International Journal of Research and Reviews in Pharmacy and Applied science

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A STUDY OF CONTROLLED RELEASE GALANTAMINE HYDROBROMIDE SOLID DOSAGE FORMULATIONS: A NOVEL APPROACH

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ABSTRACT

The present invention relates to controlled release compositions of galantamine, processes to prepare the compositions, there in vitro release profiles and methods of use and methods of treatment using the said compositions. It is a reversible inhibitor of acetylcholinesterase that binds specifically to the nicotinic receptors. Galantamine hydrobromide is been approved in the United States for treating Alzheimer's disease. The extended release pharmaceutical composition of the present study exhibits a desired in vitro dissolution profile and can serve as an economical alternative to the marketed brand product, RAZADYNE™ ER extended release capsules. The present study reveals a pharmaceutical composition comprises a capsule containing pharmacologically inert particles having a coating comprising galantamine or a salt thereof and a rate controlling substance, and having an exterior coating comprising one or more rate controlling substance. Further the formulation evaluated according to the present study includes, a pharmaceutical composition comprises a portion of the contained galantamine, which is present in more than one extended release form. In the present study, controlled release compositions of galantamine provides a release of at least about 20% to about 60% of galantamine in about 1 hour and more than about 80% of galantamine in about 12 hours, as measured in a buffer pH 6.8 at 37° C., using USP dissolution apparatus 2 at 50 rpm. The major focus of the present study was to design the controlled release composition behaving similar to the brand product using only water insoluble pharmaceutical grade excipients.

INTRODUCTION

Galantamine hydrobromide is a reversible, competitive acetylcholinesterase inhibitor. Galantamine hydrobromide is known chemically as (4a*S*,6*R*,8a*S*)-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 $C_{17}H_{21}NO_3$ •HBr and a molecular weight of 368.27. Galantamine hydrobromide is a white to almost white powder and is sparingly soluble in water. The structural formula for galantamine hydrobromide has represented in figure-1.

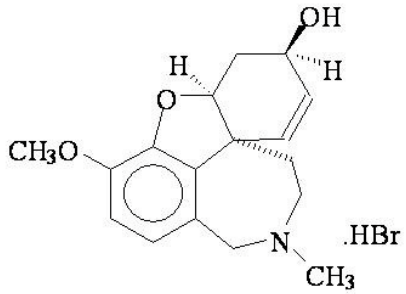


Figure-1: Chemical structure of Galantamine Hydrobromide

Mechanism of Action

Although the etiology of cognitive impairment in Alzheimer's disease (AD) is not fully understood, it has been reported that acetylcholine-producing neurons degenerate in the brains of patients with Alzheimer's disease. The degree of this cholinergic loss has been correlated with degree of cognitive impairment and density of amyloid plaques (a neuropathological hallmark of Alzheimer's disease).

Galantamine, a tertiary alkaloid, is a competitive and reversible inhibitor of acetylcholinesterase. While the precise mechanism of galantamine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this mechanism is correct, galantamine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that galantamine alters the course of the underlying dementing process.

Pharmacokinetics

Galantamine is well absorbed with absolute oral bioavailability of about 90%. It has a terminal elimination half-life of about 7 hours and pharmacokinetics is linear over the range of 8–32 mg/day. The maximum inhibition of acetylcholinesterase activity of about 40% was achieved about one hour after a single oral dose of 8 mg galantamine in healthy male subjects.

Absorption and Distribution

Galantamine is rapidly and completely absorbed with time to peak concentration about 1 hour. Bioavailability of the tablet was the same as the bioavailability of an oral solution. Food did not affect the AUC of galantamine but C_{max} decreased by 25% and T_{max} was delayed by 1.5 hours. The mean volume of distribution of galantamine is 175 L. The plasma protein binding of galantamine is 18% at therapeutically relevant concentrations. In whole blood, galantamine is mainly distributed to blood cells (52.7%). The blood to plasma concentration ratio of galantamine is 1.2.

Metabolism and Elimination

Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated, and excreted unchanged in the urine. *In vitro* studies indicate that cytochrome CYP2D6 and CYP3A4 were the major cytochrome P450 iso-enzymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly. O-demethylation, mediated by CYP2D6 was greater in extensive metabolizers of CYP2D6 than in poor metabolizers. In plasma from both poor and extensive metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity After i.v. or oral administration, about 20% of the dose was excreted as unchanged galantamine in the urine in 24 hours, representing a renal clearance of about 65 mL/min, about 20–25% of the total plasma clearance of about 300 mL/min. 24 mg Extended-Release Capsules administered once daily under fasting conditions are bioequivalent to Immediate release Tablets 12 mg twice daily with respect to AUC_{24h} and C_{min}. Dose-proportionality is observed for Extended-Release Capsules over the dose range of 8 to 24 mg daily and steady state is achieved within a week.

MATERIALS AND METHODS

In the present study, compositions comprising two separate portions may be presented in the form of particulate compositions comprising immediate release galantamine particles and extended release galantamine particles in a defined ratio either filled into a capsule shell or compressed as a tablet formulation or filled into sachets. The ratio of the two portions IR to ER may range from 10:90 to 50:50, or 20:80 to 30:70, w/w equivalent to total galantamine present in the dosage form. Immediate release particles may be prepared as powders, granules, pellets, beads and the like using manufacturing processes such as direct blending, dry granulation, wet granulation, pelletization techniques such as but not limited to extrusion-spheronization, dry powder or solution or dispersion layering of galantamine onto inert beads or pellets or particles using conventional coating

techniques or fluid bed coating techniques. Extended release particles may be prepared as powders, granules, pellets, beads and the like using manufacturing processes such as direct blending, dry granulation, wet granulation, pelletization techniques such as but not limited to extrusion-spheronization, dry powder or solution or dispersion layering of galantamine onto inert beads or pellets or particles using conventional coating techniques or fluid bed coating techniques. Extended release particles may comprise galantamine and rate controlling substance together in one layer, or galantamine and a portion of rate controlling substance together in one layer and a remaining portion of rate controlling substance in a different layer, or galantamine and rate controlling substances together in different layers. In a specific embodiment of the invention wherein galantamine and rate controlling substances are together in different layers, then a galantamine layer comprises a water insoluble component. Useful water-soluble components include, but are not limited to: cellulosic polymers such as carboxymethyl cellulose, hydroxypropyl methylcellulose and hydroxypropyl cellulose; polyethylene oxide; polyvinyl alcohol; carbomer; carageenan; sugars such as mannitol and lactose; and mixtures thereof.

Useful water-insoluble components include, but are not limited to: acrylic acid derivatives; cellulose polymers including alkyl derivatives of cellulose like ethylcellulose, cellulose esters such as cellulose acetate, cellulose propionate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, and cellulose triacetate; waxes such as beeswax, carnauba wax, and microcrystalline wax; fatty alcohols such as cetostearyl alcohol, stearyl alcohol, cetyl alcohol, and myristyl alcohol; and fatty acid esters like glyceryl monostearate, glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, and glyceryl palmitostearate, glyceryl behenate; and hydrogenated castor oil.

In the disclosed experiments, ethylcellulose and various grades of Eudragit™ products such as Eudragit NE30D were found to be useful as a water-insoluble component. Eudragit NE30D is a 30% aqueous dispersion of poly (ethylacrylate-methylmethactylate). Ethylcellulose is commercially available as Ethocel®. Ethocel® Premium is available in different viscosities like 7 cps, 10 cps, 20 cps, 45 cps and 100 cps (centipoise), if possible please give the clear data of available market brands and concentrations with table then it's really good because its main material in your research work with an average particle size more than 250 µm. It is used by dissolving in an organic solvent for the preparation of dosage form while Ethocel® standard FP premium which is available in viscosities 7 cps, 10 cps and 100 cps is very finely milled and can be used for direct compression in matrix compositions. Ethylcellulose is also available as an aqueous dispersion under the trade name of Aquacoat® ECD, Aqualon® and Surelease®.

S:No	Grades	Viscosity range in mPa.s(cP)*	Ethoxyl Content in Percentage
1	Ethocel Std 4	3-5.5	48.0-49.5
2	Ethocel Std 7	6-8	48.0-49.5
3	Ethocel Std 10	9-11	48.0-49.5
4	Ethocel Std 14	12.6-15.4	48.0-49.5
5	Ethocel Std 20	18-22	48.0-49.5
6	Ethocel Std 45	41-49	48.0-49.5
7	Ethocel Med 50	45-55	45.0-46.5
8	Ethocel Med 70	63-77	45.0-46.5
9	Ethocel Std 100	90-110	48.0-49.5
10	Ethocel Std 200	180-220	48.0-49.5
11	Ethocel Std 300	270-330	48.0-49.5

Table no: 1 Ethocel® different grades and respective Viscosity ranges

*Millipascal.seconds (mPa.s) is equivalent to Centipoise (cP).

**Viscosities are for a 5% solution measured at 25°C in an Ubbelohde viscometer.

Surelease® is a plasticized aqueous dispersion of ethylcellulose used for extended release coatings and taste masking applications, available in 25% by weight solid content and manufactured by Colorcon Ltd. of Dartford Kent, United Kingdom. As part of the formulation, the water-soluble component is used as a pore-forming agent. The term “pore-forming agent” refers to a pharmaceutically acceptable agent that dissolves in its surrounding medium and results in formation of pores in the membrane to facilitate the diffusion of active ingredient through the membrane.

Mainly, hydroxypropyl methylcellulose was found to be useful as a water-soluble component. Common diluents useful in the discussed experiments include, but are not limited to, microcrystalline cellulose, silicified microcrystalline cellulose, microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, mannitol, sorbitol, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, polymethacrylates, and mixtures thereof.

In the present study, Celphere™ microcrystalline cellulose spheres manufactured by Asahi Kasei Chemicals Corporation, Tokyo, Japan was used. In the below detailed study, ethylcellulose and various grades of Eudragit™ products such as Eudragit NE30D were found to be useful as a water-insoluble component. Eudragit NE30D is a 30% aqueous dispersion of poly(ethylacrylate-methylmethactylate).

Description of Study

The present study was concentrated on formulation design using majorly water insoluble excipients. The formulation design included filling of controlled release pellets into hard gelatin capsules. The trials included mixing of immediate release and extended release pellets at different ratios and mixing of different percentage controlled release coated pellets and filling into the hard gelatin capsules. Further these capsules were evaluated for in-vitro dissolution behavior in pharmacopoeia recommended conditions.

The below discussed formulation contains majorly two portions of the composition comprise:

IR portion comprising

1. Galantamine hydrobromide and water insoluble component loaded onto inert particles such as Celphere.
2. Drug loaded pellets are optionally coated with a film coating substance.

ER portion comprising

1. Galantamine hydrobromide and a water insoluble component loaded onto inert particles such as Celphere.
2. Drug loaded particles are coated with rate controlling substance with or without additional pharmaceutically acceptable excipients.
3. Above coated pellets are further optionally coated with a film coating substance.
4. Defined ratio of particles from a) and b) are blended with or without other pharmaceutically acceptable excipients.
5. Above blend is either filled into a capsule or compressed as a tablet. Tablets are further optionally coated.

In another embodiment of the invention, where in galantamine and at least one rate controlling substance is present in a single layer include but not limited to compositions:

1. Particulate compositions of galantamine and at least one rate controlling substance are mixed or dry or wet granulated or extruded-spheronized and said particles are further optionally coated with a film coating substance or same or different rate controlling substances.

2. Particulate compositions wherein galantamine and at least one rate controlling substance together are layered onto an inert particle or bead or pellet through powder or solution or dispersion coating using conventional or fluid bed coating systems and said particles are further optionally coated with a film coating substance or same or different rate controlling substances.
3. In the above two options, the galantamine portion mainly contain a water insoluble component.

RESULTS AND DISCUSSION

Development Strategy:

The formulation strategy was to develop a non-infringing composition of Galantamine hdyrobromide extended release capsules and the entire strategy was to design around US Patent number: 7160559 by Janssen Pharmaceutica N.V.Hence the design was majorily using water insoluble materials right from the core to coat.

EXPERIMENT NUMBER-I:

Combination of immediate release pellets and controlled release pellets filled in hard gelatin capsules

S:No	Ingredients	Mg/capsule
Immediate release pellets		
1	Celpheres*	11.7
2	Galantamine hydrobromide	1.6
3	Eudragit NE 30D**	0.38
4	Isopropyl alcohol	q.s
Extended release pellets		
5	Celpheres	48.16
6	Galantamine hydrobromide	6.4
7	Eudragit NE 30D	1.64
8	Isopropyl alcohol	q.s to 65:35 ratio
9	Purified water	
Extended release coating (approx 10% w/w)		
10	Ethylcellulose	64%
11	Eudragit EPO	2.8%
12	AcetylTributyl citrate	6.9%
13	Talc	26.4%
14	Isopropyl alcohol	q.s to 75:25 ratio
15	Purified water	

Table No:2 Batch composition for galantamine hydrobromide extended release capsules

*Celphere ™ CP507 (microcrystalline cellulose spheres, particle size range 500-710 µm) is manufactured by Asahi Kasei Chemicals Corporation, Tokyo, Japan. **Eudragit NE30D and Eudragit EPO are manufactured by Rohm and Haas.

Manufacturing Process:

Immediate Release Pellets:

Galantamine hydrobromide was dispersed in isopropyl alcohol with stirring. Water was slowly added to the dispersion of step 1 with stirring until a clear solution was obtained. Eudragit NE30D was added to the solution of above step.The solution was spray coated over Celphere™ pellets in a fluidized bed processor .Coated pellets were dried to achieve loss on drying less than about 2% w/w determined at 105° C.

Extended Release Pellets:

Galantamine hydrobromide was dispersed in isopropyl alcohol with stirring. Water was slowly added to the dispersion of step 1 with stirring until a clear solution was obtained. Eudragit NE30D was added to the solution of above step.The solution was spray coated over Celphere™ pellets in a fluidized bed processor .Coated pellets were dried to achieve loss on drying less than about 2% w/w determined at 105° C.

Eudragit EPO was dissolved in isopropyl alcohol and ethyl cellulose and acetyl tri-butyl citrate were added with stirring to the clear solution. Talc was dispersed in water under stirring. Talc dispersion was added to above solution. The drug-coated pellets were further coated with the extended release coating dispersion of step 8 till 10% weight built up was obtained. Coated pellets were dried to achieve loss on drying less than about 2% w/w determined at 105° C. The immediate release pellets and the extended release pellets were mixed and filled into a capsule

EXPERIMENT NUMBER-II

Combination of controlled release pellets and immediate release pellets filled in hard gelatin capsules (65 parts and 35 parts by weight, respectively)

Table 1: Batch composition for galantamine hydrobromide extended release capsules.

S:No	Ingredients	Quantity/batch(g)
Drug loading		
1	Celpheres	60.0
2	Galantamine hydrobromide	8.0
3	Eudragit NE 30D	2.0
4	Isopropyl alcohol	q.s to 65:35 ratio
5	Purified water	
Extended release coating (approx 6.0% w/w)		
6	Ethylcellulose	64%
7	Eudragit EPO	2.8%
8	AcetylTributyl citrate	6.9%
9	Talc	26.4%
10	Isopropyl alcohol	q.s to 75:25 ratio
11	Purified water	

Manufacturing Process:

Drug Loading:

Galantamine HBr was dispersed in isopropyl alcohol with stirring and water was slowly added to the dispersion of step 1 with stirring until a clear solution was obtained. Eudragit NE30D was added to the above solution with stirring .The above solution was spray coated over Celphere™ in a fluidized bed processor.

Extended Release Coating Solution:

Eudragit EPO was dissolved in isopropyl alcohol and ethylcellulose and acetyltributyl citrate were added with stirring to the clear solution. Talc was dispersed in water under stirring and was added to ER coating solution. The drug-coated pellets were further coated with the above suspension till the target weight build up achieved. ER pellets and IR pellets from Example 1 (65 parts and 35 parts by weight, respectively) were blended and filled into capsules.

Dissolution Conditions

Medium: pH 6.8 Phosphate buffer.

Volume: 500 ml

Apparatus: USP 2 (Paddle)

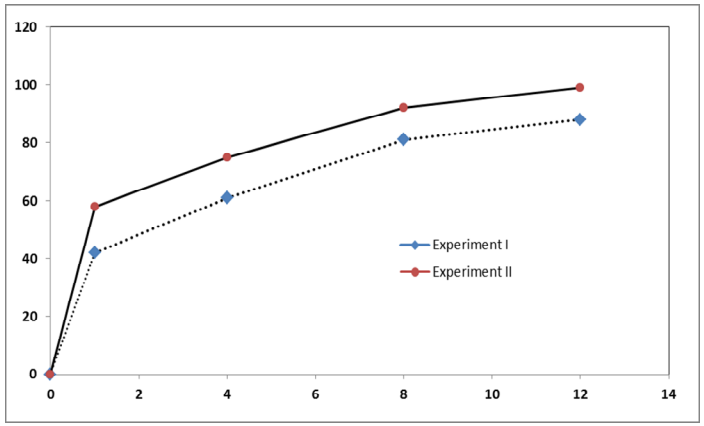
RPM: 50rpm

Assay determination: By HPLC

Time intervals: 1, 4, 8 and 12hours

Time (Hours)	Percentage of Drug Released	
	Experiment I	Experiment II
0	0	0
1	42	58
4	61	75
8	81	92
12	88	99

Table 2 : Experiment-I and II Dissolution Profile analysis results



Graph I: Comparative dissolution profile in pH 6.8 phosphate buffer

Summary & Observations:

Experiments I and II were observed to have satisfactory manufacturing process with good yield. The dissolution profile also shows a desired release profile meeting the predetermined specifications. Though Experiment II had shown much faster release at intial 1 hour which needs to be controlled to avoid any dose dumping at in vivo.

Experiment III

Capsules Comprising Mini-Formulations as Compressed Dosage Forms

S:No	Ingredients	Qty/batch(gms)
Core tablets		
1	Microcrystalline cellulose	1061.3
2	Galantamine hydrobromide	153.8
3	Povidone K90	75.0
4	Magnesium stearate	11.0
Extended release coating		
5	Ethylcellulose	90%
6	Hypromellose	10%
7	Isopropyl alcohol	q.s

Table 3: Batch composition for galantamine hydrobromide extended release capsules.

Manufacturing Process:

Preparation of Mini-Formulations:

Galantamine hydrobromide and microcrystalline cellulose were passed through an ASTM 40 mesh sieve and blended in a planetary mixer.The above blend was granulated using the povidone binder solution .The granules were dried in a fluidized bed dryer at a temperature 60° C., until the loss on drying was below 1% .The granules were milled and sized.The final granules were lubricated with presifted Magnesium stearate .The final lubricated blend was compressed in a rotary tablet-punching machine using standard concave punches of diameter 2.5 mm.

Coating of Mini-Formulations:

1. Ethylcellulose and hydroxypropyl methylcellulose were dissolved in isopropyl alcohol.
2. Compressed mini-formulations prepared in Part A were coated with the solution of step 1 in a perforated coating pan and dried at 45° C.

Filling Tablets into a Capsule:

About 11 Coated Mini-Formulations (Equivalent to 8 mg Galantamine Base) Prepared in Part B were Incorporated into a Size 1 Capsule.

Experiment IV

Capsules Comprising Mini-Formulations as pellets

S:No	Ingredients	Qty/batch(gms)
Core tablets		
1	Celpheres	695.0
2	Galantamine hydrobromide	102.5
3	Ethylcellulose 7 cps	102.5
4	Isopropyl alcohol	q.s
5	Purified water	q.s
Extended release coating		
6	Surelease	316.8
7	Hypromellose	8.8
8	Purified water	q.s

Table 4: Batch composition for galantamine hydrobromide extended release capsules.

Manufacturing Process:

Galantamine hydrobromide was dispersed in isopropyl alcohol with stirring and water was slowly added to the dispersion with stirring until a clear solution was obtained. Ethylcellulose was dissolved isopropyl alcohol with stirring .The solution was spray coated over Celphere™ in a fluidized bed processor. Hydroxypropyl methylcellulose was dissolved in water and Surelease® was added with stirring. The drug-coated pellets were further coated with the surelease suspension. Coated pellets were filled into a capsule.

In-Vitro Dissolution of Capsules Containing Galantamine Mini-Formulations

Medium: Phosphate buffer pH 6.8

Volume: 500 ml

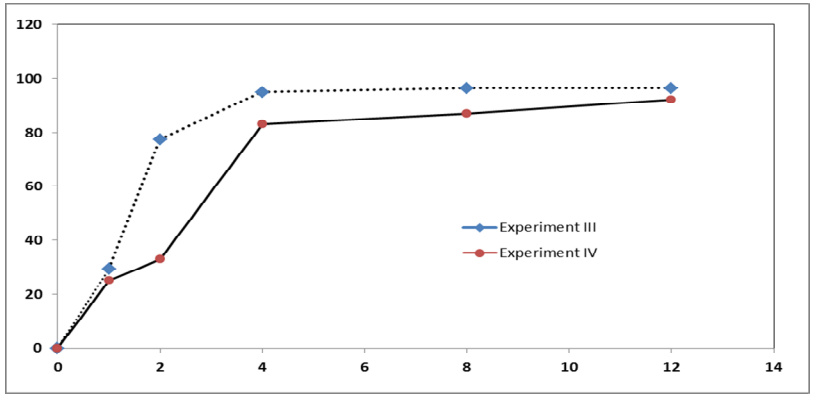
Apparatus: Type 1 (Basket type)

Stirring speed 100 rpm

Time Intervals: 1, 2, 4, 8 and 12hours

Time (Hours)	Percentage Drug Released	
	Experiment III	Experiment IV
0	0	0
1	29.5	25.0
2	77.5	33.0
4	95.0	83.0
8	96.5	87.0
12	96.5	92.0

Table-5: Dissolution profile in pH 6.8 phosphate buffer



Graph II: Comparative dissolution profile in pH 6.8 phosphate buffer

Summary & Observations:

Experiments III and IV were observed to have satisfactory manufacturing process with good yield. The dissolution profile also shows a desired release profile meeting the predetermined specifications. Experiment IV had shown much controlled and desired release in comparison to Experiment III,where in from 1 to 2 hours almost 80% of drug releases from the formulation .

DISCUSSION

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.

To overcome the above disadvantages, a controlled release dosage form was prepared which can permit once a day dosing by maintaining a stable drug plasma concentration for an extended period of time

The controlled release compositions of galantamine hydrobromide is an once a day formulation available as brand product in the market. The present study reveals alternate approaches for designing controlled release formulations of galantamine hydrobromide capsules using mainly water insoluble excipients like microcrystalline cellulose, Celphere™, Eudragit™, ethyl-cellulose etc. The explored controlled release technologies during the study were mainly reservoir system. Two different kind of controlled release formulation designs experimented in the study were pellet technology and mini tablets. Both the formulations were evaluated at the relevant physiological pH conditions of 6.8 phosphate buffer and the comparative dissolution profile was generated.

CONCLUSION

The above discussed controlled release compositions of galantamine hydrobromide extended release capsules are meeting the predefined specifications of between 20 to 60% drug release in one hour and not less than 80% in 12 hours when evaluated using pH 6.8 phosphate buffer at different compendial conditions. The revealed compositions contain controlled release pellets or mini tablets filled into capsules .The ratio of immediate release pellets to controlled release pellets can be optimized to modify the drug release characteristics.Thus the extended release pharmaceutical composition of the present invention exhibits a desired in vitro dissolution profile and can serve as an economical and simple alternative to the existing technologies and superior over immediate release compositions with a decrease in the frequency of administration and thus, better patient compliance.

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