(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 February 2009 (26.02.2009)

PCT

(10) International Publication Number
WO 2009/024858 A1

(51) International Patent Classification:
*A61K 9/20* (2006.01) *A61K 31/55* (2006.01)

(21) International Application Number:
PCT/IB2008/002179

(22) International Filing Date: 22 August 2008 (22.08.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1871/CHE/2007 22 August 2007 (22.08.2007) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declaration under Rule 4.17:**
— *of inventorship (Rule 4.17(iv))*

**Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(54) Title: CONTROLLED RELEASE DOSAGE FORM OF GALANTAMINE

(57) Abstract: The present invention relates to controlled release dosage form comprising Anti-Alzheimer's drug. More particularly, the present invention relates to controlled release dosage form of galantamine or its salts. The present invention also relates to a process for the preparation of controlled release formulations of galantamine or its salts.

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# CONTROLLED RELEASE DOSAGE FORM OF GALANTAMINE

## Field of the invention

The present invention relates to controlled release dosage form comprising Anti-Alzheimer's drug. More particularly, the present invention relates to controlled release dosage form of galantamine or its salts.

The present invention also relates to a process for the preparation of controlled release dosage form of galantamine or its salts.

## Background of the invention

Galantamine hydrobromide is a reversible, competitive acetyl cholinesterase inhibitor and is chemically known as (4aS, 6R, 8aS)-4a, 5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol hydrobromide. Galantamine hydrobromide is marketed under the trade name Razadyne ® as an oral tablet as well as solution and Razadyne ER® as an extended release capsule in United States and also available under the trade name Reminyl® in Europe for the treatment of mild to moderate dementia of the Alzheimer's type.

Galantamine has an affinity for nicotinic receptors but not for muscarinic receptors and it is capable of passing the blood-brain barrier. It is seen that immediate release therapy of galantamine hydrobromide leads to undesired peaks in the plasma profiles of galantamine and a sharp decrease in concentration after about 6 to 8 hours. Moreover, these fluctuations ranging from high to low plasma concentrations are undesirable and may lead to side effects, such as nausea, vomiting or headaches and these side effects generally precipitate in high doses. So a typical therapy with galantamine starts with a lower dose for 3 - 4 weeks and the dose is gradually increased till maximum tolerable dosage is achieved. But in this case if treatment with galantamine is interrupted for several days or longer, the patient will need to start again at the lowest dose, increasing the dose at 4-week intervals until the former dose is achieved.

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To overcome the above disadvantages, a controlled release dosage form was prepared which can permit once a day dosing by maintaing a stable drug plasma concentration for an extended period of time. Several prior art references describe compositions that are suitable for controlled release of galantamine.

Galantamine hydrobromide extended release capsule dosage form has been approved by FDA in April 2005 and is commercially available under the trade name Razadyne ER® in the United States. Razadyne ER® capsule contain gelatin, diethyl phthalate, ethylcellulose, hypromellose, polyethylene glycol, titanium dioxide and sugar sphere (sucrose and starch) as inactive ingredients.

Given below are patents/patents publications, which disclose controlled release dosage form of galantamine or its salts.

U.S. Patent No. 7,160,559, US 2006/0062856 and US 2006/0093671 disclose a controlled release formulation comprising galantamine hydrobromide and a water soluble film forming polymer wherein the galantamine hydrobromide and the water soluble film forming polymer are layered or coated on inert spheres, said particles further coated by a release rate controlling membrane coating comprises water insoluble polymer and optionally a plasticizer, and the formulation further comprises a topcoat comprising galantamine and water-soluble polymer and wherein the formulation is capable of releasing 20 to 40% of the total amount of galantamine hydrobromide in 1 hour, and more than 80% of the total amount of galantamine hydrobromide in 10 hours.

US 2004/0097484 discloses a once a day pharmaceutical composition comprising a therapeutically effective amount of galantamine and a pharmaceutically acceptable carrier, wherein the carrier comprising at least one gelling agent selected from water soluble organic gums, natural clays, synthetic clays and mixtures thereof.

US 2005/0191349 discloses a sustained-release formulation, comprising: galantamine and a release-retarding material, wherein the release-retarding

material comprising acrylate polymer, wax, modified cellulose, shellac, zein, hydrogenated vegetable oil, hydrogenated castor oil, or combinations comprising at least one of the foregoing release-retarding materials, wherein the formulation exhibits a dissolution profile such that less than about 18% of the galantamine is released in 1 hour, and less than about 80% of the galantamine is released in 10 hours.

US 2007/0092568 discloses a pharmaceutical composition comprising galantamine, a portion of the contained galantamine being present in an immediate release form and another portion being present in an extended release form, wherein immediate release form comprises inert particle coated with galantamine and extended release form comprises an inert particles coated with galantamine and further coated with rate controlling substance.

WO 05/099674 discloses sustained release composition of galantamine using starch sodium octenyl succinate as a release-retarding agent.

WO 07/029081 discloses a controlled release dosage form of galantamine comprising: a core comprising galantamine and water insoluble excipients and a rate controlling coating wherein the rate controlling coating comprising one or more water insoluble polymer, a water soluble polymer and one or more plastisizer.

WO 07/121537 discloses a controlled-release formulation comprising one or more distinct and discrete units located in physical juxtaposition to enable administration to a patient in a single dose, where each unit comprises (i) a unit dose of an active pharmaceutical ingredient or pharmaceutically acceptable salts thereof; (ii) one or more extended-release agent comprising a matrix of polymer and optionally (iii) one or more pharmaceutically acceptable excipients, wherein the sum of the unit dose(s) constitutes a pharmaceutically effective amount of the active pharmaceutical ingredient.

WO 08/048469 discloses a controlled release dosage form having a core comprising galantamine and water insoluble polymer and a release rate-

controlling coating having release rate retarding excipients and the formulation further comprises immediate release top coat comprising galantamine and other polymer.

WO 08/062426 discloses a controlled relesae formulation in the form of a hard gelatin capsule comrising a) functional coated composition of galantamine mainly comprising functional coat of surelease and b) an uncoated or seal coated composition of galantamine.

WO 08/064734 discloses a controlled release composition comprising a pellet having an inert core, a first coating that is applied to the inert core and a second coating that is applied to the first coating wherein the first coating and the second coating contain galantamine or a pharmaceutically acceptable salts or solvent thereof and further the composition of the first coating is different from the second coating in having at least a film-forming or water insoluble polymer in one of the coating.

The above prior art references disclose various controlled release dosage form of galantamine. However, still there is a need for preparing controlled release dosage form of galantamine, which is simple and cost effective. The inventors of the present invention during their continuous effort to develop controlled release dosage form found that the core comprising galantamine along with release retarding polymer, which is further layered with immediate release drug layer, releases the drug in a controlled manner and at the same time bioequivalent to the marketed dosage form.

## Objective of the invention

Accordingly, the main objective of the present invention is to provide controlled release dosage form of galantamine or its salts.

Yet another objective of the present invention is to provide controlled release dosage form of galantamine or its salts in such a way that it will comply with the reference product in terms of *in vivo* parameters like bioequivalence and *in vitro* parameters like dissolution.

Yet another objective of the present invention is to provide process for the preparation of controlled release dosage form of galantamine or its salts.

## Summary of the invention

Accordingly, the main embodiment of the present invention is to provide controlled release dosage form comprising:

(i) matrix core comprising galantamine or its salts, release retarding polymer and one or more pharmaceutically acceptable excipients and

(ii) an immediate release drug layer over the core comprising galantamine or its salts and one or more pharmaceutically acceptable excipients.

## Detailed description of the invention

In an embodiment of the present invention, the core comprises galantamine or its salts, release retarding polymer and one or more pharmaceutically acceptable excipient such as diluents, binders, glidants and lubricants.

The salts of the present invention include hydrobromide, hydrochloride, sulfuric and the like.

In an embodiment of the present invention, the release retarding polymer is selected from povidone (Kollidon®, Plasdone®), hydroxypropylmethylcellulose (Methocel®), hydroxypropylcellulose (Klucel®), methylcellulose, polyvinyl acetate, polyvinyl alcohol, carbopol, copolymers of methacrylic acids or its ester (Eudragit®), alginic acid or its salts, xanthan gum, polyethylene oxide, ethylcellulose (commercially avialble as Surelease®, Ethocel®), copolymers of polyvinyl alcohol and polyvinyl pyrrolidone (Kollicoat®) and the like or mixtures thereof. The release-retarding polymer used may be in the range of about 5-50% by weight of the core.

In yet another embodiment, the amount of galantamine present in the matrix core may be in the range of about 2-20% by weight of the core.

Suitable diluents of the present invention are selected from calcium phosphate-dibasic, calcium silicate, calcium carbonate, lactose, mannitol, sucrose, microcrystalline cellulose, starch and the like or mixtures thereof. The diluent used may be in the range of about 20-90% by weight of the core.

Suitable binders of the present invention are selected from hydroxypropyl cellulose, hydroxypropylmethyl cellulose, starch, povidone, copolyvidone, microcrystalline cellulose, pregelatinized starch and the like or mixtures thereof.

Suitable glidants of the present invention are selected from talc, sodium lauryl sulfate, colloidal silicon dioxide, magnesium trisilicate, and the like or mixtures thereof.

Suitable lubricants of the present invention include sodium stearyl fumarate, magnesium stearate, calcium stearate, hydrogenated vegetable oil, stearic acid, glyceryl behenate, talc and the like. The lubricant used may be in the range of about 0.5-5% by weight of the core.

The core of the present invention may be in the form of tablet, minitablet or spheroids.

In another embodiment, the matrix core is optionally coated with seal coating composition, which comprises polymer, plasticizer, antitacking agent and the like.

Yet in another embodiment, the immediate release drug layer over the core is in the form of a coating covering the core or a layer adjacent to the matrix core forming a bilayered tablet.

Yet in another embodiment, the immediate release drug coating layer comprises galantamine or its salts and one or more pharmaceutically acceptable excipients such as water-soluble polymer, plastisizer and antitacking agent.

Yet in another embodiment, the immediate release portion of bilayered tablet comprises galantamine or its salts and one or more pharmaceutically acceptable excipients such as water-soluble polymer, diluent, binder, glidant and lubricant.

Suitable water-soluble polymers used according to the present invention are selected from polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, acrylic acid copolymer such as eudragit, phthalates and the like.

Suitable plastisizers used according to the present invention are selected from triacetin, polyethylene glycol, diethyl phthalate and triethyl citrate or mixtures thereof.

Suitable antitacking agents of the present invention are selected from talc, sodium lauryl sulfate, colloidal silicon dioxide, glyceryl magnesium stearate and the like or mixtures thereof.

In yet another embodiment, the amount of galantamine used in the immediate release drug layer may be in the range of about 2-60% by weight of the immediate release layer.

The coating according to the present invention is applied by dissolving / dispersing the excipients in solvents such as isopropyl alcohol, water, acetone, ethanol, dichloro methane and the like or mixtures thereof.

The controlled release dosage form of the present invention may be in the form of tablet, tablets(s) / spheroids filled in capsule or bilayered tablet.

In a preferred embodiment, controlled release dosage form of the present invention in the form of tablet or spheroids filled in capsule comprises:

(i) matrix core comprising galantamine or its salts, 5-50% by weight of release-retarding polymer selected from polyvinylpyrrolidone, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, polyvinyl alcohol or mixtures thereof; 20-90% by weight of diluent selected from calcium silicate, microcrystalline cellulose and starch and

(ii) an immediate release drug layer coating the core comprising galantamine or its salts, water-soluble polymer and one or more pharmaceutically acceptable excipients such as binder, plasticizer, antitacking agent,

Yet in another preferred embodiment, controlled release dosage form of the present invention in the form of a bilayered tablet comprises:

(i) matrix core comprising galantamine or its salts, 5-50% by weight of release-retarding polymer selected from polyvinylpyrrolidone, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, polyvinyl alcohol or mixtures thereof; 20-90% by weight of diluent selected from calcium silicate, microcrystalline cellulose and starch and

(ii) immediate release drug layer over the core comprising galantamine or its salts, water-soluble polymer and one or more pharmaceutically acceptable excipients such as diluent, binder, glidant and lubricant.

The present invention also provides a process for the preparation of a controlled release dosage form comprising:

(ii) matrix tablet core comprising galantamine or its salts, release retarding polymer and one or more pharmaceutically acceptable excipients and

(ii) an immediate release drug layer over the core comprising galantamine or its salts and one or more pharmaceutically acceptable excipients, which comprises the following steps:

1) preparing the core tablet comprising galantamine or its salts and one or more pharmaceutically acceptable excipients using conventional tabletting procedures,

2) coating the tablets of step (1) with the suspension of immediate release drug layer comprising galantamine or its salt and one or more pharmaceutical acceptable excipients in solvent and

3) optionally coating the tablet with a film coating composition.

Yet in another embodiment of the present invention, the core of the present invention may also be prepared by a process, which comprises the steps of

1) blending galantamine or its salts, release retarding polymer with one or more pharmaceutical acceptable excipients,

2) granulating the blend obtained in step (1) by means of water,

3) extruding the granulated blend obtained in step (2),

4) spheronising the resulting extrudates and

5) finally drying the extrudates to obtain spherical granules or pellets.

In yet another embodiment, the controlled release dosage form of galantamine or its salts may also be prepared as a bilayered tablet, which comprises the steps of

1) blending and optionally granulating galantamine or its salts, release retarding polymer with one or more pharmaceutical acceptable excipients to form controlled release granules,

2) blending and optionally granulating galantamine or its salts with one or more pharmaceutical acceptable excipients to form immediate release granules,

3) compressing the granules obtained in step (1) and step (2) to obtain bilayered tablets and

4) optionally coating the tablet with a film coating composition.

In yet another embodiment, there is provided a method for the treatment of mild to moderate dementia of the Alzheimer's type, by administering controlled release dosage form of galantamine or its salts of the present invention.

The following examples further exemplify the invention and are not intended to limit the scope of the invention. It is obvious to those skilled in the art to find out the composition for other dosage forms and substitute the equivalent excipients as described in this specification or with the one known to the industry.

**Example 1-Matrix tablet core coated with immediate release drug layer**

| Ingredients | Qty / tab (mg) |
|---|---|
| **Core** | |
| Galantamine HBr | 7.69 |

| | |
|---|---|
| Microcrystalline cellulose | 41.31 |
| Colloidal silicon dioxide | 1.00 |
| Hydroxypropyl methylcellulose | 40.00 |
| Magnesium Stearate | 1.00 |
| **Immediate release drug layer** | |
| Galantamine HBr | 2.56 |
| Hydroxypropyl methylcellulose | 2.00 |
| Polyethylene glycol | 0.34 |
| Talc | 0.10 |
| **Film Coat** | |
| Opadry | 2.00 |

The processing steps involved in manufacturing controlled release tablet dosage form of galantamine hydrobromide are as given below:

i) galantamine hydrobromide, microcrystalline cellulose, colloidal silicon dioxide and hydroxypropyl methylcellulose were blended,

ii) lubricated the blended granules of step (i) with magnesium stearate,

iii) compressed the lubricated blend of step (ii) into tablets,

iv) a suspension of galantamine hydrobromide, hydroxypropyl methylcellulose, polyethylene glycol was prepared in purified water,

v) talc was dispersed in the above suspension obtained in step (iv),

vi) the tablets of step (iii) were coated with the drug coating suspension prepared in step (v) to obtain controlled release tablets of galantamine.

The compositions given in example 2 was prepared using similar procedure described in example 1.

**Example 2- Matrix tablet core coated with immediate release drug layer**

| Ingredients | Qty / tab (mg) |
|---|---|
| **Core** | |
| Galantamine HBr | 7.69 |
| Microcrystalline cellulose | 47.75 |

| | |
|---|---|
| Colloidal silicon dioxide | 1.00 |
| Methocel K100M (High viscosity HPMC) | 30.00 |
| Ethocel N7 cps | 10.00 |
| Magnesium Stearate | 1.00 |
| **Immediate release drug layer** | |
| Galantamine HBr | 2.56 |
| Methocel E 5 LVP (Low viscosity HPMC) | 2.00 |
| Polyethylene glycol | 0.34 |
| Talc | 0.10 |
| **Film Coat** | |
| Opadry | 2.00 |

**Example 3 - Matrix tablet core coated with immediate release drug layer**

| Ingredients | Qty / tab (mg) |
|---|---|
| **Core** | |
| Galantamine HBr | 7.69 |
| Microcrystalline cellulose | 41.31 |
| Colloidal silicon dioxide | 1.00 |
| Hydroxypropyl methylcellulose | 40.00 |
| Magnesium stearate | 1.00 |
| **Seal Coat** | |
| Hydroxypropyl methylcellulose | 1.00 |
| Polyethylene glycol | 0.40 |
| Talc | 0.60 |
| **Immediate release drug layer** | |
| Galantamine HBr | 2.56 |
| Hydroxypropyl methylcellulose | 2.00 |
| Polyethylene glycol | 0.34 |
| Talc | 0.10 |
| **Film Coat** | |
| Opadry | 2.00 |

The processing steps involved in manufacturing controlled release tablet dosage form of galantamine hydrobromide are as given below:

i) galantamine hydrobromide, microcrystalline cellulose, colloidal silicon dioxide and hydroxypropyl methylcellulose were blended,

ii) lubricated the blended granules of step (i) with magnesium stearate,

iii) compressed the lubricated blend of step (ii) into tablets,

iv) a suspension of hydroxypropyl methylcellulose and polyethylene glycol in purified water was prepared,

v) talc was dispersed in the above suspension obtained in step (iv),

vi) tablets of step (iii) were seal coated with the coating suspension of step (v),

vii) a suspension of galantamine hydrobromide, hydroxypropyl methylcellulose, polyethylene glycol was prepared in purified water,

viii) talc was dispersed in the above suspension obtained in step (vii),

ix) the seal coated tablets of step (vi) were coated with the coating suspension prepared in step (viii) to obtain controlled release tablets of galantamine.

The compositions given in examples 4 and 5 were prepared using similar procedure described in example 3.

**Example 4 - Matrix tablet core coated with immediate release drug layer**

| Ingredients | Qty / tab (mg) |
|---|---|
| **Core** | |
| Galantamine HBr | 7.69 |
| Microcrystalline cellulose | 41.31 |
| Colloidal silicon dioxide | 1.00 |
| Ethocel N7 cps | 40.00 |
| Magnesium stearate | 1.00 |
| **Seal Coat** | |
| Methocel E 5 LVP (Low viscosity HPMC) | 1.00 |
| Polyethylene glycol | 0.40 |

| | |
|---|---|
| Talc | 0.60 |
| **Immediate release drug layer** | |
| Galantamine HBr | 2.56 |
| Methocel E 5 LVP (Low viscosity HPMC) | 2.00 |
| Polyethylene glycol | 0.34 |
| Talc | 0.10 |
| **Film Coat** | |
| Opadry | 2.00 |

**Example 5 - Matrix tablet core coated with immediate release drug layer**

| Ingredients | Qty / tab (mg) |
|---|---|
| **Core** | |
| Galantamine HBr | 7.69 |
| Microcrystalline cellulose | 41.31 |
| Colloidal silicon dioxide | 1.00 |
| Methocel K100M /Methocel K4M (High viscosity HPMC) | 20.00 |
| Ethocel N7 cps | 20.00 |
| Magnesium stearate | 1.00 |
| **Seal Coat** | |
| Methocel E 5 LVP (Low viscosity HPMC) | 1.00 |
| Polyethylene glycol | 0.40 |
| Talc | 0.60 |
| **Immediate release drug layer** | |
| Galantamine HBr | 2.56 |
| Methocel E 5 LVP (Low viscosity HPMC) | 2.00 |
| Polyethylene glycol | 0.34 |
| Talc | 0.10 |
| **Film Coat** | |
| Opadry | 2.00 |

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**Example 6 – Controlled release Galantamine Capsule filled with spheroids**

| Ingredients | Qty / cap (mg) |
|---|---|
| **Core** | |
| Galantamine HBr | 7.69 |
| Microcrystalline cellulose | 60.00 |
| Colloidal silicon dioxide | 1.00 |
| Ethyl cellulose | 20.00 |
| **Seal Coat** | |
| Hydroxypropyl methylcellulose | 1.00 |
| Polyethylene glycol | 0.40 |
| Talc | 0.60 |
| **Immediate release drug layer** | |
| Galantamine HBr | 2.56 |
| Hydroxypropyl methylcellulose | 2.00 |
| Polyethylene glycol | 0.34 |
| Talc | 0.10 |

The processing steps involved in manufacturing controlled release dosage form of galantamine hydrobromide described in example 6 are as given below:

i) galantamine hydrobromide, microcrystalline cellulose, colloidal silicon dioxide and ethyl cellulose were blended,

ii) the blend of step (i) was granulated with purified water,

iii) granulated blend obtained in step (ii) was extruded,

iv) extrudates obtained in step (iii) were spheronised and dried to obtain spherical granules,

v) a suspension of hydroxypropyl methylcellulose, polyethylene glycol in purified water was prepared,

vi) talc was dispersed in the above suspension obtained in step (v),

vii) the coating suspension of step (vi) was applied on the spheroids of step (iv),

viii) a suspension of galantamine hydrobromide, hydroxypropyl methylcellulose, polyethylene glycol was prepared in purified water,

ix) talc was dispersed in the above suspension obtained in step (viii),

x) seal coated spheroids of step (vii) were coated with the coating suspension prepared in step (ix) to obtain controlled release spheroids which are further compressed into tablets or filled into capsules.

**Example 7- Bilayered tablets of Galantamine**

| Ingredients | Qty / cap (mg) |
|---|---|
| **Core** | |
| Galantamine HBr | 7.69 |
| Microcrystalline cellulose | 109.31 |
| Colloidal silicon dioxide | 2.00 |
| Hydroxypropyl methylcellulose | 80.00 |
| Magnesium Stearate | 1.00 |
| **Immediate release layer** | |
| Galantamine HBr | 2.56 |
| Microcrystalline cellulose | 43.44 |
| Colloidal silicon dioxide | 1.00 |
| Hydroxypropyl methylcellulose | 2.50 |
| Magnesium stearate | 0.50 |
| Opadry film coating | 5.00 |

The processing steps involved in manufacturing bilayered tablet of galantamine hydrobromide are as given below:

i) galantamine hydrobromide, microcrystalline cellulose, colloidal silicon dioxide, hydroxypropyl methylcellulose and magnesium stearate were blended to form a controlled release blend,

ii) galantamine hydrobromide, microcrystalline cellulose, colloidal silicon dioxide, hydroxypropyl methylcellulose and magnesium stearate were blended to form a immediate release blend,

iii) compressed the controlled release blend of step (i) and immediate release blend of step (ii) on bilayer compression machine to form bilayered tablet,

iv) the bilayered tablets were optionally coated with opadry.

The compositions given in examples 8 and 9 were prepared using similar procedure described in example 7.

**Example 8- Bilayered tablets of Galantamine**

| Ingredients | Qty / cap (mg) |
|---|---|
| **Core** | |
| Galantamine HBr | 7.69 |
| Microcrystalline cellulose | 109.31 |
| Colloidal silicon dioxide | 2.00 |
| Ethyl cellulose | 80.00 |
| Magnesium stearate | 1.00 |
| **Immediate release layer** | |
| Galantamine HBr | 2.56 |
| Microcrystalline cellulose | 43.44 |
| Colloidal silicon dioxide | 1.00 |
| Hydroxypropyl methylcellulose | 2.50 |
| Magnesium stearate | 0.50 |
| Opadry film coating | 5.00 |

**Example 9- Bilayered tablets of Galantamine**

| Ingredients | Qty / cap (mg) |
|---|---|
| **Core** | |
| Galantamine HBr | 7.69 |
| Microcrystalline cellulose | 109.31 |
| Colloidal silicon dioxide | 2.00 |
| Hydroxypropyl methylcellulose | 40.00 |
| Ethyl cellulose | 40.00 |
| Magnesium stearate | 1.00 |
| **Immediate release layer** | |
| Galantamine HBr | 2.56 |
| Microcrystalline Cellulose | 43.44 |
| Colloidal Silicon Dioxide | 1.00 |
| Hydroxypropyl methylcellulose | 2.50 |
| Magnesium stearate | 0.50 |
| Opadry film coating | 5.00 |

The controlled release dosage forms of galantamine hydrobromide prepared according to the present invention were tested for drug release in 900 ml media for 16 hours followed by phosphate buffer of pH 6.5 using USP apparatus 2 with paddle speed at 50 rpm. The samples of the media were periodically withdrawn and spectrophotometrically analyzed for galantamine content. The dissolution profile is given in Table 1.

**Table-1**

| (%) Galantamine Release | | |
|---|---|---|
| **Time (hr)** | **Razadyne ER Capsule (8mg)** | **Example 2** |
| 1.0 | 30 | 29 |
| 2.0 | 44 | 50 |
| 3.0 | 55 | 66 |
| 4.0 | 64 | 78 |
| 6.0 | 76 | 91 |
| 10.0 | 84 | 96 |
| 12.0 | 89 | 99 |
| 16.0 | 93 | 99 |

We claim:

1. A controlled release dosage form comprising:

(i) matrix core comprising galantamine or its salts, release retarding polymer and one or more pharmaceutically acceptable excipients and

(ii) an immediate release drug layer over the core comprising galantamine or its salts and one or more pharmaceutically acceptable excipients.

2. The dosage form as claimed in claim 1, wherein the core further comprise diluents, binders, glidants and lubricants.

3. The dosage form as claimed in claim 1, wherein the release retarding polymer is selected from povidone, hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, polyvinyl acetate, polyvinyl alcohol, carbopol, copolymers of methacrylic acids or its ester, alginic acid or its salts, xanthan gum, polyethylene oxide, ethylcellulose, copolymers of polyvinyl alcohol and polyvinyl pyrrolidone or mixture thereof.

4. The dosage form as claimed in claim 2, wherein the diluent is selected from calcium phosphate-dibasic, calcium silicate, calcium carbonate, lactose, mannitol, sucrose, microcrystalline cellulose, starch or mixture thereof.

5. The dosage form as claimed in claim 2, wherein the binder is selected from hydroxypropyl cellulose, hydroxypropylmethyl cellulose, starch, povidone, copolyvidone, microcrystalline cellulose, pregelatinized starch or mixture thereof.

6. The dosage form as claimed in claim 2, wherein the glidant is selected from talc, sodium lauryl sulfate, colloidal silicon dioxide or magnesium trisilicate.

7. The dosage form as claimed in claim 2, wherein the lubricant is selected from sodium stearyl fumarate, magnesium stearate, calcium stearate, hydrogenated vegetable oil, stearic acid, glyceryl behenate, talc or mixture thereof.

8. The dosage form as claimed in claim 1, wherein the immediate release drug layer over the core is in the form of a coating covering the core or a layer adjacent to the matrix core forming a bilayered tablet.

9. The controlled release dosage form as claimed in claim 1, is in the form of tablet, tablets(s) / spheroids filled in capsule or bilayered tablet.

10. A controlled release dosage form as claimed in claim 1, in the form of tablet or spheroids filled in capsule comprising:

(i) matrix core comprising galantamine or its salts, 5-50% by weight of release-retarding polymer selected from polyvinylpyrrolidone, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, polyvinyl alcohol or mixtures thereof; 20-90% by weight of diluent selected from calcium silicate, microcrystalline cellulose and starch and

(ii) an immediate release drug layer coating the core comprising galantamine or its salts, water-soluble polymer and one or more pharmaceutically acceptable excipients such as binder, plasticizer, antitacking agent.

11. A controlled release dosage form as claimed in claim 1, in the form of in the form of a bilayered tablet comprising:

(i) matrix core comprising galantamine or its salts, 5-50% by weight of release-retarding polymer selected from polyvinylpyrrolidone, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, polyvinyl alcohol or mixtures thereof; 20-90% by weight of diluent selected from calcium silicate, microcrystalline cellulose and starch and

(ii) immediate release drug layer over the core comprising galantamine or its salts, water-soluble polymer and one or more pharmaceutically acceptable excipients such as diluent, binder, glidant and lubricant.

12. A process for the preparation of a controlled release dosage form comprising:

(i) matrix tablet core comprising galantamine or its salts, release retarding polymer and one or more pharmaceutically acceptable excipients and

(ii) an immediate release drug coating layer over the core comprising galantamine or its salts and one or more pharmaceutically acceptable excipients, which comprises the steps of :

1) preparing the core tablet comprising galantamine or its salts and one or more pharmaceutically acceptable excipients using conventional tabletting procedures,

2) coating the tablets of step (1) with the suspension of immediate release drug layer comprising galantamine or its salts and one or more pharmaceutical acceptable excipients in solvent and

3) optionally coating the tablet with a film coating composition.

13. A process for the preparation of a controlled release dosage form comprising:

(i) matrix core comprising galantamine or its salts, release retarding polymer and one or more pharmaceutically acceptable excipients and

(ii) an immediate release drug layer over the core comprising galantamine or its salts and one or more pharmaceutically acceptable excipients, prepared as a bilayered tablet which comprises the steps of :

1) blending and optionally granulating galantamine or its salts, release retarding polymer with one or more pharmaceutical acceptable excipients to form controlled release granules,

2) blending and optionally granulating galantamine or its salts with one or more pharmaceutical acceptable excipients to form immediate release granules,

3) compressing the granules obtained in step (1) and step (2) to obtain bilayered tablets and

4) optionally coating the tablet with a film coating composition.

14. A method for the treatment of mild to moderate dementia of the Alzheimer's type by administering controlled release dosage form of galantamine or its salts as claimed in claim 1.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2008/002179

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/55

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)
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, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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| X | WO 2007/029081 A (RANBAXY LAB LTD [IN]; VERMA RAJAN KUMAR [IN]; VISWANATHAN NARAYANAN BA) 15 March 2007 (2007-03-15) cited in the application examples 1-6 claims 1-11 | 1-14 |
| Y | US 2006/093671 A1 (MCGEE JOHN P [BE] ET AL) 4 May 2006 (2006-05-04) cited in the application examples 4,5 | 1-14 |

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[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

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"P" document published prior to the international filing date but later than the priority date claimed

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 12 January 2009 | 20/01/2009 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040,<br>Fax: (+31–70) 340–3016 | Schüle, Stefanie |

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2008/002179

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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