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DEVELOPMENT OF EXTENDED RELEASE GALANTAMINE CAPSULES

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ABSTRACT

The objective of this study was to design oral extended release tablets of Galantamine Hydrobromide which can be used to moderate or delay the manifestation of Alzheimer's disease HPC HXF as the retardant polymer and to study the effect of various formulation factors such as polymer proportion, concentration of glidant, lubricant and their impact on the formulation. The tablets were prepared by the direct compression method. The formulated tablets were also characterized by physical and chemical parameters. The powder blend showed satisfactory flow properties, compressibility, and drug content. In vitro release studies were performed using US Pharmacopeia type II apparatus (Paddle method) in 900 ml of pH 6.8 phosphate buffer, 0.1 N HCl and pH 4.5 Acetate buffer. The total release proportions of galantamine hydro bromide from extended release tablets of optimized formula of F15 reached higher than 85 % within 12 hrs in all media.

KEYWORDS: Galantamine Hydrobromide, Alzheimer's disease, HPC HXF Polymer.

INTRODUCTION

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages. Controlled release (CR) tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high drugs.[1]

Extended release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing drug over an extended period of time after administration of a single dose. The advantages of extended release dosage forms over conventional forms include the less fluctuation in drug blood levels, frequency reduction in dosing, enhanced convenience and compliance, reduction in adverse side effects and reduction levels, reduce dose and side effects, and increase the safety margin for high-potency in overall health care costs.[2] The rate of drug release from solid dosage form may be modified by the technologies, which in general are based on modifying drug dissolution by controlling access of biologic fluids to the drug through the use of barrier coatings and controlling drug diffusion rates from dosage forms. Generally the different techniques employed to fabricate the modified release dosage forms are coated beads, granules and microspheres, multi tablet system, micro encapsulated drug, complex formation, ion exchange resins, and embedding drug in slowly eroding or hydrophilic matrix system.[3]

The use of polymeric matrix devices to control the release of a variety of therapeutic agents as become increasingly important in the development of modified release dosage forms. This device may be a swellable, hydrophilic monolithic systems, erosion controlled monolithic systems or non erodible systems. The hydrophilic gel forming matrix tablets are extensively used for oral extended release dosage forms due to their simplicity, cost effectiveness and reduction of the risk of systemic toxicity due to dose dumping.[4]

Alzheimer's disease is a slowly developing neurodegenerative disease that produces a progress loss of memory and cognitive function, i.e., Dementia. Alzheimer's disease is a gradual and irreversible decline in intellectual ability that usually appears after the age of 60. The disease has been estimated to affect 5 % of over 65 year olds. Patients experience a progressive loss of cognitive function, usually beginning with loss of shortterm memory followed by loss of other functions such as ability to calculate and ability to use everyday objects. These functional changes appear to result primarily from the loss of cholinergic transmission in the neocortex and are characterized pathologically by abundant diffuse and neurotic plaques throughout most cortical regions.[5]

Galantamine hydro bromide is a phenanthridine alkaloid

and isolated from several members of the Amaryllidaceae family plant, such as snowdrops. It can be used to moderate or delay the manifestation of AD symptoms as one of the selective and reversible acetyl cholinesterase (AChE) inhibitors, thus show the memoryenhancing effects. Further, its concentration-dependent inhibitive effect on AChE activity has antioxidative properties, involving decreased super oxide anion and NO overproduction, as well as restoring mitochondrial membrane potential Galantamine hydro bromide has been approved most recently by the FDA for symptomatic treatment for AD and vascular dementia by oral or inject able administration.[6]

MATERIALS

Galantamine Hydrobromide as a gift sample from Aurobindo pharma ltd, Hyd. Hydroxy propyl cellulose HXF, Colloidal silicon dioxide, Avicel.

METHODOLOGY[7]

Fluidised Bed Processing (FBP) Fluidized bed process or is used for drug layering, coating process and drying Procedure: Accurately the raw materials are weighed and dispensed along with specified quantities of solvents. The coating solution of HPMC E5 is prepared with specific quantity of water.And to this solution all other ingredient is added under constant stirring (1600-1900RPM). Then the solution is filtered through # 80 mesh to remove any lumps or visibleparticles. Then finally drug is loaded on to the specified quantity of sugar spheres (cores) in fluid bed processor (FBP). After drug loading these dried pellets are sieved to obtain pellets of uniform required size. For the above drug loaded pellets, HPMC E5 is coated along with PEG-6000 as a barrier coat which is prepared by is dissolving HPMC E5 and PEG-6000 in specific quantity of water. After barrier coating, pellets are sieved to obtain desired size. To the above barrier coated pellets, sustain coating of Ethyl cellulose N50 along with PEG-6000 are coated, which is prepared with specified amount of EC N50 and PEG dissolved using isopropyl alcohol (IPA) as a solvent.

Formulation TRAILS[8]

Formulation studies of Galantamine Hydrobromide extended release capsules are basedon pre formulation data, various excipients are selected and their compilation is shown in the Table.No.1.

Table 1: Formulae for trial batches.

S.No	Ingredients(gms)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	GalantamineHydrobromide	35.87	35.87	35.87	35.87	35.87	35.87	35.87	35.87	**35.87**
2	SugarPellets(16≠22)	273.2	273.2	273.2	273.2	273.2	273.2	273.2	273.2	**273.2**
3	HPMCE5	8	9	10	12	14	14	15	14.5	**14**
4	Water	478.2	478.2	478.2	478.2	478.2	478.2	478.2	478.2	**478.2**
BarrierCoating										
5	HPMCE5	15	12	14	14	12	14	14	14	**14**
6	P.E.G-6000	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	**1.4**
7	PurifiedWater	260	260	260	260	260	260	260	260	**260**
ERcoating										
10	Ethylcellulose	17.5	16.5	15.5	14	12	12	9.5	10	**10.5**
11	P.E.G-6000	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	**1.4**
12	I.P.A	493.5	493.5	493.5	493.5	493.5	493.5	493.5	493.5	**493.5**
13	PurifiedWater	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	**10.0**
14	Totalweight	350	350	350	350	359	350	350	350	**350**

Evaluation Procedure

Evaluation Tests For Galantamine Loaded Pellets:[9.10,11]

i. Physical Description: 0.5g of Galantamine pellets are transferred in to a dry Petri dish or dispensed on a white card. And the content visually is observed visually for its appearance.

ii. Bulk Density & Tap Density: Bulk density is determined by USP method-I.20g of pellets is taken and poured into a measuring cylinder. Bulk volume of pellets is noted. Bulk density = Mass of pellets / Bulk Volume. Tap Density is determined with tap density tester, by placing a graduated cylinder containing a known mass of pellets in it, which is then tapped for a fixed number of taps (500). Tapped density = Mass of pellets / Tapped Volume.

iii. Hausnersratio: Using the tapped density and bulk density values, the Hausners ratio is calculated using the formula,

Hausners ratio=ρt/ρo

Where, ρt = Tapped density ρo= Bulk density.

iv. Angle of repose Accurately weighed quantity of Galantamine pellets is poured on to a funnel kept at a height of 2.5cm from the base. The radius and height of the heap is measured. Angle of repose is calculated using the formula, θ=tan-1 (h/r).

v. Water Content By KF Titration: 30 ml of methanol is taken in a clean, dried Karl Fischer titration flask and titrated with KF reagent until the end point to neutralize the free water. Galantamine pellets are powderd finely. Accurately weighed quantity of 0.5 gm of the powdered pellets is transferred into the titration flask and dissolved

by stirring and then titrate with KF reagent to the end point. The percentage water content is calculated by the formula.

Evaluationofcapsules

i. Weight variation test 10 capsules were selected randomly and weighed individually, each capsule was emptied and the empty capsules weights were noted. The weight difference between the filled capsules and the empty capsules gives the weight of the drug content present in the capsule. This process is repeated for all the capsules and average weight was calculated according to USP specification. None of the individual capsule content weight should be less than 90% and not more than110% of the average content weight.

iii. Disintegration The capsules are placed in the basket rack assembly tubes, which is repeatedly immersed 30 times per minute into a thermostatically controlled at 37ºC and observed over the time of 30 min or as monograph. Until capsules disintegrate completely into a soft mass having no palpably firm core, and only some fragments of the gelatin shell.

iv. Dissolution 500ml of dissolution medium (pH 6.5 phosphate buffer) in USP apparatus-II at 50 rpmand temperature at 37 ± 0.5 ºC, one capsules is placed in each vessel for specific time.10ml of the solution is withdrawn from each vessel and replaced with equal volume offresh dissolution medium atspecific time intervals. Then solution is filtered through0.45µ membrane filterandthefiltrate isassayedbyHPLCmethod.

v. Moisture permeation test The USP requires determination of the moisture permeation characteristics of single unit and unit dose containers to assure their suitability for packing capsules. The degree and rate of moisture penetration is determined by packing the dosage unit together with a color revealing desiccant pellet, exposing the packaged unit to known relative humidity (75 ± 5% RH) over a specified time (3 months),The desiccant pellet is observed for color change (indicating desiccating absorption of moisture) and also comparing the pre and post weight of the packaged unit.

Stability Studies The stability of the capsules containing pellets, packed into HDPE containers is determined by conducting Accelerated stability testing at 40ºC ± 2ºC / 75 ± 5% RH and Long term stability testing at 25 ± 2ºC / 60 ± 5% RH conditions for the period of 3 months as per ICH guidelines. The product is analyzed for assay, moisture content and disintegrate on time at specified time intervals of 1month and 3month.

RESULTS AND DISCUSSION

Table 2: PhysicalpropertiesofGalantaminehydrobromide.

Bulkdensity (gm/ml)	TappedDensity (gm/ml)	Compressibility Index	Hausner's Ratio	Angleofrepose
0.248	0.328	24.39%	1.322	26.04^0

Table 3: CharacteristicsofCapsulesF1toF9.

Evaluationtest	F1	F2	F3	F4	F5	F6	F7	F8	F9
Moisturecontent %	3.2	2.9	3.2	3.6	3.3	2.9	2.3	1.8	1.72
Assay%	99 ± 3.97	101.1 ± 2.92	98.3 ± 3.17	98 ± 2.70	98 ± 2.13	100 ± 1.52	99 ± 1.35	99 ± 2.29	100.13 ± 3.07
Weight Variation (mg)	275.7	308.4	314	289	276	295	299	298.4	300.6
Capsule ContentUniformity %(24mg)	96.9 ± 2.97	108.7 ± 2.82	105 ± 2.92	102.5 ± 1.95	104.2 ± 2.67	95.7 ± 1.97	100.6 ± 1.85	98.9 ± 1.88	99.0 ± 1.97
Disintegrationtime (min)	4.30 ± 0.39	4.50 ± 0.33	4.40 ± 0.31	5.10 ± 0.23	4.50 ± 0.16	4.50 ± 0.11	4.55 ± 0.21	5.05 ± 0.51	4.25± 0.31

Dissolution Studies

Table 4: InvitrodissolutionprofileofformulationsF1-F9.

S. No	Timeinhrs	Percentagedrug release									
		RazadyneER	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	2	**38.35**	60.49	48.17	42.17	52.04	61.01	28.61	52.39	42.28	**38.25**
2	6	**67.72**	87.88	82.12	72.12	68.12	101.01	57.86	76.82	62.85	**66.94**
3	12	**81.35**	93.24	88.33	78.33	74.60	100.68	74.58	82.06	79.34	**80.97**
4	16	**90.09**	98.65	89.04	89.04	80.62	100.10	81.77	89.62	87.23	**89.68**

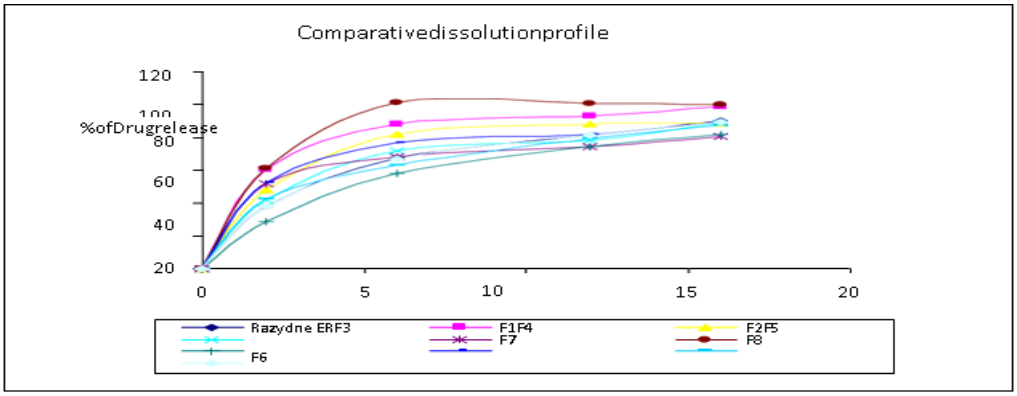

Fig. 1: ComparativedissolutionprofileofformulationsF1-F9.

Stabilitystudies

Table 5: Evaluationparametervaluesat differenttemperatureconditions.

S. No.	Test	Storage Condition 40ºC ±2ºC /75%RH±5%RH		Storage Condition 25ºc ±2ºC/60%RH±5%RH	
		Initial	90days	Initial	90days
1	PhysicalAppearance	White	White	White	White
2	% MoistureContent	1.72	1.74	1.72	1.72
3	%DrugContent	100.1	99.9	100.1	100.0%
4	Disintegrationtimeinminutes	4.30	4.27	4.30	4.28

CONCLUSION

Galantamine Hydrobromide is a Cholinesterase inhibitor which is used to treat the cognitive man infestations of Alzheimer's disease. The active pharmaceutical ingredient Galantamine Hydrobromide is subjected topre formulation study, which encompasses the "Accelerated drug excipient compatibility study", and the results obtained with selected excipients showed good compatibility with Galantamine Hydrobromide drug. In this study Galantamine Hydrobromide pellets (24mg) are prepared by FluidizedBed Processing. Nine formulations of extended release pellets are prepared byincorporating different concentrations of HPMC and Ethyl Cellulose as sustainpolymers. Trial 9 formulation containing 4% HPMC and 3% Ethyl cellulose isfound to be best of all the trials showing drug release are matching the innovator product (Razadyne). The best formulation is repeated again for reproducibility, and all the quality control tests are done for conformation. There sults are found to be super imposable with each other. Stability study is carried out for 3months at 25°C±2°C; 60%±5%RH: and 40°C±2°C; 75%±5% RH, according to ICH guidelines the formulation is found to be stable.

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