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(54) **Titre : SYSTEME THERAPEUTIQUE A LIBERATION CONTROLEE A MONOCOUCHE**
(54) **Title: SINGLE LAYERED CONTROLLED RELEASE THERAPEUTIC SYSTEM**

(57) **Abrégé/Abstract:**
The present invention relates to a controlled release therapeutic system, a process for the manufacturing the same, as well as a dosage form containing said controlled release therapeutic system. The controlled release therapeutic system comprises: an inert core; and a coating layer disposed over the inert core, said coating layer comprising: a release controlling polymeric matrix in which an active pharmaceutical agent is distributed therein.

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(54) Title: SINGLE LAYERED CONTROLLED RELEASE THERAPEUTIC SYSTEM

(57) Abstract: The present invention relates to a controlled release therapeutic system, a process for the manufacturing the same, as well as a dosage form containing said controlled release therapeutic system. The controlled release therapeutic system comprises: an inert core; and a coating layer disposed over the inert core, said coating layer comprising: a release controlling polymeric matrix in which an active pharmaceutical agent is distributed therein.

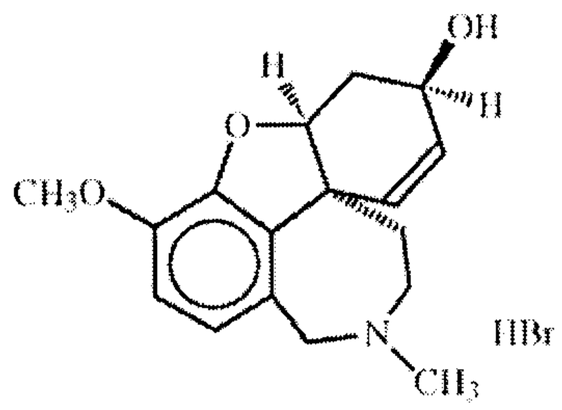
SINGLE LAYERED CONTROLLED RELEASE THERAPEUTIC SYSTEM

FIELD OF THE INVENTION

The present invention relates to a pharmaceutically acceptable oral dosage form. More specifically, it relates to a controlled release therapeutic system for use in said dosage forms.

BACKGROUND OF THE INVENTION

Galantamine hydrobromide, a reversible competitive acetylcholinesterase inhibitor, is chemically designated as (4aS,6R,8aS)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-ef][2]benzazepin-6-ol hydrobromide, It has an empirical formula of $C_{17}H_{21}NO_3 \bullet HBr$ and a molecular weight of 368.27. The structural formula for galantamine hydrobromide is:



Galantamine hydrobromide is usually used for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type. Clinical experiments in Alzheimer's disease have been reported by R. Bullock, *Exp. Rev. Neurother.* 4, 153-163 (2004).

In the same vein, U.S. Patent No. 4,663,318 (Davis), corresponding to European Patent No. 0 236 684, is directed to a method for treating Alzheimer's disease and related dementias which comprises administering to mammals, including humans, an effective Alzheimer's disease cognitively-enhancing amount of galantamine or a pharmaceutically acceptable acid addition salt thereof.

Many formulations containing galantamine hydrobromide have been reported. One such formulation is described in United States Patent No. 7,160,559 (McGee *et al.*), corresponding to Canadian Patent No. 2,358,062, which is directed to a multi-layered

particle comprising (a) a central, rounded or spherical core, (b) a layer or a coating film of a water-soluble polymer and galantamine hydrobromide (1:1), (c) optionally a seal-coating polymer layer and (d) a release rate controlling membrane coating.

A drawback associated with certain dosage forms (i.e. tablets, capsules, etc.) containing, for example, galantamine hydrobromide, is that they require several coating layers (i.e. protective, enteric layers and enstein coating layers); such being required to protect the inner core, usually in the form of spheres or particles from degradation or to modify the release of the active substances. It thus becomes apparent that the more layers the pharmaceutical manufacturer applies onto the inner core, the longer the processing time is for preparing the dosage form. In this connection, the Applicant has developed a simple method of manufacturing an extended release formulation of active substance, for example, galantamine hydrobromide, that avoids long processing times by making use of a single layer of coating.

More specifically, the Applicant has developed a controlled release therapeutic system, containing an active substance, for example, galantamine hydrobromide, and is thus capable of modifying the release of galantamine. Such is achieved by applying directly on the inert core (i.e. microcrystalline cellulose spheres) the active substance and a release controlling agent. The desired drug release profile was achieved and stable formulations were developed using the controlled release therapeutic system according to the present invention.

United States Patent No. 4,261,971, issued to AB Hassle on April 14, 1981, discloses a gastro-resistant formulation obtained by coating the surface of an inert core by a solution layering process. More particularly, this patent is directed to a body (i.e. a bead) having a core made up of a pharmaceutically indifferent material, and on the core a layer made up of a composition comprising a cardiac glycoside and an anionic carboxylic polymer being difficultly soluble or insoluble below a given pH value in the interval of pH 4-7.5, but being soluble at a pH above such given value.

In light of the above, there is still a need in the art for a formulation for extended release of an active substance, such as galantamine, where the processing of the formulation requires fewer manufacturing steps, and where the formulations can provide release profiles of up to 24 hours. United States Patent No. 4,261,971 uses a cardiac glycoside

as an active agent and also uses an anionic carboxylic polymer in the proposed formulations which imparts certain solubility properties. The present invention proposes a substantially different type of formulation which is applied directly on the core.

SUMMARY OF THE INVENTION

Thus, the present application seeks to overcome the shortcomings of the prior art by providing a controlled release therapeutic system comprising:

- an inert core; and
- a coating layer disposed over the inert core, said coating layer comprising:
    - a release controlling polymeric matrix in which an active pharmaceutical agent is distributed therein.

Preferably, the controlled release therapeutic system is made of a single layer disposed over an inert core.

Another aspect of the present invention is to provide a solid oral pharmaceutical dosage form that is therapeutically beneficial to patients.

A further aspect of the present invention is to provide a solid oral pharmaceutical dosage form that is stable, cost effective to produce and which has a process of manufacture which is industrially feasible for commercialization.

Yet another object of the invention is to provide a process of manufacturing such a solid oral pharmaceutical dosage form.

There are a number of advantages associated with the present invention, namely:

1. As there is only one layer of coating, containing the matrix of active pharmaceutical ingredient ("API") and release controlling polymer on inert spheres, it is a cost effective, continuous and faster process, as opposed to other existing formulations, which make use of numerous coating layers;

2. The present formulation makes use of non-hazardous solvents (i.e. purified water), as opposed to dichloromethane and ethanol which are evaporated during coating process in existing formulations of the prior art. The formulation according to the present invention is therefore environment friendly and cost effective compared to existing formulation;

3. The present invention can be used to manufacture sustained release formulations which have a release profile of up to 24 hours; and

4. Drugs having varying aqueous solubility can be formulated by this approach.

Other embodiments and further scope of applicability of the present invention will become apparent from the detailed description and examples given hereinafter.

DETAILED DESCRIPTION OF THE INVENTION

As aforementioned, the present invention is directed to a controlled release therapeutic system comprising:

- an inert core; and

- a coating layer disposed over the inert core, said coating layer comprising:

    - a release controlling polymeric matrix in which an active pharmaceutical agent is distributed therein.

Preferably, the inert core is made up of a water-soluble or swellable material, and may be any such material that is conventionally used as cores or any other pharmaceutically acceptable water-soluble, water-swellable or water insoluble material made into beads or pellets. Conventional beads are known to be in the shape of spheres and are generally made of sucrose/starch (Sugar Spheres NF), sucrose crystals, or extruded and dried spheres typically comprised of excipients such as microcrystalline cellulose and/or lactose. The core unit according to the present invention can be made of microcrystalline cellulose, cellulose, starch, lactose, sugar, sugar alcohols, or a combination thereof and/or any pharmaceutically acceptable inert material.

The therapeutic system is for oral administration as swallowable, chewable, buccal delivery of a drug or its pharmaceutically active salts, comprising units coated with the drug dispersed in a continuous matrix. The matrix by itself is insoluble but shall effectively release drug throughout the alimentary tract. Alternately, the matrix may be comprised of a bio-degradable natural or synthetic polymer material accepted as being generally recognized as safe ("GRAS") for use in pharmaceutical compositions.

The matrix permits the release of the drug at predetermined time intervals thereby allowing once-a-day administration of the composition. The therapeutic system comprises units coated with single layer of drug-polymer dispersion as a continuous

matrix with similar thickness, however, all units as an assembly may be chosen to release definite amount of drug from the dosage form upon administration.

Alternately, some element of plurality of thickness to drug-polymer layer may also be desired to have an effective pharmacological response.

As for the coating layer, it is preferably made up of a release controlling polymeric continuous matrix in which an active substance is distributed therein.

The release-controlling polymeric matrix may be made up of at least one hydrophobic or at least one hydrophilic polymer, or combinations thereof.

The hydrophobic polymers that can be used could be, though are not limited to, the following: alkylcellulose, polyalkyl acrylate, methacrylic acid and acrylic acid esters, polydiene, polyolefin, polylactone, polysiloxane, polyoxirane, polystyrene, polypyridine and other polymers which are capable of controlling the release of active pharmaceutical ingredients.

The hydrophilic polymers that can be used could be, though are not limited to, the following: hydroxyalkyl cellulose, poly alkyl (acrylic) acid and its salt, methacrylic acid and acrylic acid esters, povidone, polyacrylamide, poly(N,N-dimethyl acrylamide), poly(N-isopropyl acrylamide), polyethylene glycol) and polyethylene oxide, poly(methyl vinyl ether), poly(styrene sulfonic acid) and its salt, poly(vinyl alcohol), poly(2-vinyl N-methyl pyridinium iodide), poly(4-vinyl N-methyl pyridinium iodide), poly(N-vinyl imidazole-quaternized with CH_3I), poly(ethylene imine), poly(vinylamine) and poly(vinyl carboxylic acid amide), polyethylene oxide and polyethylene glycol graft polymer, polyvinyl alcohol and polyethylene glycol graft polymer, polyethylene glycols, natural or synthetic gum, alginic acid and its derivatives or salts, carbomers, chitosan, copovidones.

If an alkylcellulose polymer is to be used, this polymer could be selected from the group consisting of: ethylcellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose methyl cellulose, and sodium carboxymethyl cellulose.

According to the present invention, the release controlling polymeric matrix can optionally include one or more additional excipients, for example, plasticizing agents, anti-adherents, binders and pore forming agents. Other known pharmaceutical agents,

such as diluents, lubricants, etc., could also be incorporated into the release controlling polymeric matrix.

Suitable choices of plasticizing agents include those that are capable of lowering the glass transition temperature of release controlling polymer as well as any other agent included therein. For example, the plasticizing agents could be, though are not limited to, the following: triethyl citrate, triacetin, dibutyl phthalate, diethyl phthalate, polyethylene glycol, propylene glycol, castor oil, dibutyl sebacate, diethyl sebacate and compounds which can act as a plasticizer.

The anti-adherent according to the present invention is capable of reducing aggregate formation and improving the coating process. For example, the anti-adherent could be, though are not limited to, the following: colloidal silicon dioxide, talc, starch, glyceryl monostearate, magnesium stearate, stearic acid and its salts, magnesium aluminum silicate and compounds which can act as an anti-adherent.

As aforementioned the release-controlling polymeric matrix can also include other agents, such as a binder, pore forming agent, absorption enhancers, colors, flavours, bulking agents, and like excipients, as is necessary to shape the therapeutic system as an effective dosage form for administration to patients.

In this connection, the binder or pore forming agent is preferably a water soluble or water swellable pharmaceutically acceptable excipient. Suitable choices of binder or pore forming agents include, for example, povidone, hydroxypropylmethyl cellulose (HPMC), hydroxypropylcellulose (HPC), gum, methylcellulose, sodium carboxymethyl cellulose and its salts, alginates, sugar and sugar alcohols, water soluble organic and inorganic salts and other compounds which can act as a binder or pore forming agent, a anti-adherent or combination thereof.

The controlled release therapeutic system according to the present invention favors use of both polar and non-polar active substances. The active substance is a pharmaceutically acceptable active compound. The active substances or their salts may be present alone or in combination with other pharmaceutical active moieties to present to produce the desired therapeutic monitoring in the patients. In a preferred embodiment of the invention, the active substance is a cholinesterase inhibitor. Examples of cholinesterase inhibitors include ambenonium chloride, distigmine bromide,

eptastigmine, galantamine, phenserine, rivsastigmine, tacrine, and their pharmaceutically acceptable salts. Usually, the active substance to polymeric matrix ratio is 1: 0.1 to 0.1:100.

The preferred active substance in the controlled release therapeutic system of the present invention is galantamine and/or its pharmaceutically acceptable salts. More preferably, the active substance is galantamine hydrobromide.

Another aspect of the invention is to provide a pharmaceutical therapeutic system, more particular as bead, having similar thickness of the drug-polymer matrix, as a single layered controlled release composition with the drug distributed in a continuous matrix.

Preferably, the dosage from is a solid dosage form, such as a tablet, a capsule, or the like, administered as mucosal and / or a non-mucosal orally administered composition. The dosage form according to the present invention is capable of releasing a pharmaceutically acceptable active compound for up to 24 hours.

Manufacturing process

The stable oral pharmaceutical composition according to the present invention can be obtained by a process, which generally comprises the following steps of:

1) providing inert spheres;

2) preparing a dispersion or solution comprising:

- a mixture of release controlling polymer;

- an active substance; and

- optionally a plasticizer and/or anti-adherent and/or binder/pore forming agent using a pharmaceutically acceptable solvent or combinations of solvents;

3) coating the inert spheres with said dispersion or solution.

The process according to the present invention may further comprise a step of providing a top coat to the single layered coated inert sphere. Optionally, there can be a step of incorporating a pharmaceutically active ingredient in the top coat.

The process can preferably comprise a step of incorporating a film forming agent and/or a plasticizer and/or an anti-adherent in the top coat. Also preferably, there can be step of incorporating a release controlling agent in the top coat.

The process of the present invention is preferably performed by fluidized bed coating or powder layering.

As aforesaid, the stable oral pharmaceutical composition according to the present invention can be obtained by a process, which generally comprises the following steps:

- preparing a dispersion or solution containing a mixture of, in a pharmaceutically acceptable solvent or combination of solvents, a release controlling polymer, an active substance and optionally at least one agent (i.e. a plasticizing, an anti-adherent and/or binder/pore forming agent); and

- coating inert cores (or spheres) with said dispersion or solution by using a fluidized bed coating or powder layering.

According to a preferred embodiment of the present invention, the coated spheres are optionally mixed with an anti-adherent agent.

The single layered controlled release bead is optionally coated with a top coat. According to the present invention, the top coat may contain:

i) pharmaceutically acceptable active ingredients which may release immediately as a loading dose; and/or

ii) a film forming agent and/or plasticizer and/or anti-adherent; and/or

iii) a release controlling agent which may further control the release pharmaceutically acceptable active ingredient contained with the present invention.

EXAMPLES

The following examples are illustrative of the wide range of applicability of the present invention and are not intended to limit its scope.

All of the percentages given hereinabove and below are percentages by weight.

The following are examples of various formulations of galantamine hydrobromide extended release capsules (8, 16 and 24 mg).

Example 1:

Serial no.	Ingredients	%w/w
1.	Galantamine Hydrobromide (API)	9.58
2.	Surelease E-7 19040 clear** (Dry quantity)	28.74
3.	Purified Water*	q.s.
4.	Microcrystalline cellulose spheres	61.68
	Total	100.00

q.s.: quantity sufficient

* Removed during processing

** Surelease E-7 19040 is colloidal aqueous dispersion of ethyl cellulose containing 25%w/w solids.

Process:

1. 23.3 g of active pharmaceutical ingredient (API) was dissolved in 910 g of purified water with stirrer.
2. 279.6 g of Surelease E-7 19040 was mixed with the solution of step 1 for 15 minutes with continuous stirring.
3. 150 g of MCC spheres were spray coated with dispersion of step 2 in fluid bed coating machine using bottom spray Wurster column.
4. Coated spheres were filled in capsules to achieve desired strengths viz 8, 16 and 24 mg of galantamine base.

Example 2:

Serial no.	Ingredients	%w/w
1.	Galantamine Hydrobromide (API)	10.79
2.	Eudragit RS 30 D** (Dry quantity)	32.38
3.	Colloidal silicon dioxide	9.72
4.	Triethyl Citrate	6.47
5.	Purified Water*	q.s.
6.	Microcrystalline cellulose Spheres	40.64
	Total	100.00

q.s.: quantity sufficient

* Removed during processing

** Eudragit RS 30 D is colloidal aqueous dispersion of Ammonio Methacrylate Copolymer Dispersion Type B containing 30%w/w solids.

Process:

1. 51.265 g of API was dissolved in 2050.6 g of purified water with stirrer.
2. 30.75 g of triethyl citrate was dissolved in solution of step 1 with continuous stirring.
3. 46.15 g of colloidal silicon dioxide was dispersed in solution of step 2 and stirring was continued.
4. 512.65 g of Eudragit RS 30 D was mixed with the solution of step 3 for 15 minutes with continuous stirring.
5. 193.0 g of MCC spheres were spray coated with solution of step 4 using fluid bed coating machine.
6. Coated spheres were filled in capsules to achieve desired strengths viz 8, 16 and 24 mg of galantamine base.

Example 3:

Serial no.	Ingredients	%w/w
1.	Galantamine Hydrobromide (API)	10.79
2.	Eudragit RS 30 D** (Dry quantity)	26.98
3.	Colloidal silicon dioxide	8.10
4.	Triethyl Citrate	5.40
5.	Purified Water*	q.s.
6.	Microcrystalline cellulose Spheres	48.73
	Total	100.00

q.s.: quantity sufficient

* Removed during processing

** Eudragit RS 30 D is colloidal aqueous dispersion of Ammonio Methacrylate Copolymer Dispersion Type B containing 30%w/w solids.

Process:

1. 35.89 g of API was dissolved in 1270 g of purified water with stirrer.
2. 17.96 g of triethyl citrate was dissolved in solution of step 1 with continuous stirring.
3. 26.92 g of colloidal silicon dioxide was dispersed in solution of step 2 and stirring was continued.
4. 299.1 g of Eudragit RS 30 D was mixed with the solution of step 3 for 15 minutes with continuous stirring.
5. 162.0 g of MCC spheres were spray coated with solution of step 4 using fluid bed coating machine.
6. Coated spheres were filled in capsules to achieve desired strengths viz 8, 16 and 24 mg of galantamine base.

Example 4:

Serial no.	Ingredients	%w/w
1.	Galantamine Hydrobromide (API)	9.52
2.	Surelease E-7 19040 clear** (Dry quantity)	28.56
3.	Hydroxypropyl Methylcellulose E-5 (HPMC E-5)	0.57
4.	Purified Water*	q.s.
5.	Microcrystalline cellulose Spheres	61.35
	Total	100.00

q.s.: quantity sufficient

* Removed during processing

** Surelease E-7 19040 is colloidal aqueous dispersion of Ethyl cellulose containing 25%w/w solids.

Process:

1. 23.3 g of API was dissolved in 910 g of purified water with stirrer.
2. 1.4 g of HPMC E-5 was dissolved in the solution of step 1.
3. 279.3 g of Surelease E-7 19040 was mixed with the solution of step 2 for 15 minutes with continuous stirring.
4. 150 g of MCC spheres were spray coated with dispersion of step 3 in fluid bed coating machine using bottom spray wurster column.
5. Coated spheres were filled in capsules to achieve desired strengths viz 8, 16 and 24 mg of galantamine base.

Example 5:

Serial no.	Ingredients	%w/w
1.	Galantamine Hydrobromide (API)	10.79
2.	Eudragit RS 30 D** (Dry quantity)	25.35
3.	Colloidal silicon dioxide	7.61
4.	Triethyl Citrate	5.07
5.	Purified Water*	q.s.
6.	Microcrystalline cellulose Spheres	51.17
	Total	100.00

q.s.: quantity sufficient

* Removed during processing

** Eudragit RS 30 D is colloidal aqueous dispersion of Ammonio Methacrylate Copolymer Dispersion Type B containing 30%w/w solids.

Process:

1. 133.3 g of API was dissolved in 5000 g of purified water with stirrer.
2. 62.66 g of triethyl citrate was dissolved in solution of step 1 with continuous stirring.
3. 93.99 g of colloidal silicon dioxide was dispersed in solution of step 2 and stirring was continued.
4. 1043.9 g of Eudragit RS 30 D was mixed with the solution of step 3 for 15 minutes with continuous stirring.
5. 631.9 g of MCC spheres were spray coated with solution of step 4 using fluid bed coating machine.
6. Pellets of step 5 were mixed with 0.5% w/w of Colloidal silicon dioxide.
7. Coated spheres were filled in capsules to achieve desired strengths (i.e. 8, 16 and 24 mg of galantamine base).

Dissolution profiles of Example 1, 2, 3, 4 and 5

Dissolution was performed in using 900 ml of pH 6.5 Phosphate buffer, USP Apparatus II at speed of 50 rpm. Results are mentioned in the following table.

Time (min)	Example 1	Example 2	Example 3	Example 4	Example 5
0	0	0	0	0	0
15	17	13	28	20	13
60	29	23	48	40	27
120	42	31	62	56	42
240	60	41	76	76	62
480	85	56	92	103.3	84
600	95	62	95	--	89
720	103	67	97	--	92

CLAIMS

1. A single layered controlled release therapeutic system comprising:

- an inert core; and

- a single coating layer disposed over the inert core, said coating layer comprising:

- a release controlling polymeric matrix in which an active pharmaceutical agent is distributed therein;

wherein the active pharmaceutical agent is galantamine or pharmaceutically acceptable salts thereof.

2. The controlled release therapeutic system according to claim 1, wherein the inert core is made up of microcrystalline cellulose, cellulose, starch, lactose, sugar, sugar alcohols, or a combination thereof.

3. The controlled release therapeutic system according to claim 1 or 2, wherein the polymeric matrix comprises at least one hydrophobic polymer, at least one hydrophilic polymer, or a combination thereof.

4. The controlled release therapeutic system according to claim 3, wherein the hydrophobic polymers are selected from the group consisting of: alkylcellulose; polyalkyl acrylate; methacrylic acid and acrylic acid esters; polydiene; polyolefin; polylactone; polysiloxane; polyoxirane; polystyrene; and polypyridine.

5. The controlled release therapeutic system according to claim 3, wherein the hydrophilic polymers are selected from the group consisting of: hydroxyalkyl cellulose; poly alkyl (acrylic) acid and its salt; methacrylic acid and acrylic acid esters; povidone; polyacrylamide; poly(N,N-dimethyl acrylamide); poly(N-isopropyl acrylamide); polyethylene glycol and polyethylene oxide; poly(methyl vinyl ether); poly(styrene sulfonic acid) and its salt; poly(vinyl alcohol); poly(2-vinyl N-methyl pyridinium iodide); poly(4-vinyl N-methyl pyridinium iodide); poly(N-vinyl imidazole-quaternized with CH_3I); poly(ethylene imine); poly(vinylamine) and poly(vinyl carboxylic acid amide); polyethylene oxide and

polyethylene glycol graft polymer; polyvinyl alcohol and polyethylene glycol graft polymer; polyethylene glycols; natural or synthetic gum; alginic acid and its derivatives or salts; carbomers; chitosan; and copovidones.

6. The controlled release therapeutic system according to claim 4, wherein the alkylcellulose polymer is selected from the group consisting of: ethylcellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose methyl cellulose, and sodium carboxymethyl cellulose.

7. The controlled release therapeutic system according to any one of claims 1 to 6, wherein the release controlling polymeric matrix comprises one or more agents selected from the group consisting of plasticizing agents, anti-adherents, binders and pore forming agents.

8. The controlled release therapeutic system according to claim 7, wherein the plasticizing agent is selected from the group consisting of: triethyl citrate, triacetin, dibutyl phthalate, diethyl phthalate, polyethylene glycol, propylene glycol, castor oil, dibutyl sebacate, diethyl sebacate, and combinations thereof.

9. The controlled release therapeutic system according to claim 7, wherein the anti-adherent agent is selected from the group consisting of: colloidal silicon dioxide; talc; starch; glyceryl monostearate; magnesium stearate; stearic acid and its salts; magnesium aluminum silicate; and combinations thereof.

10. The controlled release therapeutic system according to claim 7, wherein the one or more agents is a binder or pore forming agent.

11. The controlled release therapeutic system according to claim 10, wherein the binder or pore forming agent is a water soluble or water swellable/permeable pharmaceutically acceptable excipient.

12. The controlled release therapeutic system according to claim 10 or 11, wherein the binder or pore forming agent is selected from the group consisting of: povidone; hydroxypropylmethyl cellulose; hydroxypropylcellulose; gum; methylcellulose; carboxymethyl cellulose and its salts; alginates; sugar and sugar alcohols; water soluble organic and inorganic salts; and combinations thereof.

13. The controlled release therapeutic system according to any one of claims 1 to 12, wherein galantamine is in the form of galantamine hydrobromide.

14. The controlled release therapeutic system according to any one of claims 1 to 13, wherein the active substance: polymeric matrix ratio is 1: 0.1 to 0.1:100.

15. A solid oral pharmaceutical dosage form comprising the controlled release therapeutic system according to any one of claims 1 to 14.

16. The solid oral pharmaceutical dosage form according to claim 15, wherein said dosage form releases the active pharmaceutical agent for up to 24 hours.

17. The solid oral pharmaceutical dosage form according to claim 15, wherein said dosage form releases the active pharmaceutical agent for up to 12 hours.

18. The solid oral pharmaceutical dosage form according to claim 15, wherein said dosage form releases a therapeutically effective amount of the active pharmaceutical agent for up to 24 hours.

19. The solid oral pharmaceutical dosage form according to claim 15, wherein said dosage form releases a therapeutically effective amount of the active pharmaceutical agent for up to 12 hours.

20. A process for manufacturing a controlled release therapeutic system according to any one of claims 1 to 14, said process comprising the steps of:

1) providing inert spheres;

2) preparing a dispersion or solution comprising;

- a mixture of release controlling polymer;

- the active pharmaceutical agent; and

- optionally a plasticizer and/or anti-adherent and/or binder/pore forming agent using a pharmaceutically acceptable solvent or combination of solvents;

3) coating the inert spheres with said dispersion or solution.

21. The process according to claim 20, wherein the inert spheres are further coated with a release controlled polymeric matrix coat.

22. The process according to claim 20, wherein the active pharmaceutical agent is galantamine hydrobromide that is incorporated in the coating layer.

23. The process according to claim 20, wherein the release controlling polymeric mixture comprises at least one hydrophobic polymer, at least one hydrophilic polymer, or a combination thereof.

24. The process according to claim 20, wherein the coating step is performed by fluidized bed coating or powder layering.

25. A solid oral pharmaceutical dosage form comprising the controlled release therapeutic system according to any one of claims 1 to 14, wherein the active pharmaceutical agent is galantamine hydrobromide.

26. A solid oral pharmaceutical dosage form comprising the controlled release therapeutic system according to any one of claims 1 to 14, wherein the galantamine is present in amounts of 8, 16 or 24 mg.

27. The solid oral pharmaceutical dosage form according to claim 26, wherein the galantamine is in the form of galantamine hydrobromide.