6, wherein said compound RS-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

10 The method of claim 6, wherein said compound is R(+)-*N*-Isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

11. The method of claim 6, wherein said compound is RS-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

12. The method of claim 6, wherein said compound is R(+)-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine or a pharmaceutically acceptable salt thereof.

13. The method of claim 6, wherein said disorders are selected from the group consisting of urinary incontinence and pollakiuria.

14. The method of claim 6, wherein said compound or a pharmaceutically acceptable salt thereof is administered in a dose from about 0.5 mg to about 100 mg per day.

15. The method of claim 6, wherein said compound or a pharmaceutically acceptable salt thereof is administered by inhalation or by parenteral, transdermal, rectal, sublingual or oral administration.

16. The method of claim 6, wherein said compound or a pharmaceutically acceptable salt thereof is administered orally in the pharmaceutical unit dosage form of a tablet or capsule.

17. The pharmaceutical unit dosage form of claim 16. wherein said tablet or capsule is formulated for controlled release upon administration.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TOLTERODINE METABOLITES

(57) Abstract: Methods for treating smooth muscle hyperactivity, including urinary incontinence, while avoiding concomitant liability of adverse effects associated with tolterodine and the racemic version thereof are disclosed. The methods comprise administering a therapeutically effective amount of a mono-isopropyl metabolite or a parahydroxymethyl metabolite or a parahydroxymethyl mono-isopropyl metabolite of tolterodine or racemic versions thereof or a pharmaceutically acceptable salt of either metabolite. Pharmaceutical compositions in the form of tablets and transdermal devices comprising said compounds and acceptable carriers are also disclosed.

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B. FIELDS SEARCHED

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U.S. : 514/649, 648, 647

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,559,269 A (JOHANSSON et al.) 24 September 1996, see abstract, column 1, lines 12-59, column 2, lines 1-20, column 5, lines 55-65, and column 5, lines 50-54.	6, 11-16
X — Y	US 5,686,464 A (JOHANSSON et al.) 11 November 1977, see abstract and columns 1-2 and column 6, column 5, lines 55-65, column 1, lines 57-59.	6, 11-16 ——— 1,4-6, 9-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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INTERNATIONAL SEARCH REPORT

Continuation of B. FIELDS SEARCHED Item 3:
WEST search terms include: tolterod$7, des-tolt, 5-HM, cholinerg$10, (controlled or extended or timed) near release, urin$8 near4 (incontinence), pollakiuria

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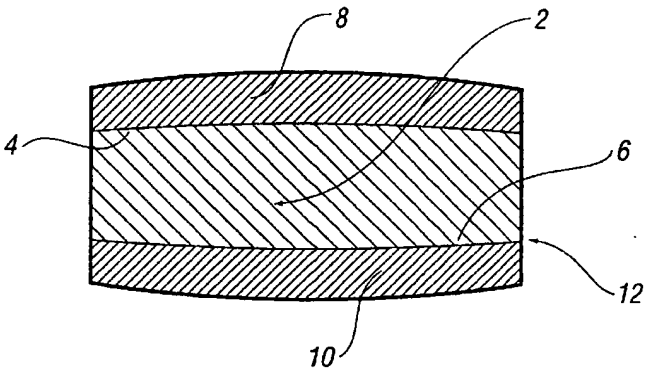
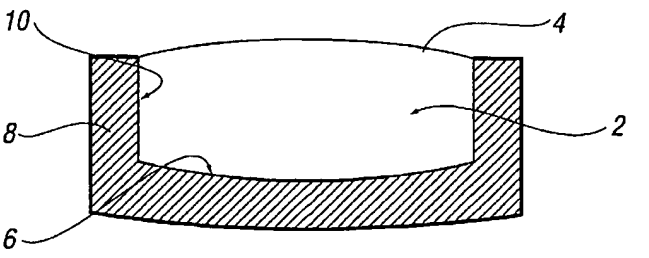
[Continued on next page]

(54) Title: ZERO ORDER CONTROLLED DRUG DELIVERY SYSTEM





(57) Abstract: A controlled release dosage form comprising: (i) a tablet core comprising a pharmaceutically active ingredient and one or more pharmaceutically acceptable matrix forming polymers, (ii) a substantially insoluble casing extended over the tablet core covering between 25 to 99% of the surface area of the tablet core, like for example covering only the major surfaces like in Figure 1 or on major surface and the sidewells like in Figure 2, the casing resulting from electrostatic deposition of a powder comprising fusible particles onto the tablet core and fusing the particles to form a thin film such that the said electrostatic coated tablet releases the active ingredient with a release profile of active ingredient for 0 to at least 50% by weight release of active ingredient defined by the equations $y = k*t^n$ in which y is the fraction of active ingredient released, k is the kinetic constant, t is time, n is the release exponent and n is the range 0.70 to 1.0 i.e. an approximately zero order release profile.

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ZERO ORDER CONTROLLED DRUG DELIVERY SYSTEM

The present invention relates to a controlled drug delivery system that releases an active material at a constant rate (i.e. zero order) into a biological fluid, in particular, the fluid of the gastrointestinal tract.

Tablets are often the preferred means of administering medicine to patients. A conventional immediate release tablet releases the drug active in the body rapidly reaching a maximum concentration then decaying expeditiously until the next administration. This method often leads to peaks and troughs of drug concentration in the blood and requires frequent administration of tablets. Consequently, this could lead to either exacerbated harmful side effects at high concentrations or diminished therapeutic effects at low concentrations. These effects can become acute with actives of relatively short biological half life. To counter these, controlled release dosage forms which release actives at a constant rate over a defined period of time (zero order release) have been frequently employed.

Many controlled release tablets are prepared either using a matrix system through the formation of polymer networks, or using a membrane system such as film coating. The dissolution kinetics over the time when the majority of drug is released can be represented by the following mathematical equation:-

$$y = k^{*}t^{n}$$

Where y is the fraction released

k is the kinetic constant

t is time

n is the release exponent

The release exponent n is characteristic of release mode, if n = 0.5, Fickian diffusion dominates, i.e. the structural relaxation of polymer network is rapid and the rate limiting step is the self-diffusion of drug active. This is termed first order release. If n = 1, the release of active is at a constant rate, i.e. zero order release. The rate-limiting step is the rate of polymer relaxation.

There are numerous factors affecting the release rate of the actives, for example the molecular weight, glass transition temperature, the swelling volume, gelation potential of the network forming polymer etc. Hence, in practice, the release rate can only be controlled to a limited extent by polymer matrix alone with the release exponent n at a value close to 0.5.

US4792448 discloses a device for the controlled release of one or more active substances into a fluid medium at a substantially constant rate (i.e. zero oder) which comprises said substance homogenously dispersed in the shape of a cylindrical tablet or bolus by means of an all-covering, essentially impermeable wall or coating except for one or more strips of removed wall or coating from the side of said device.

EP0259113 claims a device for the controlled release of one or more active substances into a fluid medium which comprises said substance homogenously disposed, with or without one or more inert diluents, and

contained substantially in the shape of a truncated cone by means of an impermeable wall or coating on the base and side of said truncated cone.

US5004614 discloses controlled release devices having a core including an active agent and an outer coating which is substantially impermeable to the entrance of an environmental fluid and substantially impermeable to the release of the active agent during a dispensing period allow the controlled release of the active agent through an orifice in the outer coating. The coating thickness, the position, number and the sizes of the orifices are the key variables influencing the release profile.

US4839177 discloses a system for the controlled-rate release of active substances, consisting of: (a) a deposit core comprising the active substance and having defined geometric form; (b) a support-platform applied to said deposit core. Said deposit core contains, mixed with the active substance, a polymeric material having a high degree of swelling on contact with water or aqueous liquids, a gellable polymeric material, said polymeric materials being replaceable by a single polymeric material having both swelling and gelling properties. Said support-platform consists of a polymeric material insoluble in aqueous liquids and partially coating said deposit-core. However, these tablets have the drawback that the rigid support can result in cracking and sometimes flaking before the active substance has been completely released. This patent was superseded by US5422123, which discloses tablets with zero order controlled rate of release of the active substances, consisting of a core of defined geometrical form containing the active substance, polymer

substances which swell on contact with aqueous liquids and polymer substances with gelling properties, and a support applied to said core or partly cover its surface, the support consisting of polymer substances which are slowly soluble and/or slowly gellable in aqueous liquids, plasticizing substances, and possible substances with an adjuvant function.

US6033685 provides a tablet for controlled release of an active agent consisting of (a) a matrix layer comprising an active agent embedded in non-swelling, non-gelling hydrophobic matrix; (b) a first barrier layer laminated to a single face of the matrix layer; and (c) an optional second barrier layer laminated to the opposite face of the matrix layer and oppositely disposed to the first barrier layer.

US6083533 discloses a layered tablet for controlled release of active substances in a liquid medium comprising at least one active substance containing, layered matrix with contact surfaces to the liquid medium which are at least partially provided with a cover layer delaying or preventing the active substance release, is characterised by the fact that the cover layer is at least one additional layer lying with thickness gradients on contact surfaces of the layered, prefabricated matrix.

US6264985 discloses a compression-coated tablet with an erodible core and a substantially erosion resistant shell. The shell has at least one opening and one end of the core extends as far as the opening.

WO 921445 discloses that electrostatic deposition may be used to apply a coating of controlled thickness and may be employed for a medicinal product containing a drug that is to be instantaneously released when administered or that is to be the subject of controlled or modulated release, such control of modulation being achieved from the nature of the coating and/or from the nature of core. Where the desired form of release is to be achieved by characteristics of the coating, it may be preferred to leave one portion of the product uncoated or coated with different material. In the case of a tablet having faces at opposite ends connected by a cylinder side wall, the portion that is uncoated or coated with different material may be one of the faces of the tablet, a small portion of one of the faces or a side wall of the tablets. However, there is no disclosure as to whether or how a zero order release profile can be achieved.

There is a need for an effective pharmaceutical dosage form having controlled release of an active ingredient at substantially constant rate.

In accordance with the present invention there is provided a controlled release dosage form comprising:

(i) a tablet core comprising a pharmaceutically active ingredient and one or more pharmaceutically acceptable matrix forming polymers, the tablet core releases the active ingredient with a release profile of active ingredient for 0 to at least 50% by weight release of active ingredient defined by the equations

$y = k*t^n$

in which y is the fraction of active ingredient released

k is the kinetic constant

t is time

n is the release exponent

and n is the range 0.30 to 0.65

(ii) a substantially insoluble casing extended over the tablet core covering between 25 to 99% of the surface area of the tablet core, the casing resulting from electrostatic deposition of a powder comprising fusible particles onto the tablet core and fusing the particles to form a thin film such that the said electrostatic coated tablet releases the active ingredient with a release profile of active ingredient for 0 to at least 50% by weight release of active ingredient defined by the equations

$y = k*t^n$

in which y is the fraction of active ingredient released

k is the kinetic constant

t is time

n is the release exponent

and n is the range 0.7 to 1.0 i.e. an approximately zero order release profile.

It has been surprisingly found that a pharmaceutical dosage form having controlled release of an active ingredient at a substantially constant rate, i.e. zero order release rate, can be obtained by electrostatic application of a thin film on the selected surface of a tablet. The release profile does not require the application of a thick film nor rely on the controlled thickness so long as a

complete and uniform coating within the defined area is obtained. Furthermore, there are no needs for a special designed geometric shape, the mechanical removal of a portion of film coating at a defined position with a defined surface area or the presence of specific matrix forming polymers.

The invention provides a simple and effective means of producing a pharmaceutical dosage form having an approximately zero order release profile for a pharmaceutical active agent. A drug reservoir, in the form of a tablet core and having an approximately first order release profile, which may be made by conventional techniques, is provided with an insoluble casing covering 25 to 99% of the surface area of the tablet. In this manner, the area of the tablet exposed to the body fluids, e.g. gastric juices when the dosage form is administered, is reduced thereby decreasing the hydration rate of the tablet core and the drug release rate such that the resulting tablet has an approximately zero order release profile.

The electrostatic coated tablet preferably has the release profile in which n = 0.7 to 1.0 over 0 to at least 50% by weight release of active ingredient, more preferably from 0 to at least 60% by weight release of active ingredient, most preferably from 0 to greater than 70% release of active ingredient. In preferred embodiments the release profile requires at least four hours, more preferably at least five hours to achieve 70% by weight release of active ingredient.

The release profile of a pharmaceutical active is determined by standard US Pharmacopoeia method using a paddle stirring element (Apparatus II), Vankel™ 7000 dissolution apparatus (Apparatus II). The assembly consists of the following: a covered vessel made of glass or other inert, transparent material; a motor; a paddle formed from a blade and a shaft. The shaft is positioned so that its axis is not more than 2mm at any point from the vertical axis of the vessel and rotates smoothly without significant wobble. The vertical centre line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The distance of 25± 2mm between the paddle and the inside bottom of the vessel is maintained during the test.

The vessel is partially immersed in a suitable waterbath which maintains the temperature inside the vessel at 37±0.5°C during the test and keeping the bath fluid in constant, smooth motion. The vessel is cylindrical, with a hemispherical bottom. Its sides are flanged at the top. A fitted cover may be used to retard evaporation. Demineralised water is added to the vessel. The dosage unit (one single tablet) is allowed to sink to the bottom of the vessel before the rotation of the blade is started. The stirring rate is set at 50 rpm. The released active ingredient with time is measured by any suitable means e.g. u.v. analysis, HPLC etc. and expressed as percentage release (w/w) of the total weight of active ingredient.

The casing extending over the tablet core results from the electrostatic deposition of a powder comprising fusible particles. This technique allows the

formation of a thin, continuous casing over the tablet core. Although the release profile does not depend on the coating thickness, it is of importance that a continuous and complete coverage is applied in order to minimise pore formation. Typically this requires the deposition of several layers of powdered material (the powders have a mean diameter of 10 μm) to give a coating thickness of at least 20 μm after fusion. Generally the maximum coating thickness of the tablets is not more than 75μm. Coating thickness in the range 20 to 50μm is preferred. Generally the coating results in a weight gain of less than 5%, often less than 4% and frequently less than 3% by weight of the tablet core. In general, the casing will cover from 25 to 99% of the surface area of the tablet core, generally 50 to 99% , preferably 65 to 95% of the surface area of the tablet core, leaving the reminder exposed.

The shape of the tablet core is not critical since the electrostatic deposition of powder can readily be achieved over a variety of shaped bodies. The tablet core is conveniently formed by conventional tableting techniques e.g. compression of powder and/or granules, although other moulding techniques may be employed. A convenient tablet core has a circular cross-section and two major opposing surfaces which may be, for example, planar, planar with a bevelled edge, concave, convex etc. The insoluble casing may conveniently extend over one of the major surfaces and the side wall leaving the other major surface exposed.

The tablet core comprises at least one adjuvant and a pharmaceutically active ingredient. Generally the adjuvant will comprise a binder. Suitable binders are well known and include acacia, alginic acid, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, dextrin, ethylcellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxypropylmethylcellulose,

maltodextrin, methylcellulose, polyethylene oxide, povidone, sodium alginate and hydrogenated vegetable oils.

The tablet core preferably comprises a release rate controlling additive. For example, the drug may be held within a hydrophobic polymer matrix so that it is gradually leached out of the matrix upon contact with body fluids. Alternatively, the drug may be held within a hydrophilic matrix which gradually dissolves or swells in the presence of body fluid.

Suitable release rate controlling polymers include polymethacrylates, ethylcellulose, hydroxypropylmethylcellulose, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, calcium carboxymethylcellulose, acrylic acid polymer, polyethylene glycol, polyethylene oxide, carrageenan, cellulose acetate, glyceryl monostearate, zein etc.

The tablet core may comprise other conventional tableting ingredients, including diluents, disintegrants, lubricants, wetting agents, glidants, surfactants, release aids, colourants, gas producers, etc.

Suitable diluents include lactose, cellulose, dicalcium phosphate, sucrose, dextrose, fructose, xylitol, mannitol, sorbitol, calcium sulphate, starches, calcium carbonate, sodium carbonate, dextrates, dextrin, kaolin, lactitol, magnesium carbonate, magnesium oxide, maltitol, maltodextrin and maltose.

Suitable lubricants include magnesium stearate and sodium stearyl fumarate.

Suitable glidants include colloidal silica and talc.

Suitable wetting agents include sodium lauryl sulphate and docusate sodium.

Suitable gas producers include sodium bicarbonate and citric acid.

The pharmaceutically active ingredient may be selected from a wide range of substances which may be administered orally. Suitable ingredients include acid-peptic and motility influencing agents, laxatives antidiarrhoeials, colorectal agents, pancreatic enzymes and bile acids, antiarrhythmics, antianginals, diuretics, anti-hypertensives, anti-coagulants, anti-thrombotics, fibrinolytics, haemostatics, hypolipidaemic agents, anti-anaemia and neurotropenia agents, hypnotics, anxiolytics, anti-psychotics, anti-depressants, anti-emetics, anti-convulsants, CNS stimulants, analgesics, anti-pyretics, anti-migraine agents, non-steroidal anti-inflammatory agents, anti-gout agents, muscle relaxants, neuro-muscular agents, steroids, hypoglycaemic agents, hyperglycaemic agents, diagnostic agents, antibiotics, anti-fungals, anti-malarials, anti-virals, immunosuppressants, nutritional agents, vitamins, electrolytes, anorectic agents, appetite suppressants, bronchodilators, expectorants, anti-tussives, mucolytic, decongestants, anti-glaucoma agents, oral contraceptive agents, diagnostic and neoplastic agents.

The electrostatic application of powder material to a substrate is known. Methods have already been developed in the fields of electrophotography and electrography and examples of suitable methods are described, for example, in Electrophotography and Development Physics, Revised Second Edition, by L.B. Schein, published by Laplacian Press, Morgan Hill California. The electrostatic application of powder material to a solid dosage form is known and techniques are disclosed, for example, in GB9929946.3, WO92/14451, WO96/35413, WO96/35516 and PCT/GB01/00425, and British Patent Application No. 9929946.3.

For example, WO92/14451 describes a process in which the cores of pharmaceutical tablets are conveyed on an earthed conveyor belt and electrostatically charged powder is deposited on the cores to form a powder coating on the surface of the cores.

A powder material for electrostatic application to a substrate should have certain properties. For example, the electrical properties of the powder material should be such as to make the powder material suitable for electrostatic application, and other properties of the powder material should be such that the material can be secured to the substrate once electrostatic application has taken place.

WO96/35413 describes a powder material which is especially suitable for electrostatic application to a poorly-conducting (non-metal) substrate such as a pharmaceutical tablet. Because it may be difficult to find a single component capable of providing the powder material with all the desired properties, the powder material comprises a number of different components which together are capable of providing the material with all or at least as many as possible of the desired properties, the components being co-processed to form "composite particles". For example, the powder material may comprise composite particles including one component which is fusible to form a continuous film on the surface of the substrate, and another component which has desirable electrical properties.

A potential disadvantage of the above mentioned powder materials, however, is that they are not readily adaptable to changes in formulation. The formulation of a powder material may be changed for a number of different reasons. For example, if the material is a coloured material, there may be a change in the colourant, or if the material is an active material, for example a physiologically active material there may be a change in the type of active

material, or in the concentration of that active material. Because all the components of the powder material are intimately mixed, any change in the components will alter the material's electrical properties and hence its performance in electrostatic application. Whenever there is a change in formulation, it may therefore be necessary, for optimum performance, to adjust the content of the component(s) that make the material suitable for electrostatic application, or perhaps even to use a different component.

PCT/GB01/00425 discloses a method of electrostatically applying a powder material to a substrate, wherein at least some of the particles of the material comprise a core and a shell surrounding the core, the core and the shell having different physical and/or chemical properties.

Where the particles of the powder material comprise a core and a shell surrounding the core, it is possible to place those components which are likely to be altered, for example colourant in the core, and to provide a more universal shell composition which is suitable for use with various core compositions, so that alterations may be made to the components that are in the core without substantially affecting the overall suitability of the powder material; thus, the shell ensures that the change in composition of the core does not affect the performance of the material in electrostatic application. Accordingly, alterations to one component of the powder material may be made with minimum alteration in the amounts of other components.

Generally, the powder material includes a component which is fusible, and that component may be present in the shell or in the core or in both the shell and the core. Advantageously, the fusible component is treatable to form a continuous film coating. Examples of suitable components are as follows: polyacrylates, for example polymethacrylates; polyesters; polyurethanes; polyamides, for example nylons; polyureas; polysulphones; polyethers;

polystyrene; polyvinylpyrrolidone; biodegradable polymers, for example polycaprolactones, polyanhydrides, polylactides, polyglycolides, polyhydroxybutyrates and polyhydroxyvalerates; sugars, for example lactitol, sorbitol xylitol, galactitol, maltitol, fructose, xylose and galactose; hydrophobic waxes and oils, for example vegetable oils and hydrogenated vegetable oils (saturated and unsaturated fatty acids) e.g. hydrogenated castor oil, carnauba wax, and beeswax; hydrophilic waxes; polyalkenes and polyalkene oxides; polyethylene glycol. Clearly there may be other suitable materials, and the above are given merely as examples. One or more fusible materials may be present. Preferred fusible materials generally function as a binder for other components in the powder.

In general the powder material should contain at least 30%, usually at least 35%, advantageously at least 80%, by weight of material that is fusible, and, for example, fusible material may constitute up to 95%, e.g. up to 85%, by weight of the powder. Wax, if present, is usually present in an amount of no more than 6%, especially no more than 3% by weight, and especially in an amount of at least 1% by weight, for example 1 to 6%, especially to 1 to 3%, by weight of the powder material.

Of the materials mentioned above, polymer binders (also referred to as resins) should especially be mentioned. Examples include polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate and methacrylate polymers, for example an ammonio-methacrylate copolymer, for example those sold under the name Eudragit.

Often resin will be present with a wax as an optional further fusible component in the core; the presence of a wax may, for example, be useful where fusing is to take place by a contact system for example using a heated roller, or where

it is desired to provide a glossy appearance in the fused film. The fusible component may comprise a polymer which is cured during the treatment, for example by irradiation with energy in the gamma, ultra violet or radio frequency bands. For example, the core may comprise thermosetting material which is liquid at room temperature and which is hardened after application to the substrate.

Preferably, the powder material includes a material having a charge-control function. That functionality may be incorporated into a polymer structure, as in the case of Eudragit resin mentioned above, and/or, for a faster rate of charging, may be provided by a separate charge-control additive. Material having a charge-control function may be present in the shell or in the core or in both shell and core. Examples of suitable charge-control agents are as follows: metal salicylates, for example zinc salicylate, magnesium salicylate and calcium salicylate; quaternary ammonium salts; benzalkonium chloride; benzethonium chloride; trimethyl tetradecyl ammonium bromide (cetrimide); and cyclodextrins and their adducts. One or more charge-control agents may be used. Charge-control agent may be present, for example, in an amount of up to 10% by weight, especially at least 1% by weight, for example from 1 to 2% by weight, based on the total weight of the powder material.

The powder material may also include a flow aid. The flow aid reduces the cohesive and/or other forces between the particles of the material to improve the flowability of the powder. Suitable flow aids (which are also known as "surface additives") are, for example, as follows: colloidal silica; metal oxides, e.g. fumed titanium dioxide, zinc oxide or alumina; metal stearates, e.g. zinc, magnesium or calcium stearate; talc; functional and non-functional waxes, and polymer beads, e.g. poly-methyl methacrylate beads, fluoropolymer beads and the like. Such materials may also enhance tribocharging. A mixture of flow aids, for example silica and titanium dioxide, should especially be mentioned. The powder material may contain, for example, 0 to 3% by

weight, advantageously at least 0.1%, e.g. 0.2 to 2.5%, of surface additive flow aid.

Often the powder material includes a colourant and/or an opacifier. When the powder comprises a core and shell such components are preferably present in the core. Examples of suitable colourants and opacifiers are as follows: metal oxides, e.g. titanium dioxide, iron oxides; aluminium lakes, for example, indigo carmine, sunset yellow and tartrazine; approved food dyes; natural pigments. A mixture of such materials may be used if desired. Opacifier preferably constitutes no more than 50%, especially no more than 40%, more especially no more than 30%, for example no more than 10% by weight of the powder material, and may be used, for example, in an amount of at least 5% by weight of the powder. Titanium dioxide is an especially useful opacifier, providing white colour and having good hiding power and tinctorial strength. Colourant present with opacifier may, for example, constitute no more than 10%, preferably from 1 to 5%, by weight of the powder. If there is no opacifier, the colourant may be, for example, 1 to 15%, e.g. 2 to 15%, especially 2 to 10%, by weight of the powder. To achieve optimum colour, amounts of up to 40% by weight of colourant may be needed in some cases, for example if inorganic pigments, e.g. iron oxides, are used. However, the powder material usually contains, for example, from 0 to 25% by weight in total of colourant and/or opacifier.

The powder material may also include a dispersing agent, for example a lecithin. The dispersing agent is preferably present with the colourant/opacifier (that is, preferably in the core), serving to improve the dispersion of the colourant and opacifier, more especially when titanium dioxide is used. The dispersing component is preferably a surfactant which may be anionic, cationic or non-ionic, but may be another compound which would not usually be referred to as a "surfactant" but has a similar effect. The dispersing component may be a co-solvent. The dispersing component may

be one or more of, for example, sodium lauryl sulphate, docusate sodium, Tweens (sorbitan fatty acid esters), polyoxamers and cetostearyl alcohol. Preferably, the powder material includes at least 0.5%, e.g. at least 1%, for example from 2% to 5%, by weight of dispersing component, based on the weight of the powder material. Most often it is about 10% by weight of the colourant and opacifier content.

The powder material may also include a plasticiser, if necessary, to provide appropriate rheological properties. A plasticiser may be present in the core and/or the shell, but usually, if present, a plasticiser is included with resin used for the core to provide appropriate rheological properties, for example for preparation of the core by extrusion in a melt extruder. Examples of suitable plasticisers include polyethylene glycols, triethyl citrate, acetyltributyl citrate, acetyltriethyl citrate, tributyl citrate, diethyl phthalate, dibutyl phthalate, dimethyl phthalate, dibutyl sebacate and glyceryl monostearate.

A plasticiser may be used with a resin in an amount, for example, of up to 50% by weight of the total of that resin and plasticiser, the amount depending inter alia on the particular plasticisers used. The powder may contain an amount of up to 50% by weight of plasticiser.

The powder coating material may further include one or more taste modifiers, for example aspartame, acesulfame K, cyclamates, saccharin, sugars and sugar alcohols or flavourings. Preferably there is no more than 5%, more preferably no more than 1%, of flavouring based on the weight of the powder material, but larger or smaller amounts may be appropriate, depending on the particular taste modifier used.

If desired the powder material may further include a filler or diluent. Suitable fillers and diluents are essentially inert and low cost materials with generally little effect on the colour or other properties of the powder. Examples are as follows: alginic acid; bentonite; calcium carbonate; kaolin; talc; magnesium aluminium silicate; and magnesium carbonate.

The particle size of the powder material has an important effect on the behaviour of the material in electrostatic application. Although materials having a small particle size are recognised as having disadvantages such as being more difficult to produce and to handle by virtue of the material's cohesiveness, such material has special benefits for electrostatic application and the benefits may more than counter the disadvantages. For example, the high surface to mass ratio provided by a small particle increase the electrostatic forces on the particle in comparison to the inertial forces. Increasing the force on a particle has the benefit of increasing the force that causes it to move into contact with the substrate, whilst a reduction in the inertia reduces the force needed to accelerate a particle and reduces the likelihood of a particle arriving at the substrate bouncing back off the substrate. However, very small particle sizes may not be achievable where the coating material comprises a high proportion of a particular ingredient, for example a high proportion of active material.

Preferably, at least 50% by volume of the particles of the material have a particle size no more than 100μm. Advantageously, at least 50% by volume of the particles of the material have a particle size in the range of 5μm to 40μm. More advantageously, at least 50% by volume of the particles of the material have a particle size in the range of 10 to 25μm.

Powder having a narrow range of particle size should especially be mentioned. Particle size distribution may be quoted, for example, in terms of

the Geometric Standard Deviation ("GSD") ratios d_{90}/d_{50} or d_{50}/d_{10} where d_{90} denotes the particle size at which 90% by volume of the particles are below this figure (and 10% are above), d_{10} represents the particle size at which 10% by volume of the particles are below this figure (and 90% are above) , and d_{50} represents the mean particle size. Advantageously, the mean (d_{50}) is in the range of from 5 to 40μm, for example, from 10 to 25μm. Preferably, d_{90}/d_{50} is no more than 1.5, especially no more than 1.35, more especially no more than 1.32, for example in the range of from 1.2 to 1.5, especially 1.25 to 1.35, more especially 1.27 to 1.32, the particle sizes being measured, for example, by Coulter Counter. Thus, for example, the powder may have d_{50} = 10μm, d_{90} = 13μm, d_{10} = 7μm, so that d_{90}/d_{50} = 1.3 and d_{50}/d_{10} = 1.4.

The powder material is fusible so that it is treatable to form a continuous film coating.

It is important that the powder can be fused or treated without degradation of any active material in the powder and without degradation of the tablet core. For some materials it may be possible for the treatment step to involve temperatures up to and above 250°C. Preferably, however, the powder material is fusible at a pressure of less than 100lb/sq. inch, preferably at atmospheric pressure, at a temperature of less than 200°C, and most commonly below 150°C, and often at least 80°C, for example in the range of from 100 to 140°C.

Fusing of the powder material may be carried out by any of a number of different fusing methods. If desired, rupture of the shell and fusing of the material may be carried out in a single step. The powder material is preferably fused by changing the temperature of the powder, for example by radiant fusing using electromagnetic radiation, for example infra red radiation or ultra-violet radiation, or conduction or induction, or by flash fusing. The

amount of heat required may be reduced by applying pressure to the powder material, for example by cold pressure fusing or hot roll fusing.

Preferably, the powder material has a glass transition temperature (Tg) in the range of 40°C to 120°C. Advantageously, the material has a Tg in the range of 50°C to 100°C. A preferred minimum Tg is 55°C, and a preferred maximum Tg is 70°C. Accordingly, more advantageously, the material has a Tg in the range of 55°C to 70°C. Generally, the powder material should be heated to a temperature above its softening point, and then allowed to cool to a temperature below its Tg.

The powder material once fused is substantially insoluble, preferably completely insoluble in aqueous media at temperatures up to the body temperature. Thus, the powder material will comprise a significant amount of an insoluble material. Preferred material comprises a polymer resin selected from polymethacrylates, polyvinyl alcohols and esters, cellulose and its derivatives, cellulose ethers and esters and cellulose acetate phthalate.

The electrostatic coating of the tablet core by the powder material may be conducted by any of the methods disclosed in the above referenced patents. The partial coating of the tablet core may be achieved by the use of a mask. However, preferably the partial coating is achieved by coating one face and the sides of a tablet core in accordance with the first stage of coating as described in the above mentioned patents. Thereafter the electrostatically deposited powder is fused to form a tablet core having a casing covering one face and the sides, leaving the other face exposed.

The invention will be illustrated by the following Examples and drawings in which:

Figures 1 and 2 represent diagrams of different solid dosage forms in accordance with the invention.

Figure 3a shows the release profile of a tablet core containing diltiazem and mixed hydrophobic/hydrophilic polymers as described in Example 1.

Figure 3b to 3g shows the release profile of a coated tablet containing diltiazem and mixed hydrophobic/hydrophilic polymers on the two major faces of the tablets, with 0.5%, 0.7%, 1.4%, 1.9%, 2.3% and 2.8% weight gains respectively as described in Example 1.

Figures 4a and 4b show the release profiles of a tablet core and the coated tablet containing salbutamol and hydrophobic matrix as described in Example 2.

Figures 5a and 5b show the release profiles of a hydrophilic tablet core and the coated tablet as described in Example 3.

Figures 6a and 6b show the release profiles of a mixed hydrophilic/hydrophobic tablet core and the coated tablet as described in Example 4.

Figures 7a and 7b show the release profiles of a hydrophilic tablet core and the coated tablet as described in Example 5.

Figures 8a and 8b show the release profiles of a hydrophobic tablet core and the coated tablet as described in Example 6.

Figures 9a and 9b show the release profiles of a hydrophilic tablet core and the coated tablet as described in Example 7.

Figure 1 shows a dosage form in accordance with the invention comprises a tablet core (2), which is circular in shape and has opposing major faces (4,6), which are convex. The faces (4,6) are coated with an insoluble coating (8, 10) leaving the sidewall (12) exposed.

Referring to Figure 2, which illustrates a cross-section through a dosage form with the invention, a tablet core (2) has a circular cross-section and opposing major convex surfaces (4, 6). The insoluble casing (8) extends over the major surface (6) and side (10) leaving major surface (4) exposed.

The following materials were used in the Examples:

Eudragit RS30D	a methacrylate polymer commercially available from Rhom
Methocel 66LV	hydroxy propyl methyl cellulose commercially available from Dow Chemicals
Methocel K4M	hydroxy propyl methyl cellulose commercially available from Dow Chemicals

Methocel K15M	hydroxy propyl methyl cellulose commercially available from Dow Chemicals
Methocel K100M	hydroxy propyl methyl cellulose commercially available from Dow Chemicals
Eudragit RSPO	a methacrylate copolymer commercially available from Rohm
Eudragit RLPO	a methacrylate copolymer commercially available from Rohm
Eudragit NE30D	a methacrylate copolymer commercially available from Rohm

In the Examples all parts and percentages are by weight unless otherwise stated.

Example 1

Effect of coating thickness: mixed polymer coated on both major faces with insoluble coat

The construction of the dosage form is shown in Figure 1.

Tablet cores were formulated by mixing:

Diltiazem HCl	17.14%
Eudragit RS30D	5.00% (added as 30% aqueous solution)
Methocel 66LV	2.00%
Microcrystalline cellulose	20.00%

DCPA (dihydrogen calcium phosphate anhydrous)	44.86%
Eudragit RSPO	10.00%

The mixture was oven dried to approximately 1% moisture. 1.00% magnesium stearate was added to the dried granules and mixture was compressed into 10mm standard biconvex tablets. The tablet cores had an average weight of about 350 mg and a hardness of about 19 kp.

Two coating formulations for the casing were prepared. Coating Formulation I had the following composition:

Eudragit RSPO	89.8%
Polyethylene glycol 6000	2.7%
Titanium dioxide	5.0%
Indigo Carmine (blue)	2.5%

Coating Formulation II was blended with 0.2% Aerosil 200 before application and it has the following composition:

Eudragit RSPO	87.2%
Triethyl citrate	5.37%
Titanium dioxide	5.0%
Sunset yellow (orange)	2.5%

To prepare the coating powder, the above ingredients were weighed, blended, then extruded. The extrudates were pin-milled, micronised and classified in an air jet mill to give a median particle size of approximately 10 μm.

A blend containing 4.5% of Coating Formulation I and 95.5% of a silicone coated ferrite was prepared. The tablets were coated electrostatically using the coat/carrier blend in a conventional dual component delivery device adapted from the electrophotographic industry such that the Coating Formulation I (without ferrite carrier) was applied to both faces of the tablet leaving the sides uncoated. Details of the coating process are disclosed in British Patent Application No. 9929946.3. The coat was fused onto the tablets at approximately 100°C, to provide a range of coating thickness between 10 and 60μm . The tablets were then turned over and the second coating applied on the other sides of the tablets by the same technique using Coating Formulation II.

Six uncoated and six coated tablets of each coating thickness (as expressed by % weight gain) were assessed for release rate in 900 ml of demineralised water at 37°C using USP Apparatus II (paddles) at 50 rpm as described above and diltiazem analysed by UV.

The results are summarised in Table 1.

Table 1

Sample		Coat thickness I (centre μm)		Coat thickness II (edges μm)		Release exponent (n)
% Weight gain		Side 1	Side 2	Side 1	Side 2	
a	0 (core)	0	0	0	0	0.37
b	0.5%	10	14	12	13	0.50
c	0.7%	43	<10	14	<10	0.45
d	1.4%	33	33	23	30	0.78
e	1.9%	26	28	22	26	0.80
f	2.3%	33	30	26	23	0.79
g	2.8%	39	64	30	44	0.82

The release rate with time for each different tablet is shown in Figures 3a to 3g.

These results demonstrate that electrostatic application of a thin coat on the selected surface of a tablet core, which had a release profile close to first order release, i.e. release exponent n = 0.30 –0.65, resulted in a dosage form having a release profile substantially close to zero order, i.e. n = 0.7 –1.0.

It is known that conventional solvent coating results in a substantial thick coating with a weight gain of at least 5%, or frequently above 10% for modified release systems. The present results demonstrate that zero order release can be achieved with a very thin coat by electrostatic coating and the release profiles are insensitive to coating thickness provided a continuous and complete coverage of the coated area is achieved, i.e. the deposition of several layer coating powder to give a fused coat of approximately 20 μm thick.

Example 2

Hydrophobic tablet core coated on both major faces with insoluble coat

The construction of the dosage form is as illustrated in Figure 1.

Tablet cores were formulated by mixing:

2.74% Salbutamol sulphate

71.26% anhydrous DCPA

25% Eudragit RLPO

1% magnesium stearate

The mixture was compressed into 10 mm standard biconvex tablets. The tablet cores had an average weight of about 350 mg and a hardness of 10 kp. Coating Formulation III was used to coat both sides of the tablets as described in Example 1 to provide a casing of 20 to 50 μm. Coating Formulation III comprises:

84.0% Eudragit RSPO

8.5% polyethylene glycol 6000

5.0% titanium dioxide

2.5% sunset yellow lake

Three uncoated and three coated tablets were assessed for release rate in 500 ml of demineralised water at 37°C using USP Apparatus II (paddles) at 50 rpm and the release rate analysed by UV over 12 hours. The release rate with time is shown in Figures 4a and 4b. The following kinetic models can be used to describe the release characteristics from the cores and coated tablets (0 - 100% release range):

Core: $y = 22.3t^{0.59}$

Coated: $y = 10.8t^{0.90}$

It is evident that electrostatic application of a thin coat substantially modified the release profile of a tablet core comprising hydrophobic polymers.

Example 3

Hydrophobic tablet core comprising a different active coated on both major faces with insoluble coat

The construction of the dosage form is as shown in Figure 1.

Tablet cores were formulated by mixing:

17.14% ditiazem hydrochloride

20.00% microcrystalline cellulose

51.86% anhydrous DCPA

10.00% Eudragit RS30D added as 30% aqueous dispersion

The mixture was oven dried to approximately 1% moisture. 1% magnesium stearate was added to the dried granules and the mixture compressed into 10 mm standard biconvex tablets. The tablet cores had an average weight of about 350 mg and a hardness of 19 kp.

A blend containing 10% of Coat Formulation III as described in Example 2 and 90% of a silicone coated strontium ferrite carrier was prepared. The tablet cores were coated on both major faces using the materials and method as described in Example 2 with the exception that the coat was fused at 120°C. The coating thickness was in the range 20 to 50µm

Six cores and six coated tablets were assessed for release rate in 900 ml of demineralised water at 37°C using USP Apparatus II (paddles) at 50 rpm and the release rate analysed by HPLC.

The release of diltiazem over time is shown in Figures 5a and 5b respectively. The following kinetic models can be used to describe the release characteristics from the cores and coated tablets (0 – 90% release range):

Core: $y = 52t^{0.43}$

Coated: $y = 22t^{0.70}$

It is evident that electrostatic application of a thin coat on the major faces of the tablet substantially modified the release profile of a tablet core comprising hydrophobic polymers.

Example 4

Mixed hydrophobic/hydrophilic tablet core coated on both major faces with insoluble coat

The construction of the dosage form is as illustrated in Figure 1.

The tablet cores were formulated by mixing:

17.14% Diltiazem hydrochloride

20.00% microcrystalline cellulose

50.86% anhydrous DCPA

1% Methocell K15M

10% (as solid) Eudragit NE30D (30% aqueous dispersion)

The mixture was oven dried to approximately 1% moisture. 1% magnesium stearate was added to the dried granules and the mixture was compressed into 10 mm standard biconvex tablets. The tablet cores had an average weight of about 350 mg and a hardness of about 19 kp.

The tablet cores were coated using the materials and method as described in Example 3. The release rate was determined as described in Example 3 and the results are shown in Figures 6a and 6b. The following kinetic models can be used to describe the release characteristics from the cores and coated tablets (0 – 80% release):

Core: $y = 38.5t^{0.56}$

Coated: $y = 10.5t^{0.85}$

It is evident that electrostatic application of a thin coat on the major faces of tablets substantially modified the release profile of a tablet core comprising mixed hydrophilic/hydrophobic polymers.

Example 5

Hydrophilic tablet core coated on both faces of the tablet

The construction of the dosage form is shown in Figure 1.

Tablet cores were formulated by mixing:

2.74% Salbutamol sulphate

46.26% anhydrous lactose DC (directly compressible)

50.00% Methocel K4M

1.00% magnesium stearate

The mixture was compressed into 10 mm standard biconvex tablets. The tablet cores had an average weight of 350 mg and a hardness of about 19 kp. Coating Formulation III was applied on the major opposite faces of the tablet core as described in Example 2 to provide a coating having a thickness in the range of from 20 to 50µm.

The release rate with time was determined according to the method described in Example 2 and the results are shown in Figures 7a and 7b respectively. The following kinetic models can be used to describe the release characteristics from the cores and coated tablets (0 – 80%):

Core: $y = 22.1t^{0.56}$

Coated: $y = 11.0t^{0.80}$

It is evident that electrostatic application of a thin coat on the major faces of tablets substantially modified the release profile of a tablet core comprising hydrophilic polymers.

Example 6 Hydrophobic tablet core coated on one face and the sides of the tablet

The construction of the dosage form is shown in Figure 2.

Tablet cores were formulated by mixing:

2.74% Salbutamol sulphate

71.26% anhydrous DCPA

25.00% Eudragit RLPO

1.00% magnesium stearate

The mixture was compressed into 10 mm standard biconvex tablets. The tablet cores had an average weight of 350 mg and a hardness of about 11 kp. Coating Formulation III was applied on one major face and the sides of the tablet core and the method of coating was as described in Example 2 to provide a coating thickness in the range 20 to 50µm.

The release rate with time was determined according to the method described in Example 2 and the results are shown in Figures 8a and 8b respectively.

The following kinetic models can be used to describe the release characteristics from the cores and coated tablets (0 – 95% for the core and 0 – 80% for the coated tablet):

Core: $y = 70\ t^{0.47}$

Coated: $y = 16.3\ t^{0.90}$

It is evident that electrostatic application of a thin coat on the major faces of tablets substantially modified the release profile of a tablet core comprising hydrophilic polymers.

Example 7:

Hydrophilic tablet core coated on one face and the sides of the tablet

The construction of the dosage form is shown in Figure 2.

Tablet cores were formulated by mixing:

2.74% Salbutamol sulphate

46.26% anhydrous lactose DC (directly compressible)

50.00% Methocel K100M

1.00% magnesium stearate

The mixture was compressed into 10 mm standard biconvex tablets. The tablet cores had an average weight of 350 mg and a hardness of about 15 kp. Coating formulation III was applied on one face and the sides of the tablet core and the method of coating was as described in Example 2 to provide a coating thickness in the range 20 to 50μm.

The release rate with time was determined according to the method described in Example 2 and the results are shown in Figures 9a and 9b respectively. The following kinetic models can be used to describe the release characteristics from the cores and coated tablets (0 – 70%):

Core: $y = 21.0\ t^{0.55}$

Coated: $y = 10.9\ t^{0.78}$

It is evident that electrostatic application of a thin coat on one face and the sides of tablets substantially modified the release profile of a tablet core comprising hydrophilic polymers.

CLAIMS

1. A controlled release dosage form comprising:

(i) a tablet core comprising a pharmaceutically active ingredient and one or more pharmaceutically acceptable matrix forming polymers, the tablet core releases the active ingredient with a release profile of active ingredient for 0 to at least 50% by weight release of active ingredient defined by the equations

$y = k*t^n$

in which y is the fraction of active ingredient released

k is the kinetic constant

t is time

n is the release exponent

and n is the range 0.30 to 0.65

(ii) a substantially insoluble casing extended over the tablet core covering between 25 to 99% of the surface area of the tablet core, the casing resulting from electrostatic deposition of a powder comprising fusible particles onto the tablet core and fusing the particles to form a thin film such that the said electrostatic coated tablet releases the active ingredient with a release profile of active ingredient for 0 to at least 50% by weight release of active ingredient defined by the equations

$y = k*t^n$

in which y is the fraction of active ingredient released

k is the kinetic constant

t is time

n is the release exponent

and n is the range 0.70 to 1.0.

2. A solid pharmaceutical dosage form as claimed in Claim 1 in which the insoluble casing covers from 65 to 95% of the surface area of the tablet core.

3. A solid pharmaceutical dosage form as claimed in Claim 1 or Claim 2 in which the tablet core comprises two major opposing surfaces separated by a sidewall(s) at least the major surfaces being covered by the casing.

4. A solid pharmaceutical dosage form as claimed in Claim 1 or Claim 2 in which the tablet core comprises two major opposing surfaces separated by a sidewall(s) one major surface and the sidewall(s) being covered by the casing .

5. A solid pharmaceutical dosage form as claimed in any preceding claim in which the controlled release dosage form has a release profile in which n = 0.7 to 1.0 over from 0 to at least 70% by weight release of the active ingredient.

6. A solid pharmaceutical dosage form as claimed in any preceding claim in which the release profile of the controlled release dosage form requires at least 4 hours to achieve 70% by weight release of active ingredient.

7. A solid pharmaceutical dosage form as claimed in any preceding claim in which the tablet core comprises a binder selected from acacia, alginic acid, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydrogenated vegetable oil, hydroxypropylmethylcellulose, magnesium aluminium silicate, Maltodextrin, methylcellulose, polyethylene oxide, povidone, sodium alginate and hydrogenated vegetable oils.

8. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the tablet core additionally comprises a release rate controlling polymer is selected from polymethacrylates, ethylcellulose, hydroxypropylmethylcellulose, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, calcium carboxymethylcellulose, acrylic acid polymer, polyethylene glycol,

polyethylene oxide, carrageenan, cellulose acetate, glyceryl monostearate and zein.

9. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the tablet core additionally comprises a diluent selected from lactose, cellulose, dicalcium phosphate, sucrose, dextrose, fructose, xylitol, mannitol, sorbitol, calcium sulphate, starches, calcium carbonate, sodium carbonate, dextrates, dextrin, kaolin, lactitol, magnesium carbonate, magnesium oxide, maltitol, maltodextrin and maltose.

10. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the tablet core comprises a hydrophobic matrix containing an active ingredient, a hydrophilic matrix containing an active ingredient, or a mixture of hydrophilic and hydrophobic materials

11. A solid pharmaceutical dosage form as claimed in any preceding claim in which the active ingredient is selected from acid-peptic and motility influencing agents, laxatives, antidiarrheials, colorectal agents, pancreatic enzymes and bile acids, antiarrhythmics, antianginals, diuretics, anti-hypertensives, anti-coagulants, anti-thrombotics, fibrinolytics, haemostatics, hypolipidaemic agents, anti-anaemia and neurotropenia agents, hypnotics, anxiolytics, anti-psychotics, anti-depressants, anti-emetics, anti-convulsants, CNS stimulants, analgesics, anti-pyretics, anti-migraine agents, non-steroidal anti-inflammatory agents, anti-gout agents, muscle relaxants, neuro-muscular agents, steroids, hypoglycaemic agents, hyperglycaemix agents, diagnostic agents, antibiotics, anti-fungals, anti-malarials, anti-virals, immunosuppressants, nutritional agents, vitamins, electrolytes, anorectic agents, appetite suppressants, bronchodilators, expectorants, anti-tussives, mucolytes, decongestants, anti-glaucoma agents, oral contraceptive agents, diagnostic and neoplastic agents.

12. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the tablet core comprises a polymeric material which swells on contact with aqueous liquid, said swellable polymeric material being selected

from cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, high molecular weight hydroxypropylcellulose, carboxymethylamide, potassium methacrylatedivinylbenzene copolymer, polymethylmethacrylate, cross-linked polyvinylpyrrolidone and high molecular weight polyvinylalcohols.

13. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the casing comprises a polymer resin selected from polymethacrylates, cellulose and its derivatives, cellulose ethers and esters and cellulose acetate phthalate.

14. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the casing additionally comprises one or more adjuvants selected from opacifiers, colourants, plasticisers, flow aids and charge control materials.

15. A solid pharmaceutical dosage form as claimed in Claim 14 in which the casing comprises a plasticiser selected from polyethylene glycols, triethyl citrate, acetyltributyl citrate, acetyltriethyl citrate, tributyl citrate, diethyl phthalate, dibutyl phthalate, dimethyl phthalate, dibutyl sebacate and glyceryl monostearate.

16. A solid pharmaceutical dosage form as claimed in any preceding claim in which the casing has an average thickness of from 20 to 50μm.

17. A solid pharmaceutical dosage form as claimed in any preceding claim in which the casing results in a weight gain of less than 4% by weight of the tablet core.

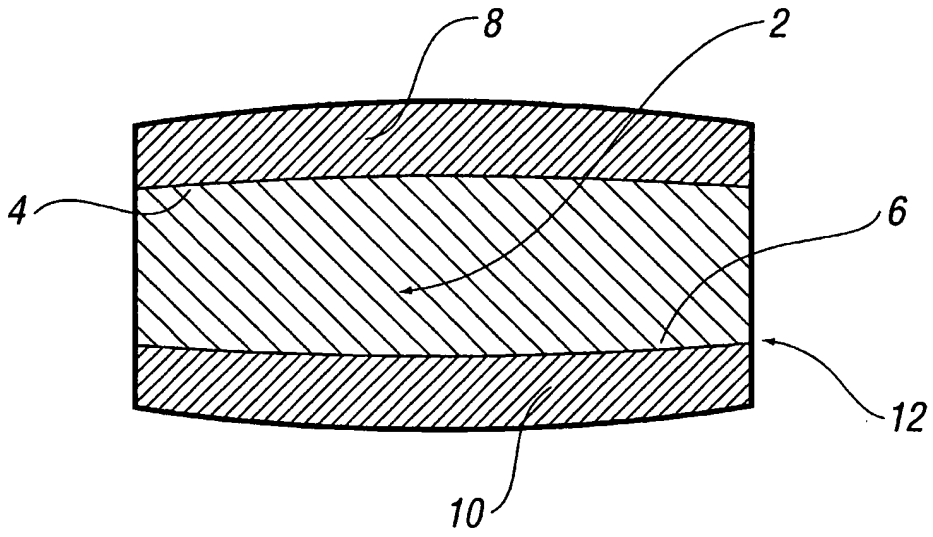

FIG. 1

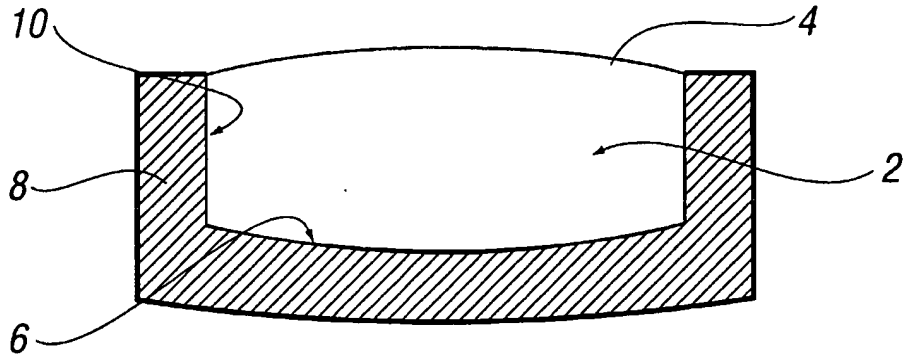

FIG. 2

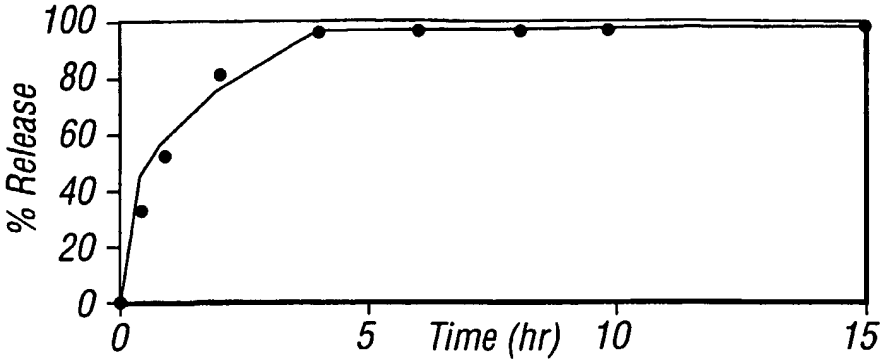

FIG. 3A

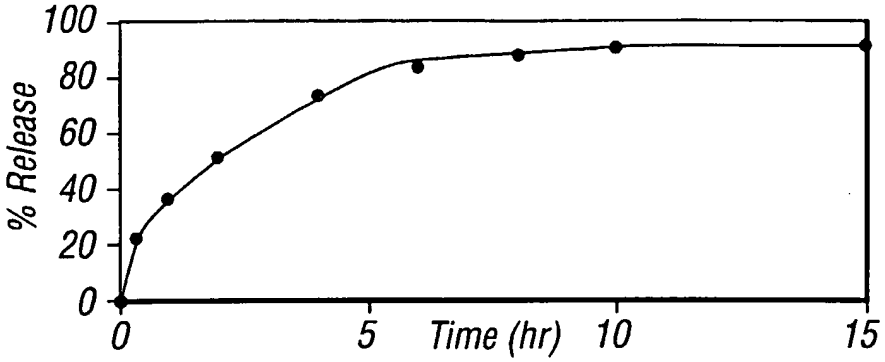

FIG. 3B

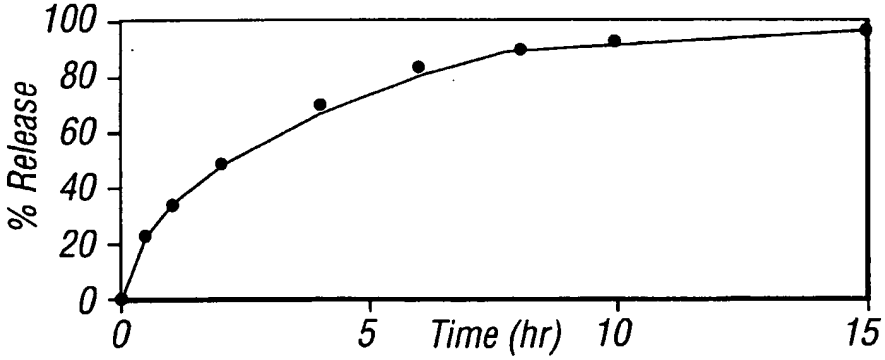

FIG. 3C

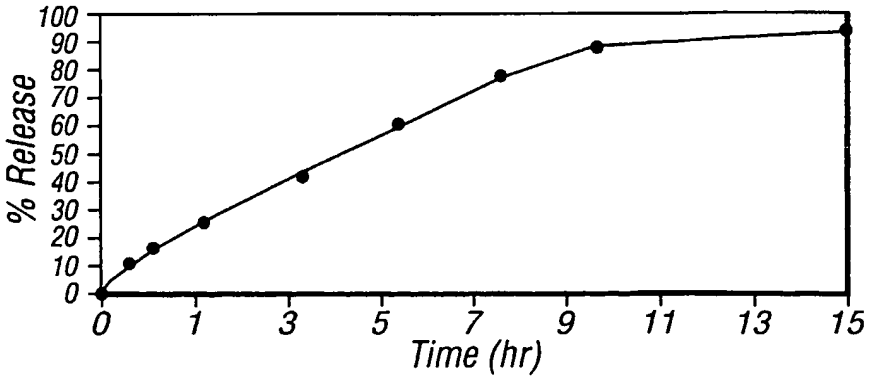

FIG. 3D

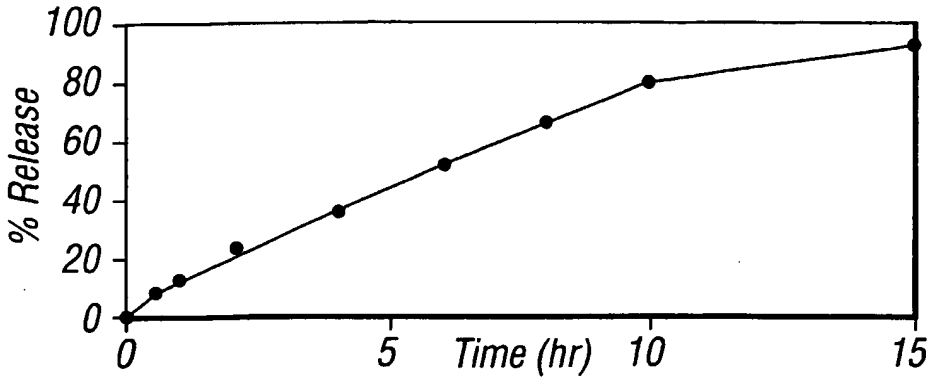

FIG. 3E

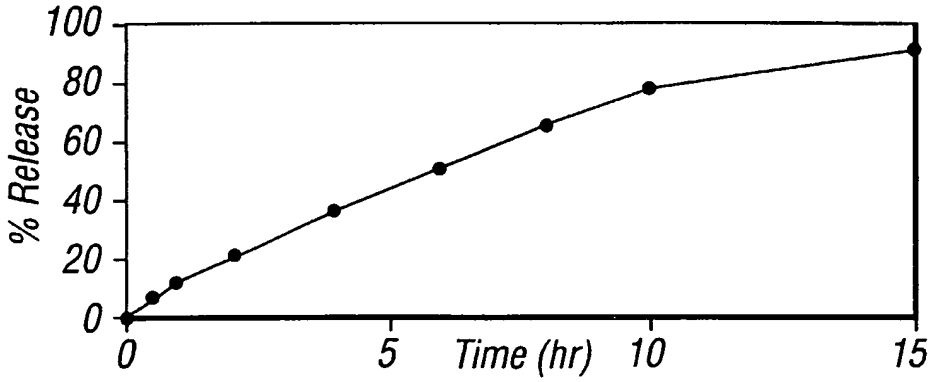

FIG. 3F

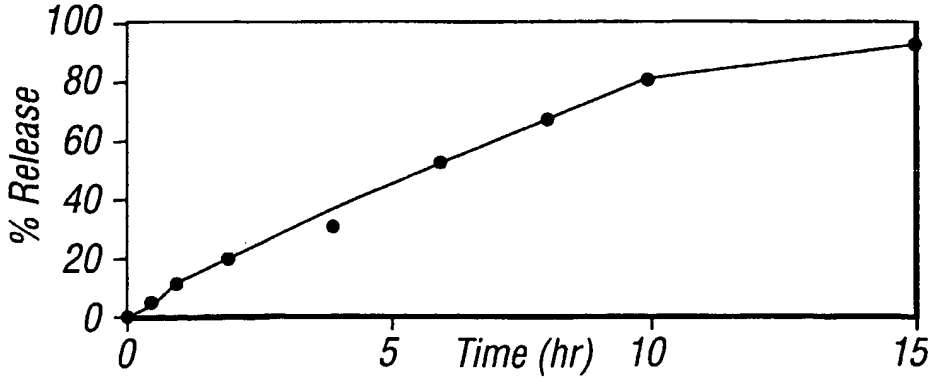

FIG. 3G

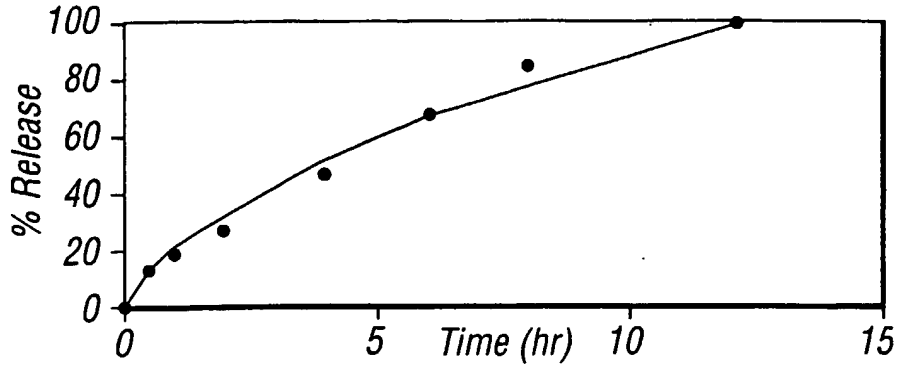

FIG. 4A

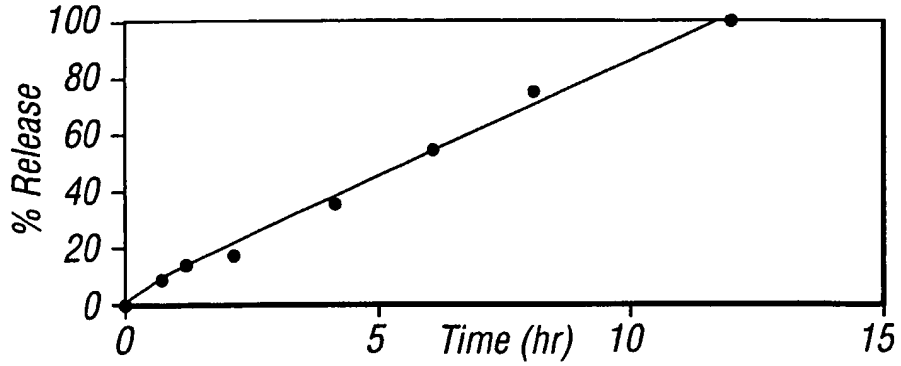

FIG. 4B

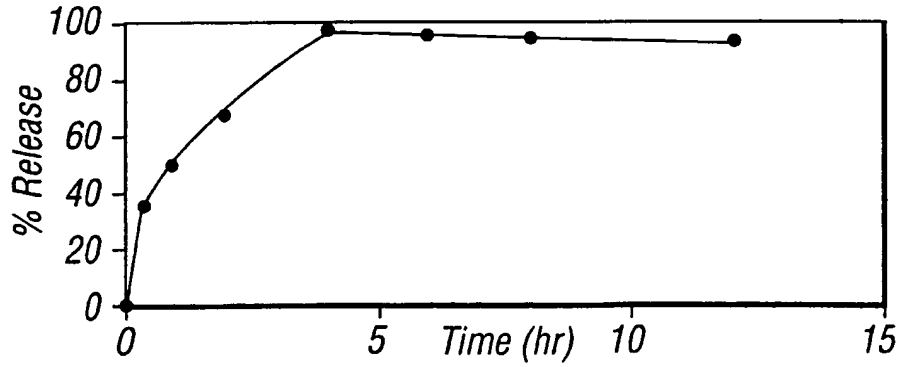

FIG. 5A

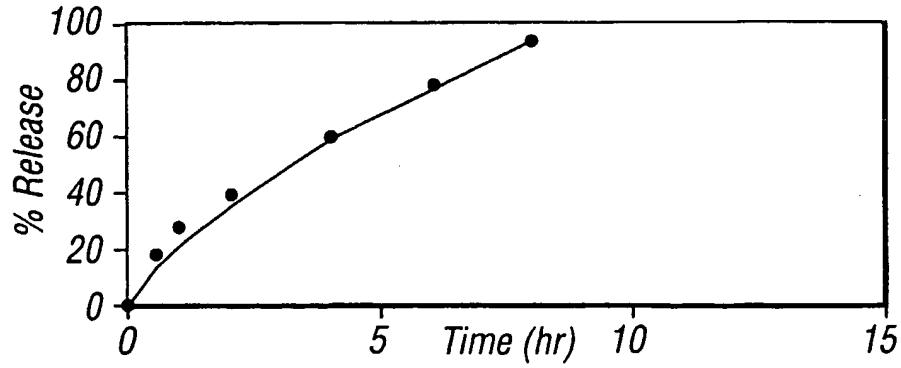

FIG. 5B

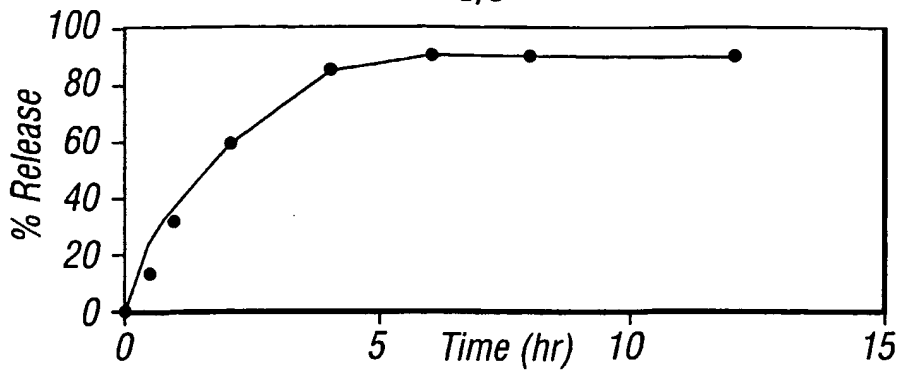

FIG. 6A

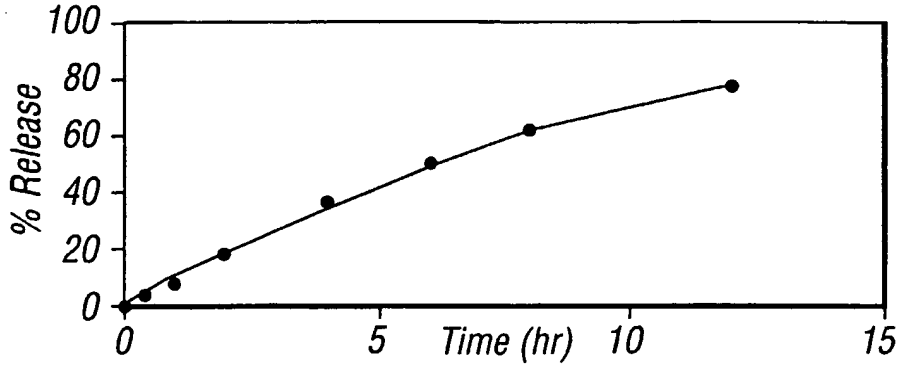

FIG. 6B

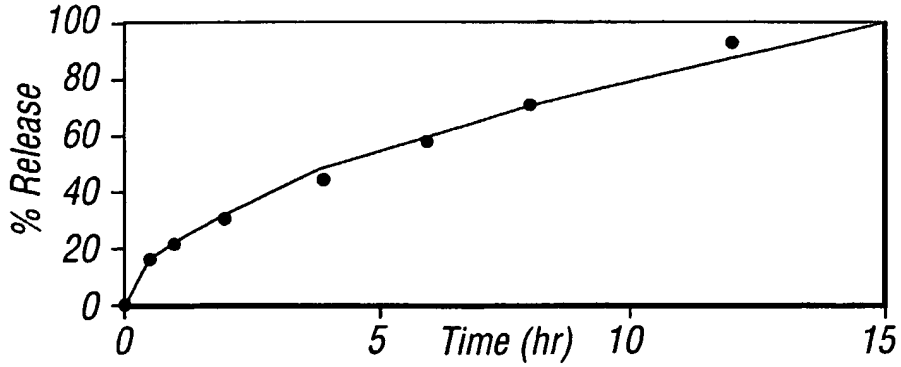

FIG. 7A

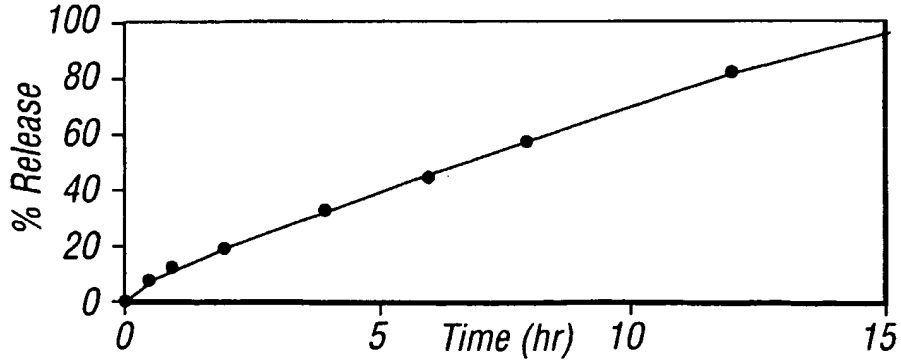

FIG. 7B

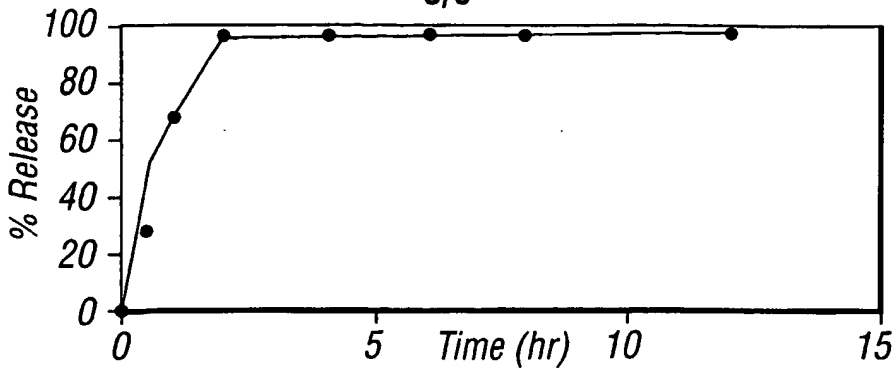

FIG. 8A

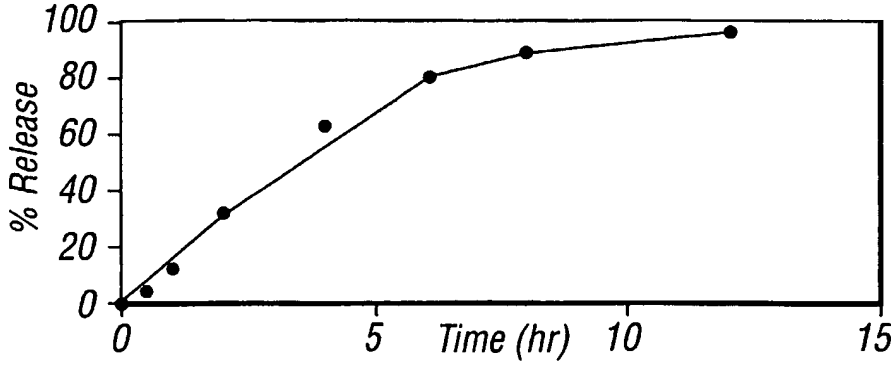

FIG. 8B

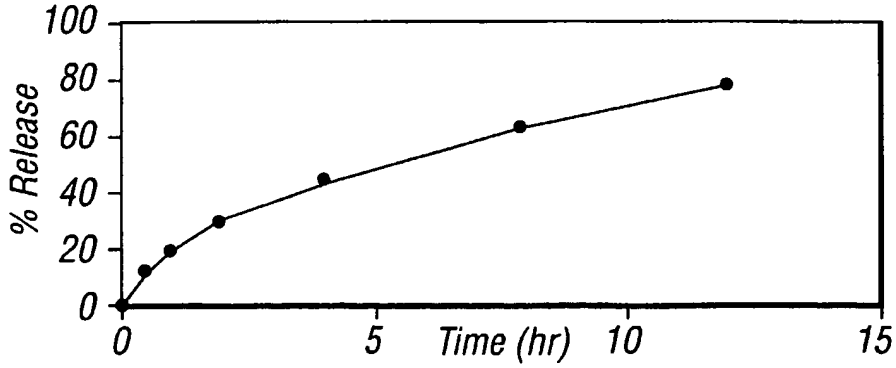

FIG. 9A

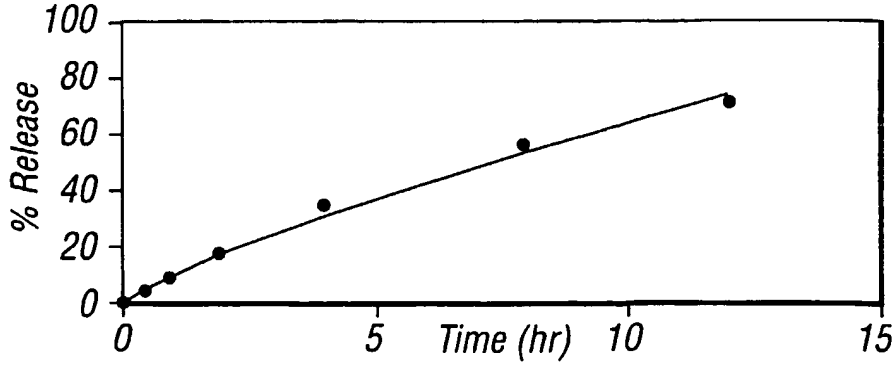

FIG. 9B

INTERNATIONAL SEARCH REPORT

PCT/GB 02/03292

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 470 603 A (STANIFORTH JOHN N ET AL) 28 November 1995 (1995-11-28)	1-4,14
Y	column 2, line 1 - line 17 column 2, line 27 - line 28 column 5, line 3,4 column 5, line 6 - line 18 column 5, line 38 - line 52	5-13,16, 17
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Y	column 3, line 1 column 6, line 25 - line 41 column 7, line 9 - line 13 claims 1-84	2-6, 8-12,16, 17

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 2002	25/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Giacobbe, S

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

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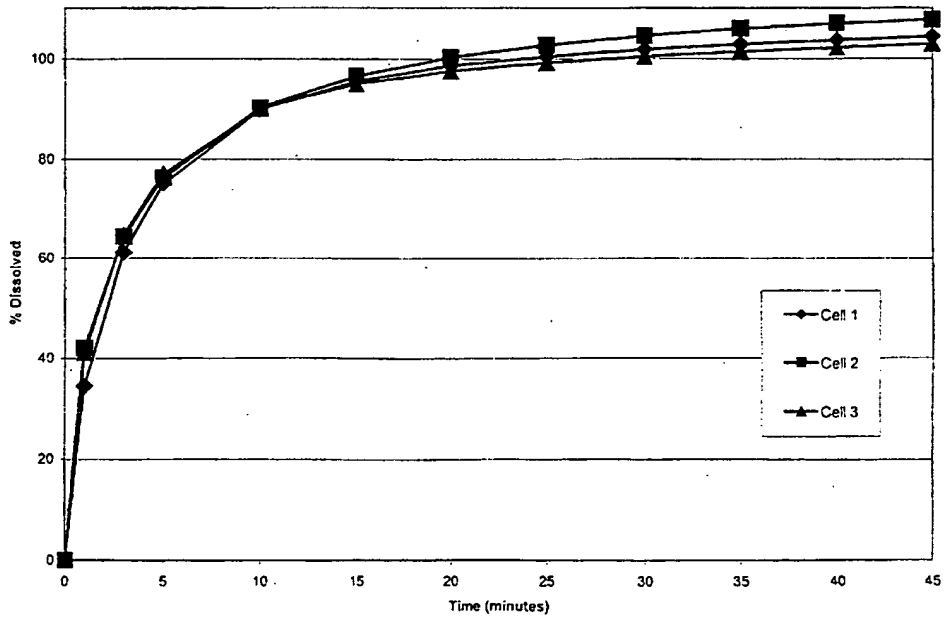
[Continued on next page]

(54) Title: FUNCTIONAL POWDERS FOR ORAL DELIVERY



(57) Abstract: In certain embodiments the invention is directed to a drug formulation for gastrointestinal deposition comprising a non-compressed free flowing plurality of particles comprising a core comprising a drug and a pharmaceutically acceptable excipient, said core overcoated with a functional coating, said drug particles having a mean diameter of greater than 10 μm to about 1 mm.

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TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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FUNCTIONAL POWDERS FOR ORAL DELIVERY

This application claims the benefit of U.S. Provisional Serial No. 60/317,522, filed September 5, 2001, the entire disclosure of which is hereby incorporated by reference.

FIELD OF THE INVENTION

[0001] The present is directed to a functional powders for oral use. Preferably, the powders are used in a multiple dose delivery device which dispenses a unit dose of the powder upon actuation.

BACKGROUND OF THE INVENTION

[0002] The most prominent mode of delivery of therapeutic agents is by the oral route by means of solid dosage forms such as tablets and capsules. Oral administration of solid dosage forms is more convenient and accepted than other modes of administration, e.g. parenteral administration. However, the manufacture, dispensing and administration of solid dosage forms are not without associated problems and drawbacks.

[0003] With the manufacture of solid dosage forms, in addition to the active agent, it is necessary to combine other ingredients in the formulations for various reasons, such as to enhance physical appearance, to provide necessary bulk for tableting or capsuling, to improve stability, to improve compressibility or to aid in disintegration after administration. However, these added excipients have been shown to adversely influence the release, stability and bioavailability of the active ingredient. The added excipients are a particular problem with drugs which require a high dose in order to provide a therapeutic effect, e.g., biphosphonate drugs. The inclusion of the additional excipient can make the final tablet extremely large which could result in esophogeal damage due to the physical characteristics of the dosage form if it is not swallowed properly. Esophogeal damage can also be caused by toxicity caused by the drug itself, if the tablet becomes lodged in the throat or has an increased transit time through the esophagus, due to its increased size.

[0004] Further, the tableting of certain drugs has many associated production problems. In particular, many drugs, e.g., acetaminophen, have poor compressibility and cannot be directly compressed into solid dosage forms. Consequently, such drugs must either be wet granulated or manufactured in a special grade in order to be tableted which increases manufacturing steps and production costs.

[0005] The adherence to good manufacturing practices and process controls is essential in order to minimize dosage form to dosage form and batch to batch variations of the final product. Even strict adherence to these practices still is not a guarantee that acceptable variation will occur.

[0006] With the high cost of industrial scale production and governmental approval of solid dosage forms, such formulations are often available in a limited number of strengths, which only meet the needs of the largest sectors of the population. Unfortunately, this practice leaves many patients without acceptable means of treatment and physicians in a quandary with respect to individualizing dosages to meet the clinical needs of their patients.

[0007] The dispensing of oral solid dosage forms also makes the formulations susceptible to degradation and contamination due to repackaging, improper storage and manual handling.

[0008] There are also many patients who are unable or unwilling to take conventional orally administered dosage forms. For some patients, the perception of unacceptable taste or mouth feel of a dose of medicine leads to a gag reflex action that makes swallowing difficult or impossible. Other patients, e.g., pediatric and geriatric patients, find it difficult to ingest typical solid oral dosage forms, e.g., due to tablet size.

[0009] Other patients, particularly elderly patients, have conditions such as achlorhydria which hinders the successful use of oral solid dosage forms. Achlorhydria is a condition wherein there is an abnormal deficiency or absence of free hydrochloric acid in the gastric secretions of the stomach. This condition hinders the disintegration and/or dissolution of oral

solid dosage forms, particularly dosage forms with high or insoluble excipient payloads. Thus, as the present dosage form is in multiparticulate form, it does need to undergo disintegration and/or dissolution to the same extent as solid dosage forms.

[0010] Flavored solutions/suspensions of some therapeutic agents have been developed to facilitate the oral administration of oral agents to patients normally having difficulty ingesting conventional solid oral dosage forms. While liquid formulations are more easily administered to the problem patient, liquid/suspension formulations are not without their own significant problems and restrictions. The liquid dose amount is not as easily controlled compared with tablet and capsule forms and many therapeutic agents are not sufficiently stable in solution/suspension form. Indeed, most suspension type formulations are typically reconstituted by the pharmacist and then have a limited shelf life even under refrigerated conditions. Another problem with liquid formulations which is not as much a factor with tablets and capsules is the taste of the active agent. The taste of some therapeutic agents is so unacceptable that liquid formulations are not a viable option. Further, solution/suspension type formulations are typically not acceptable where the active agent must be provided with a protective coating, e.g. a taste masking coating or an enteric coating to protect the active agent from the strongly acidic conditions of the stomach.

[0011] Due to the disadvantages of known drug delivery discussed above (as well as other disadvantages) there exists a need in the art for the development of a multiparticulate formulation for facilitating delivery of a wide range of therapeutic agents for gastrointestinal deposition and which minimize pulmonary deposition of materials having undesirable or unknown pulmonary toxicology but which are approved for oral delivery. In preferred embodiments, the formulation contains minimal excipient and is used in a multiple dose delivery device which dispenses a unit dose of the powder upon actuation.

OBJECTS OF THE INVENTION

[0012] It is an object of the invention to provide a multiparticulate formulation containing a therapeutic agent for gastrointestinal deposition.

[0013] It is an object of certain embodiments of the invention to provide a multiparticulate formulation having at single coating which aids in the functionality of the formulation.

[0014] It is an object of certain embodiments of the invention to provide a multiparticulate formulation having at least two coatings which aid in the functionality of the formulation.

[0015] It is an object of certain embodiments of the invention to provide a high load multiparticulate formulation with minimal use of excipient.

[0016] It is a further object of certain embodiments of the invention to provide a multiparticulate formulation with improved weight variability, from dose to dose and batch to batch.

[0017] It is a further object of certain embodiments of the invention to provide a multiparticulate formulation which has minimal change in cohesiveness in response to humidity change

[0018] It is a further object of certain embodiments of the invention to provide a multiparticulate formulation which has minimal potential for water coalescence on the surface of the particles.

[0019] It is a further object of certain embodiments of the invention to provide a multiparticulate formulation which has minimal static charge between the particles.

[0020] It is an object of certain embodiments of the invention to provide a coated multiparticulate formulation which provides a controlled or delayed release of the active

agent contained therein.

[0021] It is an object of certain embodiments of the invention to provide a coated multiparticulate formulation which tastemasks the active agent therein.

[0022] It is an object of certain embodiments of the invention to provide a coated multiparticulate formulation which contains a salivary stimulant to facilitate the swallowing of a unit dose of the multiparticulates upon oral delivery.

[0023] It is an object of the certain embodiments of invention to provide a coated multiparticulate formulation which contains a texture modifier to improve mouthfeel upon oral delivery.

[0024] It is an object of certain embodiments of the invention to provide a coated multiparticulate formulation which has a desired particle range in order to minimize pulmonary aspiration of particles.

[0025] It is an object of certain embodiments of the invention to provide a coated multiparticulate formulation which has a desired particle range in order to improve functionality of a the formulation in a multiple unit dosing device which delivers a unit dose of the formulation for oral administration or delivery upon actuation.

[0026] It is an object of certain embodiments of the invention to provide a coated multiparticulate formulation which has improved performance when used in a multiple unit dosing device which delivers a unit dose of the formulation for oral administration or delivery upon actuation.

[0027] It is an object of certain embodiments of the invention to provide a coated multiparticulate formulation which when divided into unit doses (e.g. with the use of a multiple unit dosing device) has weight uniformity of the formulation which is within the

acceptable range of the weight uniformity of equivalent dosage forms which are tablets or capsules. A detailed discussion of weight uniformity is found in the USP/NF 23/18 section 905, hereby incorporated by reference in its entirety for all purposes.

[0028] It is an object of certain embodiments of the invention to provide methods of preparation of the coated multiparticulate dosage form disclosed herein.

[0029] It is an object of certain embodiments of the invention to provide methods of preparation of the multiple unit delivery systems containing the coated multiparticulate dosage form disclosed herein.

[0030] It is an object of certain embodiments of the invention to provide methods of preparation of multiparticulate dosage forms having a desired particles range.

[0031] It is an object of certain embodiments of the invention to provide methods of administering an active agent comprising administering a coated multiparticulate dosage form disclosed herein.

[0032] It is an object of certain embodiments of the invention to provide methods of administering an active agent comprising administering a coated multiparticulate dosage form disclosed herein via the use of a multiple unit delivery systems.

[0033] The above objects of the invention, and others are achieved by virtue of the present invention, which in certain embodiments is directed to a drug formulation for gastrointestinal deposition comprising a non-compressed free flowing plurality of particles comprising a core comprising a drug, the core overcoated with a functional coating.

[0034] In certain embodiments, the invention is directed to a drug formulation for gastrointestinal deposition comprising a non-compressed free flowing plurality of particles comprising a core comprising a drug and a pharmaceutically acceptable excipient, said core

overcoated with a functional coating.

[0035] In certain embodiments, the invention is directed to a drug delivery system for delivery of a drug for gastrointestinal deposition. The system comprises a multiple unit dosing device comprising a housing and an actuator, the device containing multiple doses of the multiparticulate formulation disclosed herein, the device upon actuation delivering a unit dose of the multiparticulates for gastrointestinal deposition, the multiparticulates having a mean particle size of greater than 10 μm and preferably less than about 1mm in order to minimize pulmonary deposition of the multiparticulates and such that an effective dose of the drug cannot be delivered into the lower lung of a human patient. The drug delivery system can be used to administer the unit dose of multiparticulates into the oral cavity of the patient (*in-vivo*) or to dispense the unit dose into an intermediate receptacle (*ex-vivo*) for subsequent gastrointestinal deposition. Oral drug delivery systems and devices for oral powders are disclosed in PCT/IB01/00251, hereby incorporated by reference in its entirety for all purposes.

[0036] In certain embodiments, the invention provides a method of preparing a drug delivery system for delivering multiple doses of a drug for gastrointestinal deposition comprising preparing a multiparticulate drug formulation as disclosed herein in a manner wherein the drug particles when placed in the oral cavity and swallowed are deposited to the gastrointestinal tract and not deposited in any substantial amount to the lungs; and placing multiple unit doses of said drug formulation in a device which meters a single unit dose for delivery.

[0037] In certain embodiments, the invention provides a method of treating a patient in need of multiple doses of a drug for gastrointestinal deposition comprising preparing multiparticulates comprising drug particles as disclosed herein in a manner wherein the drug particles when placed in the oral cavity and swallowed are deposited to the gastrointestinal tract and not deposited in any substantial amount to the lungs; placing multiple unit doses of the multiparticulates in a device which meters a single unit dose for delivery; and either (a)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

into the gastrointestinal tract of a mammal.

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DETAILED DESCRIPTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

propionate, cellulose acetate butyrate and mixtures thereof.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

Example 1

Controlled-release Propranolol HCl

Step 1: Granulation of Propranolol HCl

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

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

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

Step 2: Spray coating with Surelease

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

Step 3: Overcoating with LustreClear

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

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

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

Example 2

Enteric Coated Indomethacin

Step 1: Granulation of Indomethacin

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

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

Step 2: Spray coating with Sureteric

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Step 3: Overcoating with LustreClear

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

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

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

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

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

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

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

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

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

Example 3

Controlled-release Clarithromycin

Step 1: Granulation of Clarithromycin

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

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

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

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

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

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

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

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

Step 3: Overcoating with LustreClear

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

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

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

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

Example 4

Controlled-release enteric-coated Clarithromycin

Step 1: Granulation of Clarithromycin

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

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

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

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

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

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

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

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

Step 3: Spray coating with Sureteric

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

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

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

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

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

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

Step 4: Overcoating with Aquacoat CPD

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

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

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

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

Example 5

Taste-masked Acetaminophen

Step 1: Granulation of Acetaminophen

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

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

Step 2: Spray coating with Surelease

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

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

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

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

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

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

Example 6

Taste-masked Verapamil Hydrochloride

Step 1: Granulation of Verapamil

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

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

Step 2: Spray coating with Eudragit RD-100

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

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

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

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

Step 3: Overcoating with neutralised Carbopol 971

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

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

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

Example 7

Taste-masked Amoxycillin

Step 1: Granulation of Amoxycillin

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

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

Step 2: Spray coating with Opadry AMB

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

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

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

Step 2: Overcoating with Surelease

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

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

Example 8

Enteric-coated Mesalazine

Step 1: Granulation of Mesalazine

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

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

Step 2: Spray-coating with Aquacoat CPD

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

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

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

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

Step 3: Overcoating with Xanthan Gum

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

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

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

Example 9

Controlled-release Sodium Valproate

Step 1: Granulation of Sodium Valproate

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

Step 2: Spray coating with Surelease

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

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

Stage 3: Overcoating with Eudragit L30 D-55

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

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

Example 10

Wet-granulated Indomethacin

Step 1: Granulation of Indomethacin

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

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

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

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

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

Table 1

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

Example 11

Enteric Coated Melt Granulated Indomethacin Formulation

Step 1: Melt Granulation of Indomethacin

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

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

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

Table 2

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

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

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

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

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

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

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

Table 3

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

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

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

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

Table 4

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

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

Example 12

Melt-granulated Sureteric Coated Indomethacin Formulation

Step 1: Sureteric Coating of Indomethacin

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

Step 2 Melt Granulation

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

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

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

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

Table 5

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

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

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

Table 6

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

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

Example 13

Indomethacin Wet Granulation with a 15% Sureteric Enteric Coat

Step 1: Wet Granulation of Indomethacin

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

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

Step 2: Spray Coating of Wet-Granulated Indomethacin

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

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

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

Table 7

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

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

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

Table 8

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

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

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

Example 14

Sureteric and LustreClear Coated Indomethacin

Steps 1 and 2: Sureteric Coating of Indomethacin

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

Step 3: Overcoating with LustreClear

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

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

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

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

Table 9

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

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

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

Table 10

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

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

Example 15

Lab Scale melt granulation of Indomethacin and PEG 6000

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

Example 16

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

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

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

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

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

We Claim:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

FIG. 1

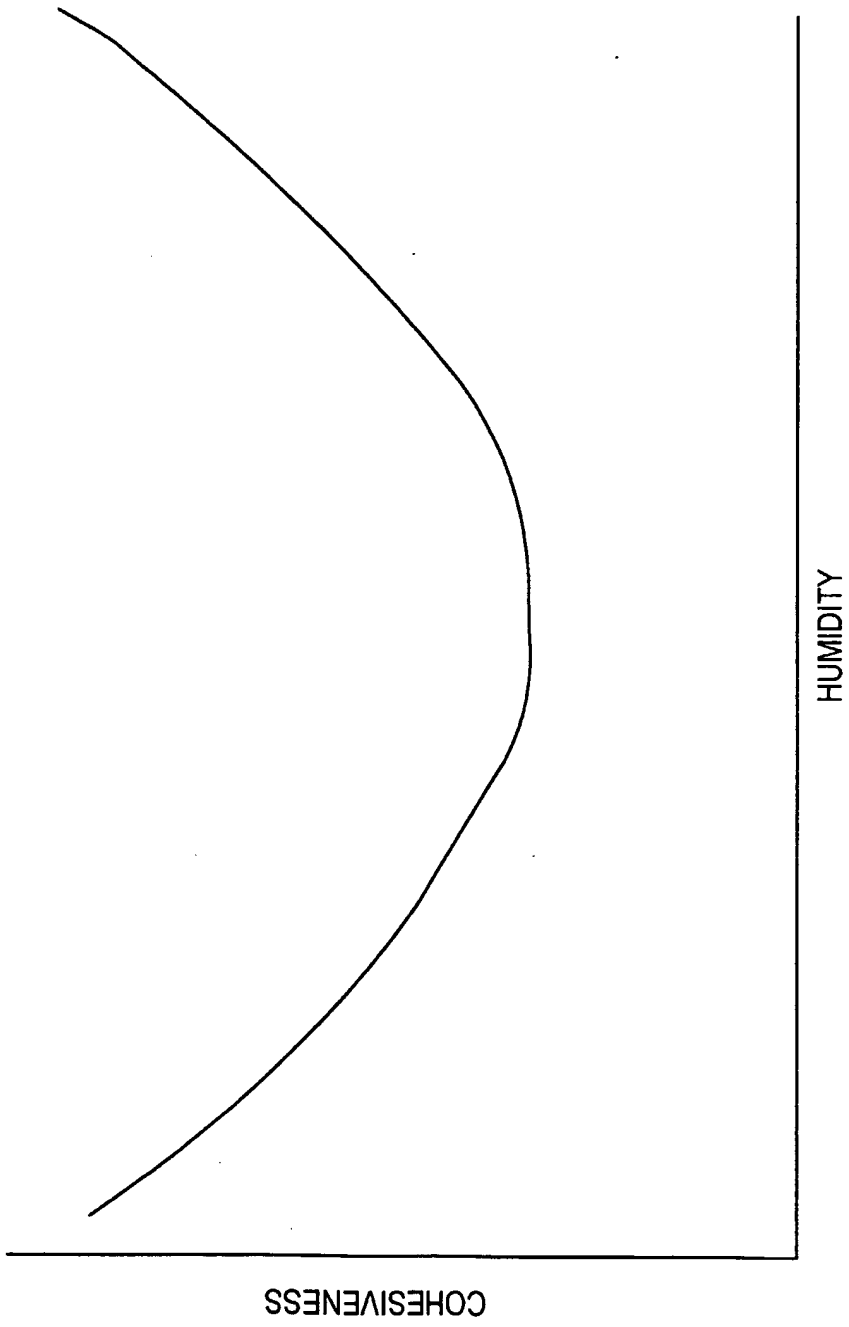


FIG. 2

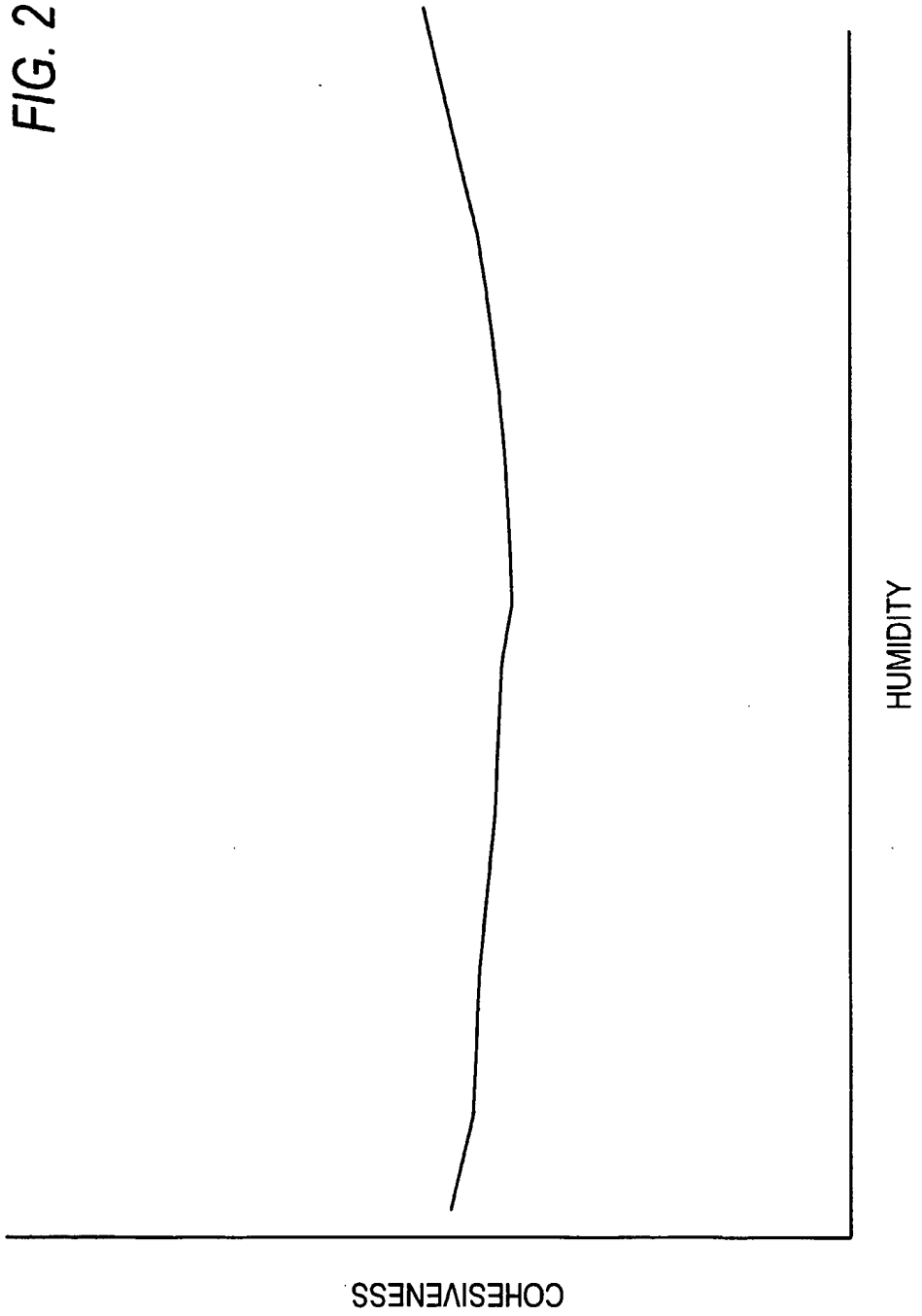


FIG. 3

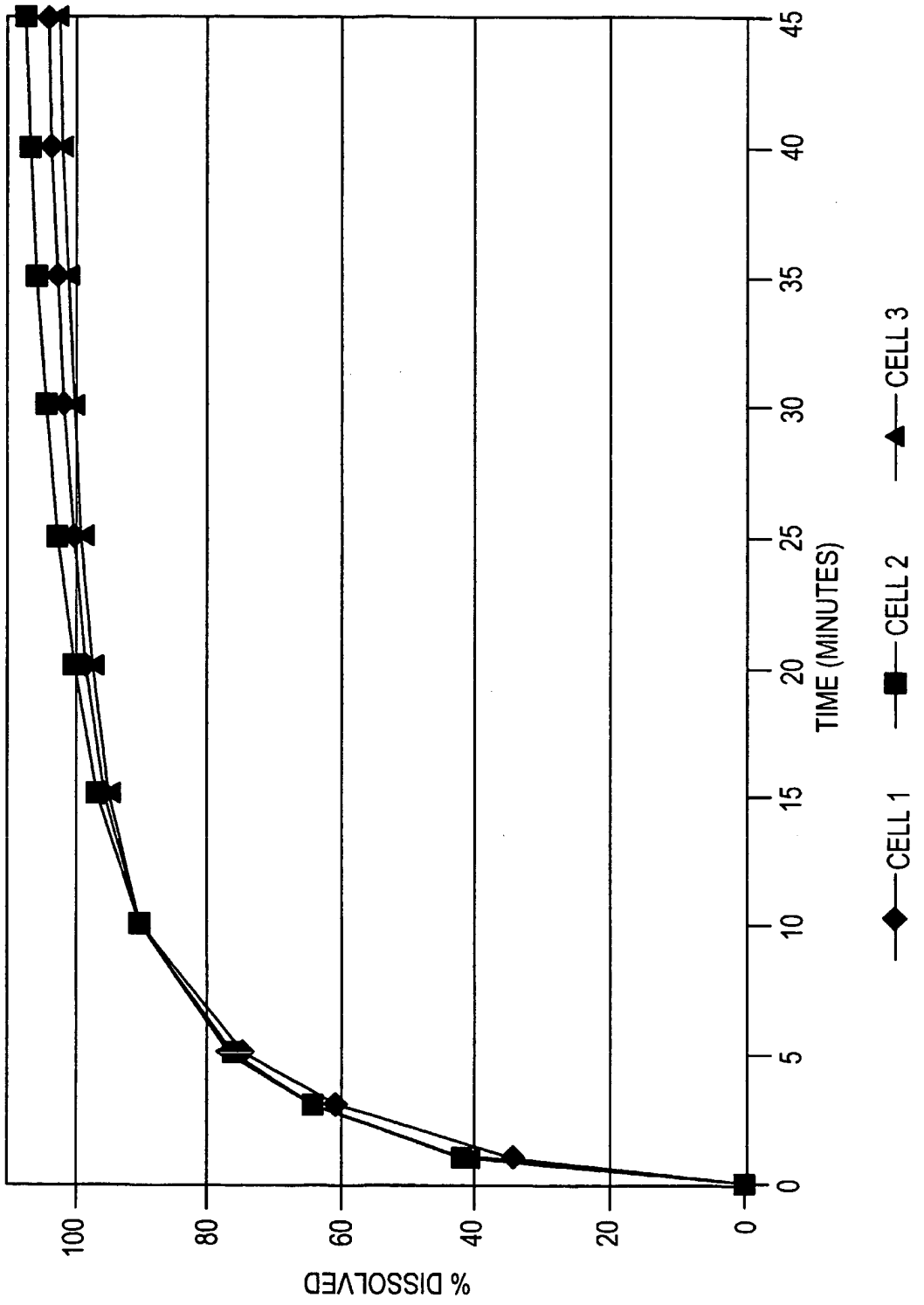


FIG. 4

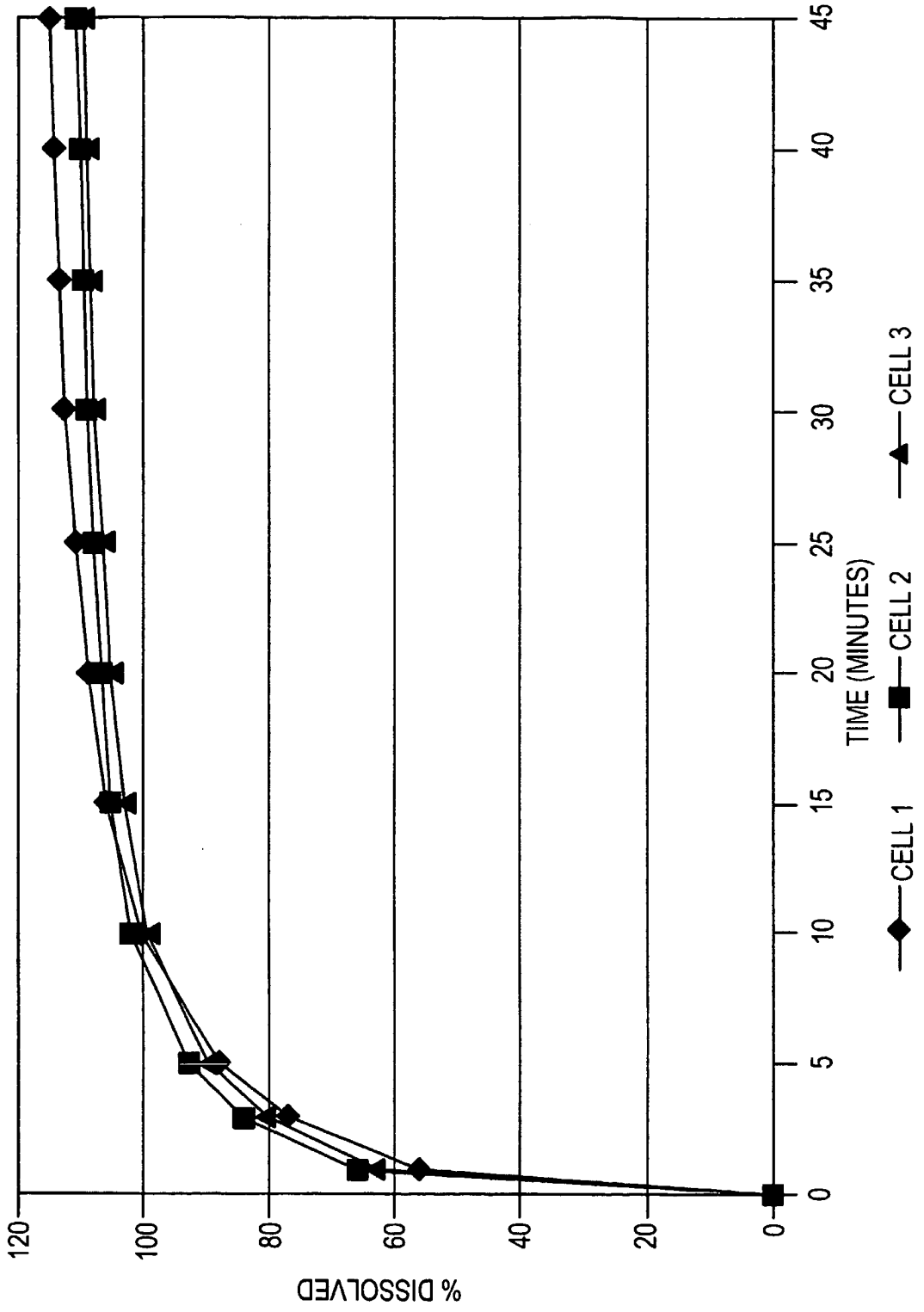


FIG. 5

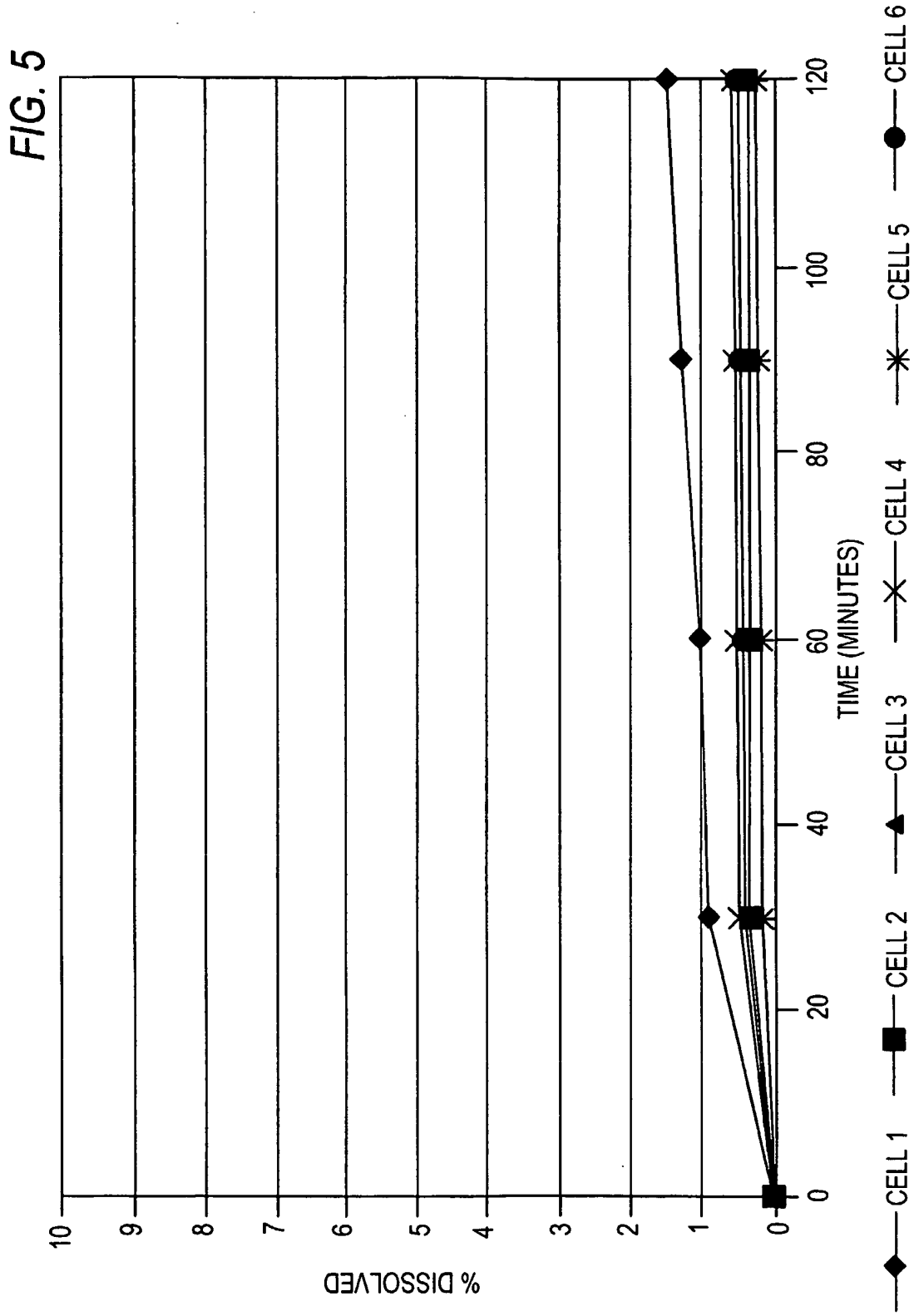


FIG. 6

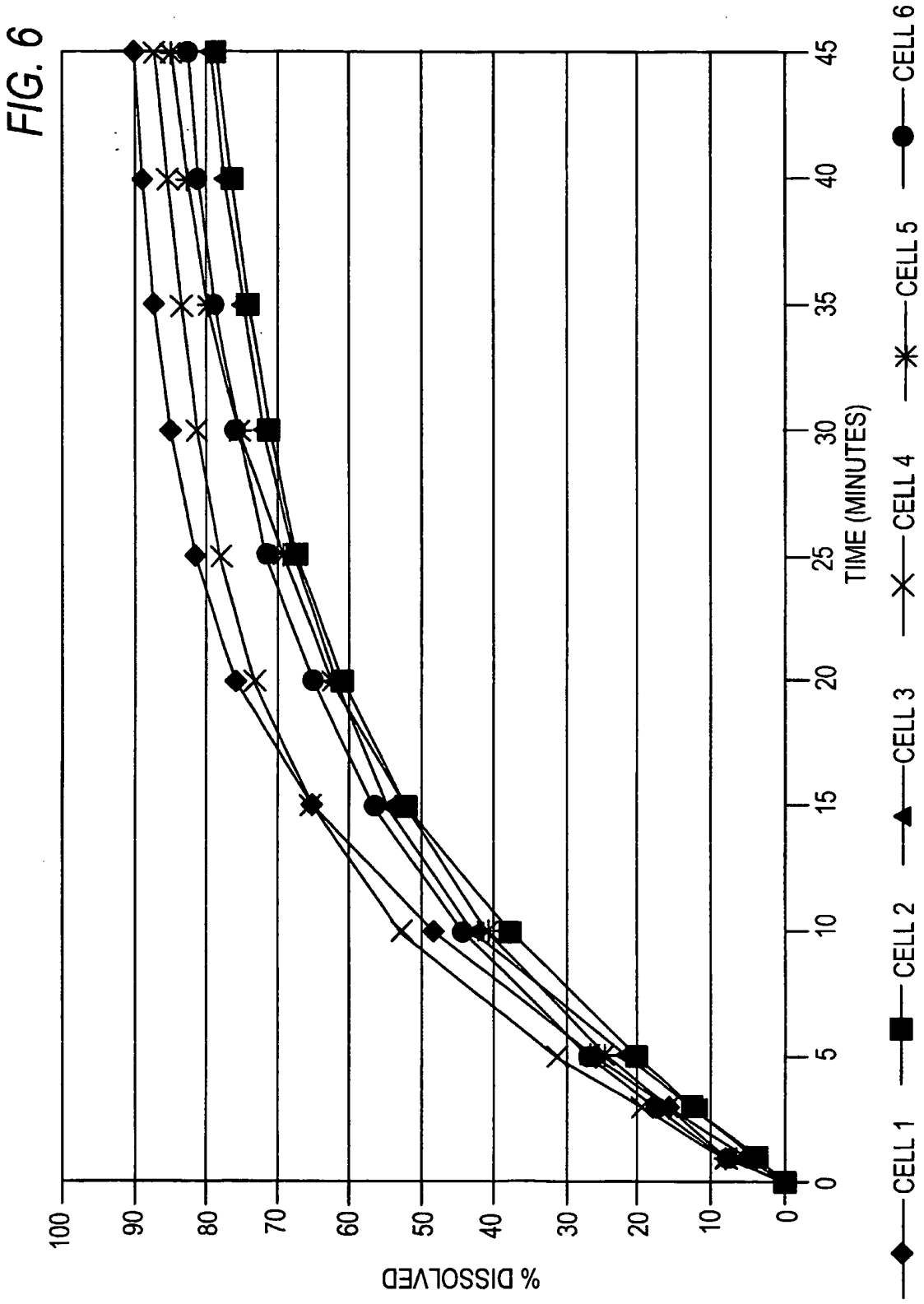


FIG. 7

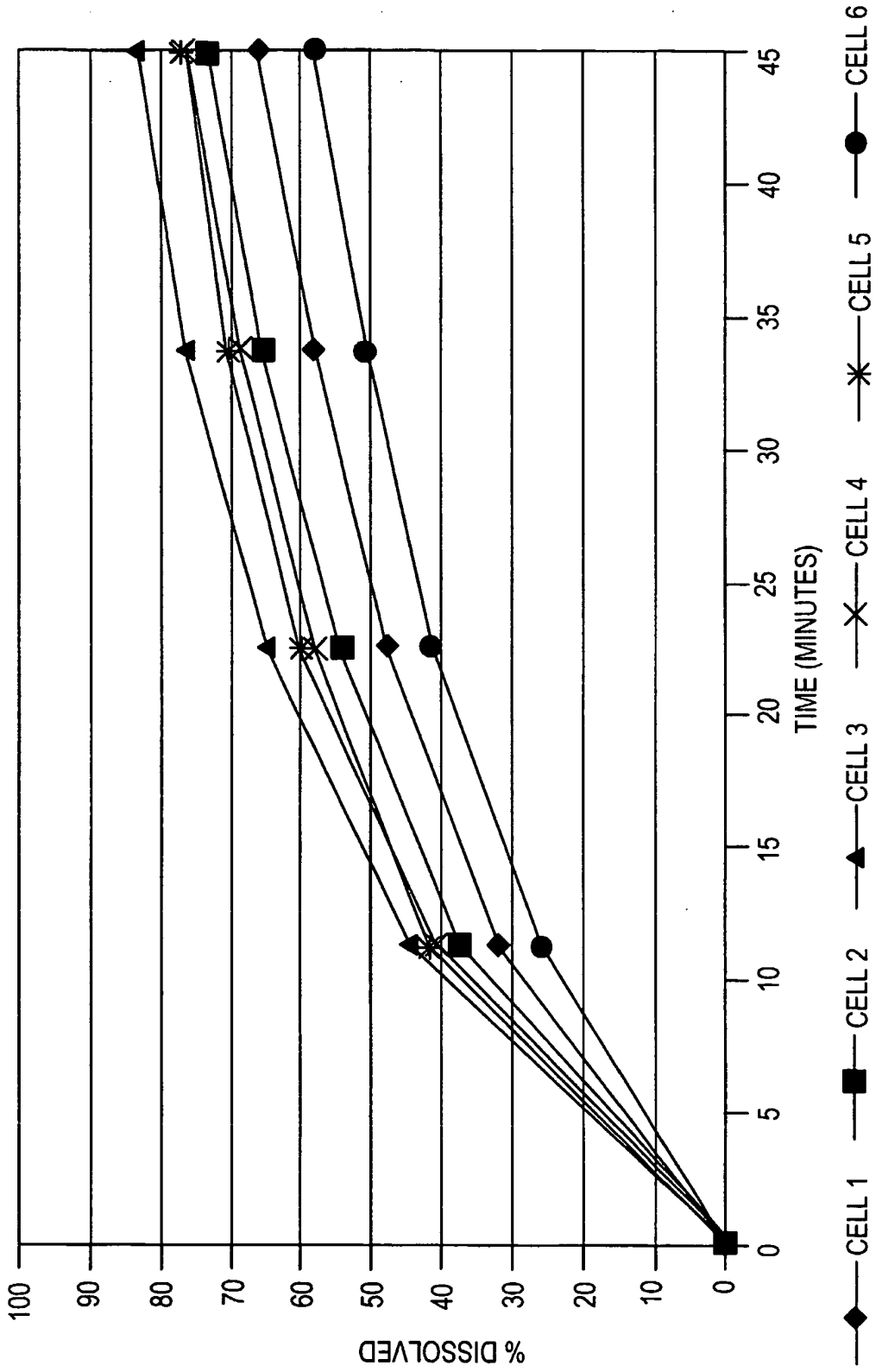


FIG. 8

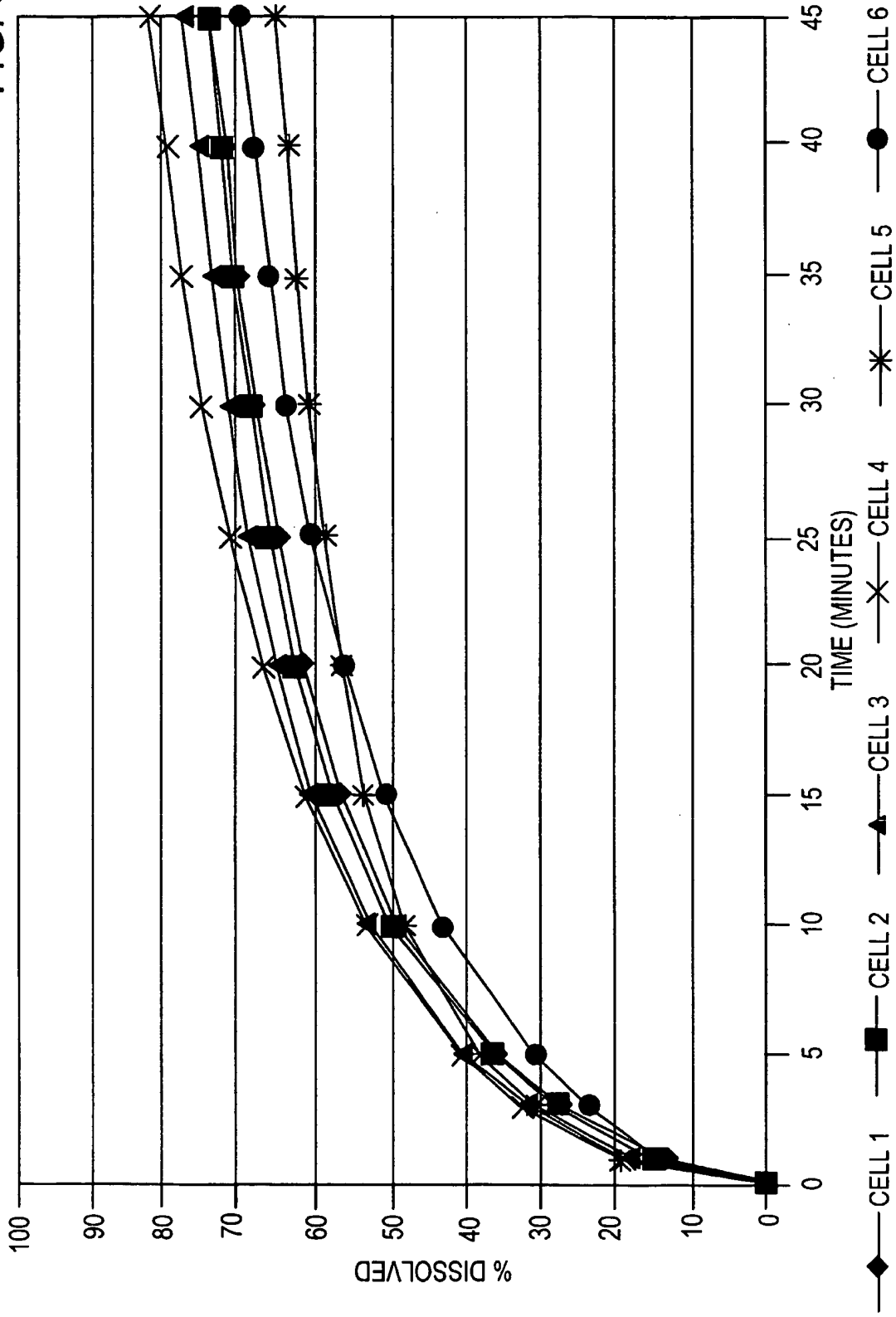


FIG. 9

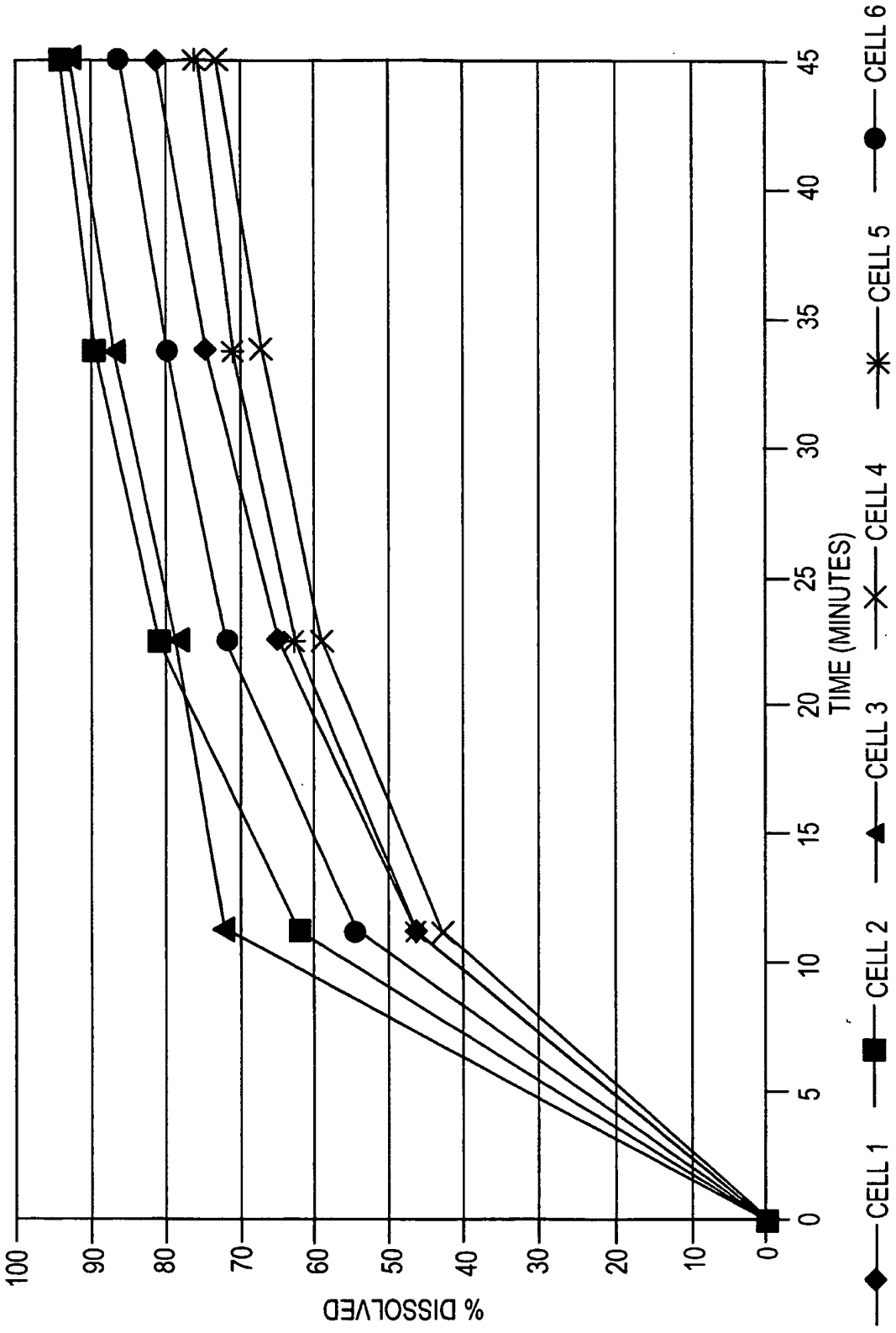


FIG. 10

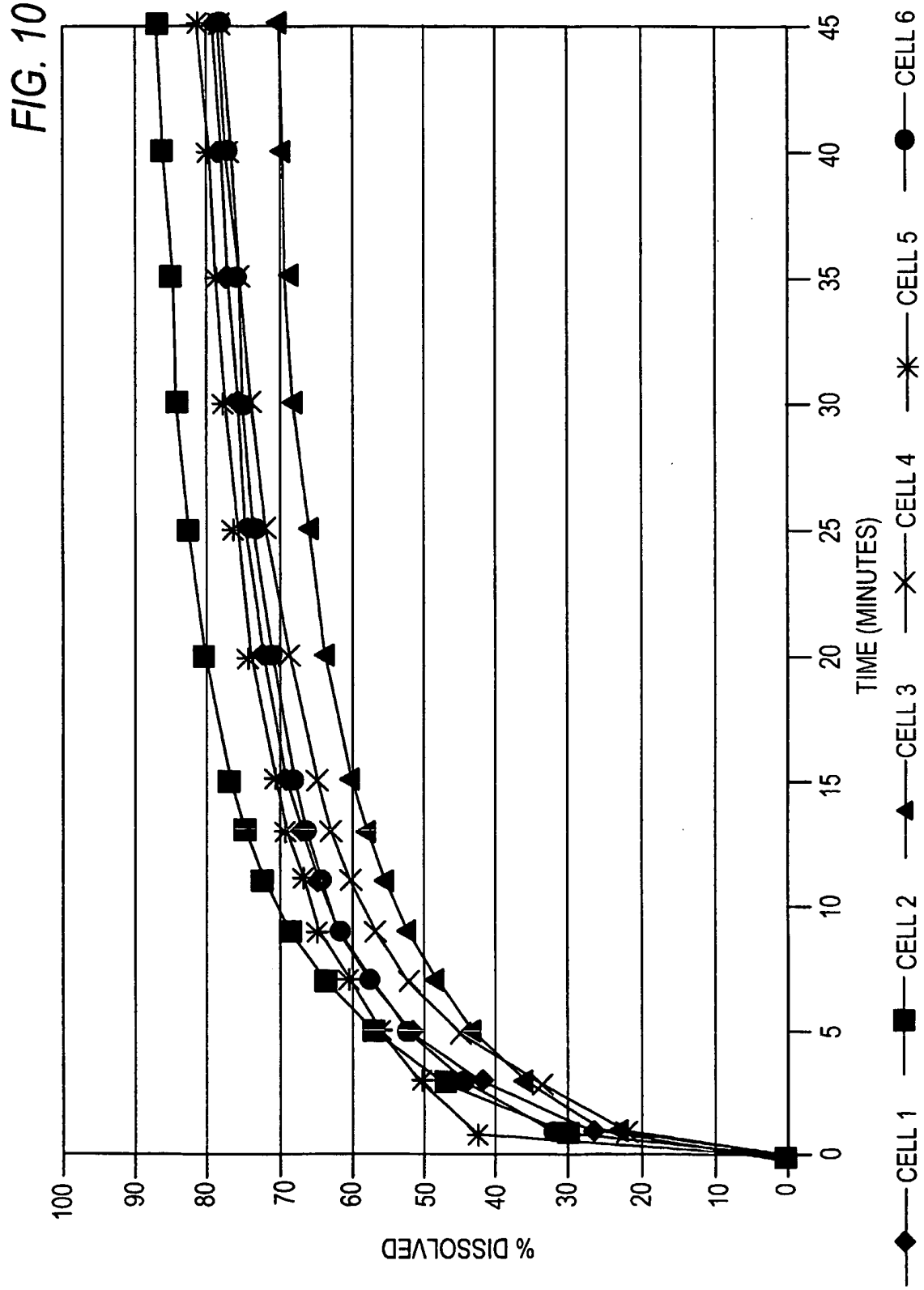


FIG. 11

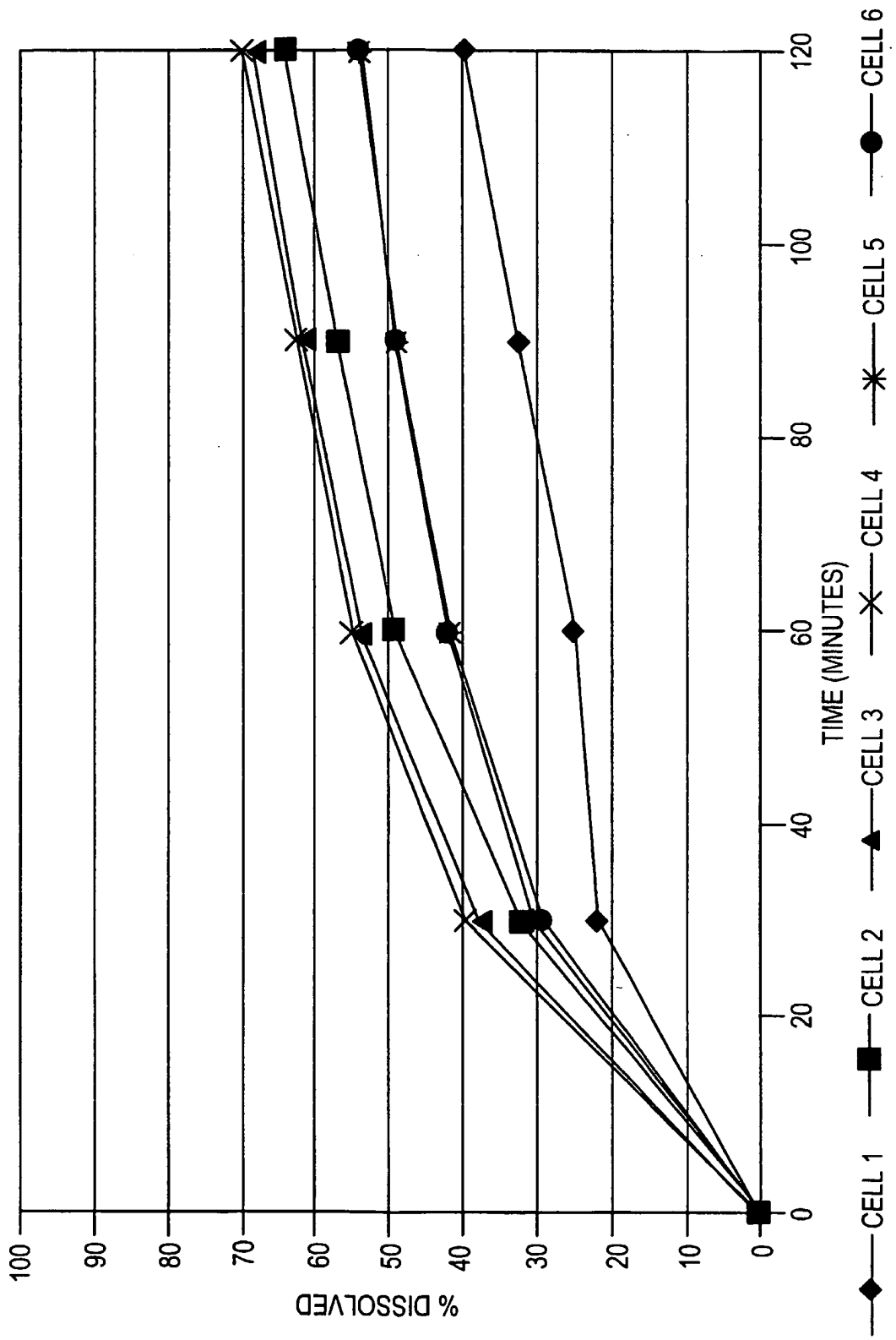
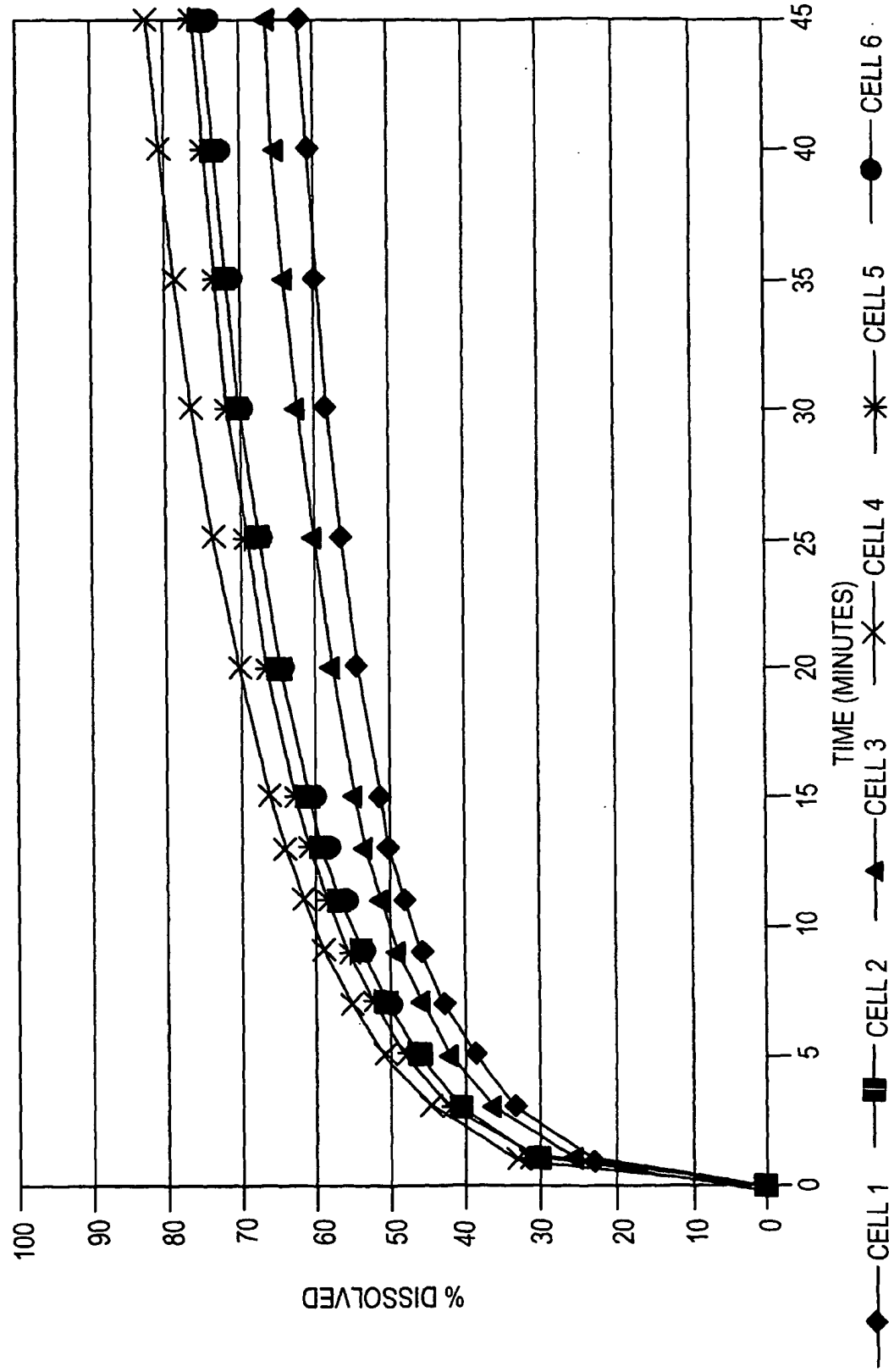


FIG. 12



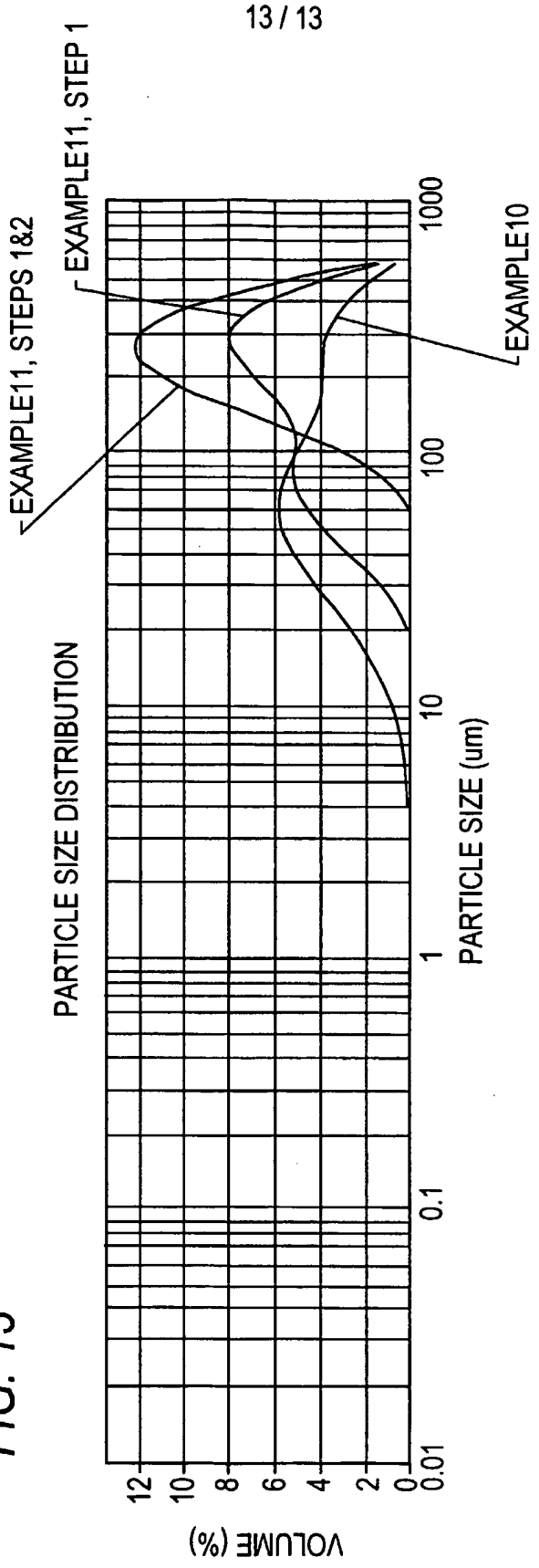


FIG. 13

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

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

WO 2003/026564 A3

Pharmaceutical compositions for the treatment of urinary disorders.

Technical field

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

Background of the invention

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

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

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

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

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

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

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

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

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

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

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

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

Summary of the invention

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Description of the invention

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

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

and

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Examples

Example 1

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

Example 2

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

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

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

Example 3

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

Example 4

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

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

CLAIMS

1. A pharmaceutical composition comprising a pharmaceutically effective combination of

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

which depression is concomitant with said urinary disorder.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(iii) instructions for use of the kit.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01748

A. CLASSIFICATION OF SUBJECT MATTER

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

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

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

SE,DK,FI,NO classes as above

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

CHEM. ABS DATA, EPO, INTERNAL, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01748

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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

International application No.
PCT/SE 02/01748

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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

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