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FORMULATION AND CHARACTERIZATION OF GALANTAMINE HYDROBROMIDE EXTENDED RELEASE TABLETS

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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 symptoms, using 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.1 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-potency drugs.

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

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in overall health care costs. 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.

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.

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 short-term 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.

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.

MATERIALS:

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

METHODOLOGY:

Table 1Composition of different trials taken for development of final formula

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Galatamine HCL	10.252	10.252	10.252	10.252	10.252	10.252	10.252	10.252	10.252	10.252	10.252	10.252	10.252	10.252	10.252
Hydroxyl Propyl Cellulose	48.647	66.647	48.647	64.568	74.868	64.568	64.568	64.568	64.568	64.568	64.568	64.568	64.568	64.568	64.568
Talc	1.860	1.860	1.860	1.860	1.860	1.860	1.66	1.860	2.06	1.860	1.860	1.860	1.860	1.860	1.860
Aerosol 200	0.620	0.620	0.620	2.400	2.400	2.400	2.400	2.400	2.200	2.400	2.600	2.400	2.400	2.400	2.400
Magnesium stearate	0.620	0.620	0.620	0.620	0.620	0.620	0.620	0.620	0.620	0.620	0.620	0.420	0.620	0.820	0.620
Avicel	--	--	--	--	--	0.500	0.300	0.100	0.500	0.300	0.100	0.500	0.300	0.100	0.300
Tablet total Weight	62.00	80.00	62.00	80.00	90.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00

Analytical Method

An in-house developed and validated chromatographic method (HPLC, Schimadzu), was used for the estimation of drug in bulk, formulations, and dissolution samples.

Chromatographic conditions:

- Column : X-Terra RP-18, 5m (150mm ´ 4.6mm)
- Pump mode : Isocratic
- Flow rate : 1.0 ml/min
- Detection : UV, 220 nm
- Injection Volume : 10 ml
- Column temperature : 40°C
- Run time : 12 minutes.

Procedure:

Inject 10 ml of sample solution in duplicate into the chromatograph. Record the chromatograms and measure the peak areas. Retention time of Galantamine peak is about 6.5 minutes.

Formulation development & formula optimization

Formulation 1: Trial batch of Galantamine Hydrobromide Extended Release Tablets by direct compression approach.

Formulation 2: Trial batch to reduce the rate and extent of drug release by increasing the concentration of polymer i.e. Hydroxypropyl cellulose.

Formulation 3, 4 & 5: Trial to optimize the concentration of Release rate controlling Polymer i.e. Hydroxypropyl Cellulose.

Formulation 6, 7 & 8: Trial to optimize the concentration of Glidant i.e. Talc.

Formulation 9, 10 & 11: Trial to optimize the concentration of Glidant i.e. Silica, Colloidal anhydrous.

Formulation 12, 13 & 14: Trial to optimize the concentration of Lubricant i.e. Magnesium stearate.

Formulation 15: Trial batch to improve flow properties of the final blend by increasing the concentration of Glidant i.e. Silica Colloidal Anhydrous and Diluent i.e. Cellulose microcrystalline.

Table 2. Final unit composition of Galantamine Hydrobromide Extended Release Tablets

Ingredients	Qty per tablet (mg)
Galantamine hydrobromide	10.252
Cellulose microcrystalline	0.3
Hydroxypropyl cellulose	64.568
Silica Colloidal Anhydrous	2.4
Talc	1.86
Magnesium stearate	0.62
Tablet weight	***80.00 mg***

Manufacturing process development- direct compression approach

Weigh accurately all excipients and dispense separately. Co sift talc and Galantamine hydrobromide through # 30 sieve. Co sift Silica Colloidal Anhydrous and step - 2 and pass through # 30 sieve. Sift Hydroxy propyl cellulose through # 30 sieve. Resift the step - 3 and step - 4 through # 30 sieve. Unload the blend of step - 5 into blender and mix for 15 minutes. Magnesium stearate was sifted through # 60 sieve mesh, loaded into blender and blended for 5 minutes. The blend of step-7 was compressed using 5.2 mm round, standard concave punches.

RESULTS & DISCUSSIONS:

Characterization of Bulk Drug and Effect of Various Formulation Excipients

The bulk drug was characterized by various tests of identification according to the certificate of analysis given by the supplier and analyzed by the above-mentioned UV spectrophotometric method. The infrared (IR) spectrum obtained (IR spectrophotometer; IR Report 100, Jasco) was compared with that of the standard. To study the compatibility of various formulation excipients with Galantamine, solid admixtures were prepared by mixing the drug with each formulation

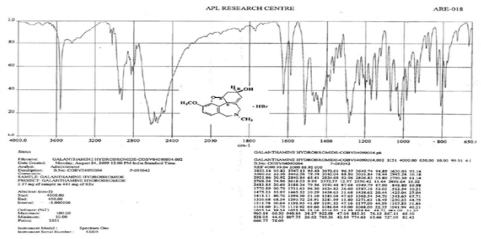


Figure 1. FTIR Spectrum

excipients separately in the ratio of 1:1 and then stored in airtight containers at 30-C ± 2-C/65% relative humidity (RH) ± 5% RH.

The solid admixtures were characterized using Fourier transform infrared spectroscopy (FTIR) (IR Prestige-21, Shimadzu, Kyoto, Japan).

The drug substance is structurally elucidated and characterized based upon spectroscopy, analytical testing and inference.

Various characteristics of Drug substance were evaluated as follows:

Particle size, shape and Surface area.

Powder characteristics:

- Bulk &Tapped density
- Compressibility Index

API Solubility:

The saturation solubility of Galantamine Hydrobromide API drug substance in different physiological media with different pH has been determined and the results are tabulated below.

Table 3. Results for Lubricated Blend parameters

Test	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Bulk Density(g/ml)	0.360	0.382	0.315	0.308	0.320	0.313	0.308	0.323	0.318	0.308	0.318	0.311	0.308	0.314	0.315
Tapped Density(g/ml)	0.548	0.609	0.465	0.438	0.490	0.460	0.438	0.468	0.457	0.438	0.475	0.472	0.438	0.458	0.438
Compressibility Index(%)	34.30	37.25	32.25	29.68	34.69	32.39	29.68	30.98	30.41	29.68	33.05	34.11	29.68	31.44	29.68

Table 4. Results for Compressed Tablet parameters

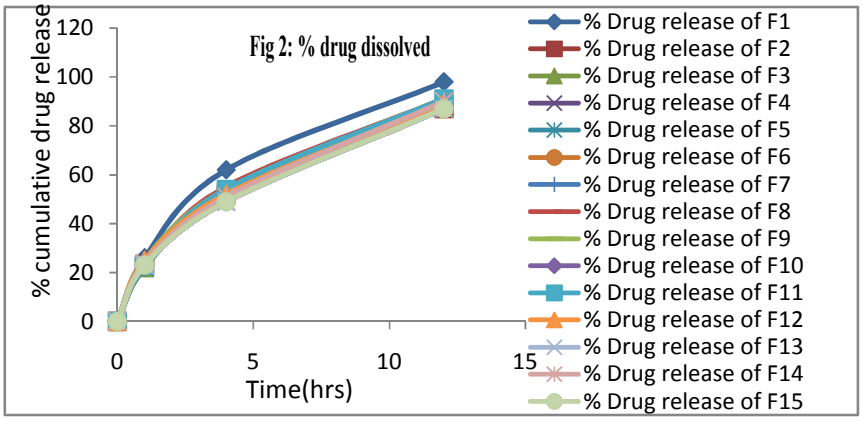
BATCH NO	Compressed tablet parameters results														
Test	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
AVG.WT.	62.00	80.00	66.00	80.30	90.20	80.70	80.30	80.20	80.50	80.30	80.60	80.30	80.30	80.80	80.00
THICKNESS	3.17-3.27	3.8-4.10	3.78-3.86	3.87-3.97	4.32-4.40	3.90-3.94	3.87-3.97	3.90-3.93	3.90-3.94	3.87-3.97	3.89-3.92	3.89-3.95	3.87-3.97	3.90-3.96	3.87-3.97
FRIABILITY	0.02	0.02	0.03	0.03	0.02	0.05	0.03	0.03	0.05	0.03	0.03	0.02	0.03	0.03	NIL.

Table 5: Solubility studies

Solvent	Approximate pH of the solvent buffer	Mean solubility (mg/mL)	Dose/solubility
0.1N HCl	1.2	63	0.38
pH 4.5 Acetate Buffer	4.5	59	0.41
pH 6.8 Phosphate Buffer	6.8	59	0.41
pH 7.2 Phosphate Buffer	7.2	61	0.40
Purified Water	6.5	61	0.40

Table 6: % drug dissolved

% Drug dissolved in 900ml pH 6.8 Phosphate buffer															
Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
1	26	23	22	23	22	23	23	24	25	23	23	25	23	24	23
4	62	52	52	49	52	52	49	55	54	49	54	52	49	51	49
12	98	87	89	87	90	87	87	91	91	87	91	89	87	90	87



From above data it is evident that Galantamine Hydrobromide API has a high solubility over the entire pH range from pH 1.2 – pH 7.2. Further the solubility was found to be pH independent, being a modified release dosage formulation, pH 6.8 phosphate buffer was selected as a Suitable dissolution medium for testing Galantamine Hydrobromide Extended Release tablets.

Dissolution parameters:

- Medium: 50M Phosphate Buffer pH 6.8, 900mL
- Apparatus: USP Apparatus II [Paddle]
- Rotation Speed: 50 rpm
- Temperature: 37.0 ± 0.5°C
- Time: 1, 4 and 12 Hours

Drug product release profile in different dissolution media: As a part of the development activity, the dissolution studies were carried out on various strengths of Galantamine Hydrobromide Extended Release Tablets at different pH (viz., pH 6.8 Phosphate buffer, 0.1N HCl and pH 4.5 Acetate buffer) to determine the most relevant medium for dissolution of the drug. The mean results (n=12) are as follows:

Table 7 :Dissolution Profile of Optimized Batch in 0.1N HCl

Dissolution Profile (% Drug release in 900ml 0.1N Hcl)							
Tablet No.	**Galantamine Hydrobromide Extended Release Tablets 8mg Batch No. F15**						
Time (Hrs)	**1**	**2**	**4**	**6**	**8**	**10**	**12**
1	24	40	60	76	86	95	99
2	23	38	58	73	85	93	100
3	26	40	61	75	86	94	99
4	25	40	60	75	87	97	102
5	25	40	60	74	85	93	98
6	27	42	62	77	87	95	100
7	26	41	63	77	88	96	101
8	25	42	64	79	90	98	103
9	25	41	61	75	86	94	99
10	24	39	59	74	85	93	99
11	24	40	61	76	88	96	102
12	25	39	60	72	84	92	98
Average	**25**	**40**	**61**	**75**	**86**	**95**	**100**
% RSD	**4.35**	**2.97**	**2.73**	**2.54**	**1.94**	**1.93**	**1.65**

Table 8: Dissolution Profile of Optimized Batch in pH 4.5 Acetate Buffer

Dissolution Profile (% Drug release in 900ml pH-4.5 Aceteate buffer)							
Tablet No.	**Galantamine Hydrobromide Extended Release Tablets 8mg Batch No. F15**						
Time (Hrs)	**1**	**2**	**4**	**6**	**8**	**10**	**12**
1	21	40	58	79	90	10	106
2	26	42	63	78	89	98	104
3	23	40	61	75	86	94	99
4	22	38	59	74	85	94	100
5	22	40	62	77	88	96	101
6	21	38	60	77	89	98	104
7	25	41	62	79	90	97	102
8	21	39	62	77	89	97	104
9	27	42	62	77	89	98	104
10	21	38	59	75	86	95	102
11	24	41	62	76	88	98	98103
12	28	41	61	76	88	98	104
Average	**23**	**40**	**61**	**77**	**88**	**97**	**103**
% RSD	**10.84**	**3.69**	**2.57**	**2.03**	**1.84**	**1.89**	**1.95**

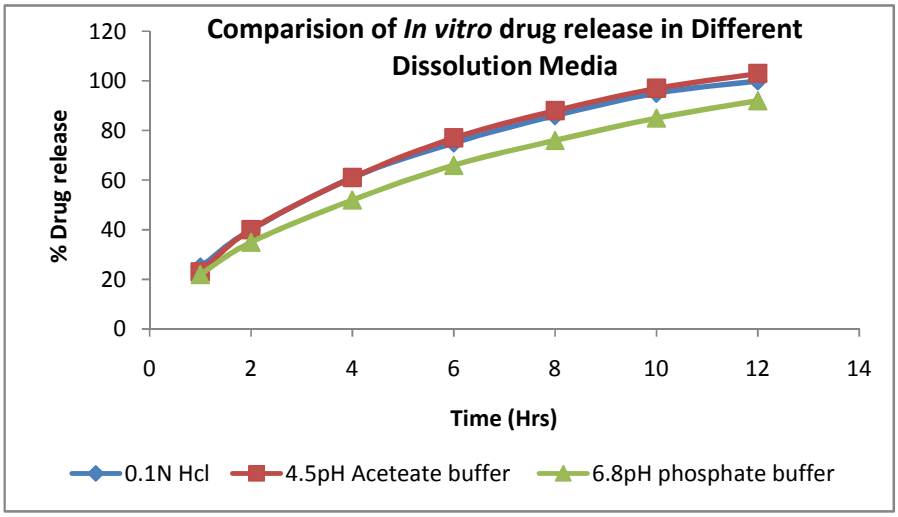


Fig : 3 comparison of in vitro drug release in different dissolution media

Table 9 : Dissolution Profile of Optimized Batch in pH 6.8 Phosphate Buffer

Dissolution Profile (% Drug release in 900ml pH-6.8 Phosphate buffer)							
Tablet No.	**Galantamine Hydrobromide Extended Release Tablets 8mg Batch No. F15**						
Time (Hrs)	**1**	**2**	**4**	**6**	**8**	**10**	**12**
1	20	35	53	66	77	85	92
2	23	35	52	65	75	84	91
3	22	36	54	68	79	88	95
4	21	35	53	66	76	85	90
5	23	35	52	66	76	82	92
6	21	34	51	64	74	84	89
7	20	34	52	65	76	84	9
8	23	35	52	65	76	84	92
9	22	35	53	67	77	86	93
10	22	35	53	66	77	86	92
11	23	35	52	66	76	85	92
12	20	34	52	65	75	84	90
Average	**22**	**35**	**52**	**66**	**76**	**85**	**92**

CONCLUSION:

In vitro release studies were performed using US Pharmacopeia type II apparatus (Paddle method) in 900 ml of pH 6.8 phosphate buffer. From the above obtained lubricated blend parameters, compressed profiles it indicates that amongst all the trial batches, F15 of Galantamine Hydrobromide Extended Release Tablets showed good results. In order to analyze and standardize the extended release of drug from F15, further the study was carried out with 3 different buffer media namely pH 6.8 phosphate buffer, 0.1 N HCl and pH 4.5 Acetate buffer and it was observed the total release proportions of galantamine hydro bromide from extended-release tablets reached higher than 85 % within 12 h in all buffer media.

REFERENCES:

1. Kun Li and Shuoye Yang, Study on novel galantamine hydrobromide sustained-release tablets and it's in vitro releasing property, Pak. J. Pharm. Sci., Vol.27, No.5(Suppl), September 2014, pp.1621-1626
2. Chavan Ritesh A. And Mayee Rahul, Formulation and evaluation of extended release pellets of an antialzhimer drug, ijpi.,Volume 3, Issue 4, PP.65-75
3. Arunkanth Krishnakumar Nair*, Dr.Subhash pandurang Gore, Anand shankaranarayanan and Balaji sathurappan et al, A study of controlled release galantamine hydrobromide solid dosage formulations: a novel approach, ijrrpas, dec-2012, 2(6).965-980
4. Biswajit Biswal and Darshan Sharma, Design, Development and Evaluation of Galantamine Hydrobromide Bilayer Sustained Release Tablet, Der Pharmacia Lettre, 2013, 5 (6):12-19
5. Punna Rao Ravi,1 Sindhura Ganga,1 and Ranendra Narayan Saha1, Design and Study of Lamivudine Oral Controlled Release Tablets, AAPS pharmscitech 2007; 8 (4) Article 101
6. Avinash G.Thombre, Assessment of the feasibility of oral controlled release in an exploratory development setting DDT • Volume 10, Number 17 • September 2005
7. Margret Chandira1*, B.S.Venkateswarlu1 ,jadhavanup Shankarrao1, debjitbhowmik1, B.Jayakar1, T.V.Narayana2, Formulation and Evaluation of Extended Release Tablets containing Metformin hcl/Int.J. Chemtech Res.2010,2(2)
8. Kuldeep Malodia1, Anil Kumar1, Sunil Kumar1 and Pankaj Rakha2,

Formulation and evaluation of extended release tablets of salbutamol sulphate, Der Pharmacia Lettre, 2013, 5 (1):177-181

9. Sathish Ummadi, B. Shravani, N. G. Raghavendra Rao*, M. Srikanth Reddy, B. Sanjeevnayak, Overview on Controlled Release Dosage Form, Int J Pharma Sci. 2013, 3(4): 258-269
10. Vijay D. Wagh* and Kailas S. Patil, Formulation, development and evaluation of extended release tablets of metoprolol succinate J Pharm Phytother 2013, 1:4 (ISSN 2321-5895)
11. Vijay J, Sahadevan JT1, Prabhakaran R2, Mehra Gilhotra R, Formulation and Evaluation of Cephalexin Extended-release Matrix Tablets Using Hydroxy Propyl Methyl Cellulose as Rate-controlling Polymer, Journal of Young Pharmacists Vol 4 / No 1
12. Lloyd N. Sansom, Oral extended-release products - Australian Prescriber, http://www.australianprescriber.com/magazine/22/4/88/90
13. Shashidhar Reddy Dodda1, Prakash Rao Boggrapu2* Development and in Vitro-in Vivo Evaluation of Controlled Release Matrix Tablets of Desvenlafaxine Pharmacology & Pharmacy, 2012, 3, 15-19
14. Basavaraj K Nanjwade*, Sunil R Mhase and FV Manvi, Formulation of Extended-Release Metformin Hydrochloride Matrix Tablets, Trop J Pharm Res, August 2011;10 (4): 375
15. Mohammad Usman3, Irshad Ali1, Hafsa Bibi1, Javeid Iqbal2 and Kashif Iqbal3* Preparation and Evaluation of Controlled Release Tablets Containing Mefenamic Acid Clin Exp Pharmacol 2:107
16. Narasimharao R*, Anusha Reddy M, Swetha Reddy N, Divyasagar P and Keerthana K, Design and Evaluation of Metformin Hydrochloride Extended Release Tablets by Direct Compression, www.ijrpbsonline.com, Vol. 2 (3) Jul – Sep 2011
17. Vamsy krishna.a*3, K.R.Srinath2,C.Pooja Chowdary2 Palanisamy.p3, G.R.Vijayasankar1, Stavudine Loaded Microtablets using various Cellulose Polymers: Preparation and In-Vitro Evaluation www.ijrpbsonline.com, Vol. 2 (2) Apr – Jun 2011
18. K. P. Sampath Kumar*1, Debjit Bhowmik2, Chiranjib2, Margret Chandira, K. K.Tripathi2, Innovations in Sustained Release Drug Delivery System and Its Market Opportunities, J. Chem. Pharm. Res., 2010, 2(1): 349-360

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