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Formulation development and characterization of galantamine hydrobromide extended-release capsules (8mg)

Alli Srija *, M. Sunitha Reddy, K. Hari Krishna and A. Vijay Reddy

Department of Pharmaceutics, Centre for Pharmaceutical Sciences, UCEST, Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad, 500085, Telangana, India.

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Abstract

The aim of the present work is to develop extended-release capsules of Galantamine HBr (8mg) and compare them with the reference listed drug (Reminyl or Razadyne). The capsules were prepared using Pelletization technique and evaluated for preformulation characteristics, physical, and chemical parameters. The *In-vitro* dissolution studies were conducted using USP type II (paddle apparatus) in 900 ml of pH 6.5 phosphate buffer. Among all the formulations, F7 was found to be pharmaceutically equivalent to reference listed drug due to its similarity factor (f2= 96) in drug release profile. The F7 formulation was loaded for stability study and no change was observed, which indicates that the optimized F7 formulation was stable.

Keywords: Galantamine HBr; Reminyl or Razadyne; Pelletization technology; USP type II.

1 Introduction

Alzheimer's disease (AD) is an irreversible, deteriorative, and untreatable neurodegenerative condition. According to prevalence estimates in Europe, approximately 3% of individuals who are 70 years old are affected by AD, and this percentage increases to approximately 20% among individuals over the age of 80. [1] In the United Kingdom, the Alzheimer's Society estimates that there are approximately 650,000 individuals with dementia, out of which around 325,000 individuals likely have AD. In the United States, it is estimated that 4 million people are affected by this disease. [2] The disease is characterized by a progressive decline in cognitive functioning, which results in changes in emotions and behavior. This decline is often accompanied by neuropsychiatric symptoms such as hallucinations and delusions, and it ultimately leads to a loss of independence, institutionalization, and death. [3]

Galantamine hydrobromide (GH) was authorized by the Food and Drug Administration (FDA) in 2001 for the treatment of AD. [4,5] It is a neuroactive drug with the ability to traverse the blood-brain barrier and decelerate the progression of AD. GH belongs to the category of acetylcholinesterase inhibitors (AChEI). The mechanism of action of this drug involves the inhibition of the acetylcholinesterase enzyme (AChE), a degradative enzyme found in the brain. By preventing the hydrolysis of the neurotransmitter acetylcholine (ACh), it remains active and performs its cognitive functions in the brain. Studies conducted by Kumar et al. and Suh et al. have demonstrated the effectiveness of GH and its derivatives in alleviating the behavioral, functional, and cognitive symptoms of AD. [6–8]

Extended-release dosage forms are designed to have a long-lasting therapeutic effect by continuously releasing the medication over an extended period after a single dose. The release patterns of these systems are primarily regulated by the unique technological structure and design of the system. Formulation scientists have encountered challenges in developing oral extended-release systems due to difficulties in confining and localizing the system in specific areas of

* Corresponding author: Alli Srija

the gastrointestinal tract. Extended-release dosage forms offer advantages over conventional forms, including a decrease in drug concentration fluctuations in the bloodstream, a reduced dosing frequency, improved convenience and adherence, and a decrease in adverse side effects. [9]

The present work is to develop the Galantamine HBr extended-release capsules (8mg) using the layer pelletization technique through the FBC process and compare them with the reference listed drug (Reminyl or Razadyne).

2 Materials and methods

2.1 Materials

Galantamine HBr was purchased from Aurobindo Pharma (Hyderabad), Sugar Spheres #20/#25 (Globtech Lifesciences, Haryana), Ethylcellulose 7CPS (Asha cellulose, Mumbai), PEG 6000 (Clariant, Mumbai), Isopropyl Alcohol (Deepak Fertilizers, Hyderabad), Cetyl Alcohol (Sainor Lifesciences, Hyderabad), and Purified Water from In-house.

2.2 Preformulation studies

2.2.1 API Description

The colour and appearance of Galantamine HBr can be known by visual inspection.

2.2.2 Melting point [10]

The melting point is determined using Thiele's tube method, whereby a small quantity of Galantamine HBr is placed within a capillary tube sealed at one end is attached to a thermometer and inserted into a Thiele's tube filled with 75% of concentrated sulphuric acid, and the temperature at which fusion starts is recorded.

Limits**:** 269 –270^{o}C

2.2.3 %LOD [11]

Take the small amount of pellets and place in the moisture analyzer and heat at 105^{o}C and note the % LOD.

Limits: NMT 0.5%

2.2.4 Solubility [12]

An excess amount of drug was added to known volume of various solvents to form the supersaturated solution and the solutions were sonicated and kept at room temperature to achieve equilibrium.

2.2.5 Determination of absorption maxima [13]

Galantamine HBr solution (1µg/ml) in pH 6.5 phosphate buffer was analyzed on spectrophotometer in the UV range 200 to 400 nm. The scanned λmax is compared with literature values.

2.2.6 Construction of calibration curve

Standard stock solution

Dissolve 100 mg of Galantamine HBr in a 100 ml volumetric flask containing pH 6.5 phosphate buffer and make up to the mark to obtain a solution of 1000 µg/ml. The final solution was sonicated for about 5 minutes for complete solubilization of the drug.

Working solution

Pipette 10 ml of stock solution into a 100 ml volumetric flask and dilute with phosphate buffer pH 6.5 up to the mark to obtain a solution of 100 µg/ml.

Procedure

Pipette out different aliquots (0.1,0.2...0.5ml) from the working solution (100 µg/ml) into 10 ml volumetric flasks individually and make up to the mark with phosphate buffer pH 6.5 to get the series of concentrations (1,2...5 µg/ml).The absorbance of each dilution was measured using a UV spectrophotometer at λmax 289 nm, and plot the concentration of Galantamine HBr (x-axis) against the corresponding absorbance (y-axis) to obtain a calibration curve.

3 Manufacturing procedure

3.1. Drug coating

3.1.1 Preparation of drug coating solution

The required quantity of purified water and isopropyl alcohol are taken into separate beakers and an accurately weighed amount of Galantamine HBr and all remaining ingredients are dissolved in water and isopropyl alcohol respectively. The above two solutions are mixed by stirring continuously at 1600 – 1900 RPM by using the mechanical stirrer until a clear solution is obtained.

3.1.2 Drug coating process

Load the accurately weighed sugar spheres (#20/#25) into FBC bowl, then coat these cores with the drug coating solution by bottom spray wurster method. The obtained drug coated pellets are dried and sifted through #20/#25 mesh.

3.2. Extended-release coating

3.2.1 Preparation of extended-release coating solution

The required quantity of purified water and isopropyl alcohol are taken into separate beakers and an accurately weighed amount of Ethyl cellulose MP 50, PEG 6000 are dissolved in water and isopropyl alcohol respectively. The above two solutions are mixed by stirring continuously at 1600 – 1900 RPM by using the mechanical stirrer until a clear solution is obtained.

3.2.2 Extended-release coating process

Load the drug loaded pellets into FBC bowl, then coat these pellets with the ER coating solution by bottom spray wurster method. The obtained drug coated pellets are dried and sifted through #20/#25 mesh.

Process control parameters

Spray gun:	:	Needle
Spray type	:	Bottom spray
Wurster height	:	22 mm
Blower RPM	:	40-60
Inlet temperature	:	45 ± 5^{o}C
Bed temperature	:	40 ± 5^{o}C
Exhaust temperature	:	33-37^{o}C
Pump RPM	:	1-10
Air Pressure	:	0.5-5 Kg/cm^{2}
Drying time	:	10 min

Note: If lumps formation was observed, unload the pellets and sifting was done

3.3. Capsule filling

All formulated batches (F1- F7) of Galantamine HBr pellets 8 mg are taken and filled in the “size- 4” hard gelatin capsules by using the Automated capsule filling machine.

Table 1 Formulation trials of Galantamine HBr Extended-Release Capsules 8mg

A. Drug Loading (5% w/w)								
S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7
1	Galanatamine HBr	10.25	10.25	10.25	10.25	10.25	10.25	10.25
2	Sugar Spheres (#20/#25)	77.45	78.75	80.95	80.35	78.35	76.15	76.51
3	Ethyl Cellulose 7cps	2.00	2.00	2.00	2.00	4.00	8.00	8.00
4	Cetyl Alcohol	0.20	0.20	0.20	0.20	0.20	0.80	0.80
5	Isopropyl Alcohol (60%)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
6	Purified Water (40%)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
B. Extended-Release Coating (3% w/w)								
7	Ethyl Cellulose 50cps	10.00	8.00	6.00	6.00	6.00	4.00	3.70
8	Polyethylene glycol 6000	0.10	0.80	0.60	1.20	1.20	0.80	0.74
9	Isopropyl Alcohol (85%)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
10	Purified Water (15%)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total		100	100	100	100	100	100	100

4 Evaluation parameters

4.1. In-vitro Evaluation tests for Galantamine HBr ER pellets

4.1.1 % Yield [14]

Percentage yield of Galantamine HBr ER Pellets were calculated by using the following formula.

$$\text{Percentage yield of pellets (\%)} = \frac{\text{Practical yield of pellets}}{\text{Theoretical yield of pellets}} \times 100$$

4.1.2 Flow properties [15,16]

Bulk density

A precisely measured amount of pellets (W) was poured into a measuring cylinder and the volume (Vb) occupied by pellets without settling was measured. The bulk density is then determined using the following equation:

$$\text{Bulk density } (\rho b) = \frac{\text{Weight of pellets (W)}}{\text{Bulk volume (Vb)}}$$

Tapped density

After recording the bulk volume of the measuring cylinder with pellets, it was sealed and repeatedly tapped in increments of 500, 750, and 1250 taps at a rate of 250 drops per minute using a tapped density tester until no significant change in volume or mass observed. The tapped density can be determined using the following equation.

$$\text{Tapped density } (\rho t) = \frac{\text{Weight of pellets (W)}}{\text{Tapped volume (Vt)}}$$

Carr's index

Carr's index is also called as compressibility or carr's consolidation index and it can be calculated by using below formula.

$$\% \text{ CI} = \frac{(\rho t) - (\rho b)}{(\rho t)} \times 100$$

Where, ρt is the Tapped density and ρb is the Bulk density of the pellets

Hausner's Ratio

Hausners' ratio is a ratio of tapped density to bulk density. It can be calculated by below formula.

$$\text{Hausners' ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of Repose

The pellets are poured through a funnel to form a pile and the diameter of a cone was noted. The angle of repose is determined by the following equation.

$$\theta = \tan^{-1}(h/r)$$

Where, 'h' is the height and 'r' is the radius of the pile

4.2 Invitro Evaluation Tests for Galantamine HBr ER Capsules

4.2.1 Weight variation test [17]

20 capsules were selected randomly and weighed individually. The average weight was calculated. The percentage deviation of capsules was calculated by using following formula.

$$\% \text{ Wt variation} = \frac{\text{W1-W2}}{\text{W2}} \times 100$$

Limits: NMT ± 10%

4.2.2 Lock length

Lock length is determined by using Vernier caliper.

4.2.3 Disintegration [18]

Place 1 capsule in each 6 tubes of the basket assembly which is repeatedly immersed 30 times per minute into a pH 6.5 phosphate buffer at the temperature of 37 ± 2°C and record disintegration time of each capsule.

4.2.4 Assay by HPLC [19]

Preparation of Buffer

5.3g/L of disodium hydrogen orthophosphate in water, and adjust pH to 6.50 with dilute Ortho phosphoric acid.

Solution A	:	Buffer and methanol (95:5)
Solution B	:	Acetonitrile and methanol (95:5)
Mobile Phase	:	Solution A and solution B (75:25)
Diluent	:	Methanol and water (5:95)

Preparation of Standard Solution

Weigh accurately about 8 mg of Galantamine HBr working standard and transfer to a 100 ml volumetric flask, add 20 ml of diluent, sonicate to dissolve the contents and add diluent up to the mark. Transfer 5 mL of the above solution to a 50 mL volumetric flask and add diluent up to the mark. Filter the solution through a 0.45 µm nylon filter.

Preparation of Sample Solution

Open NLT 20 capsules, crush the pellets, and accurately weigh a portion of the sample equivalent to 8 mg of Galantamine HBr into a 100 ml volumetric flask. Add 20 ml of diluent, sonicate for 30 minutes with intermittent shaking, and make up to the mark with diluent. Filter the solution through a 0.45 µm nylon filter, transfer 5 ml of the above solution into a 50 ml volumetric flask, and make up to the mark with diluent.

Chromatographic Conditions

Column	:	Inertsil ODS 3V C18, 250mm x 4.6mm x 5 um.
Flow rate	:	1.0 mL/min
Wavelength	:	230 nm
Column Temperature	:	25°C
Injection Volume	:	20µL
Run Time	:	8 min

System Suitability

Relative standard deviation: NMT 2.0%

Tailing factor: NMT 2.0

Theoretical plates: 2000

Procedure

Separately inject diluent, five replicate injections of standard solution, and a duplicate injection of sample solution into the chromatograph. Then record the chromatograms and measure the peak responses.

Calculation

$$\% \text{ Galantamine HBr} = \frac{AT}{AS} \text{ X } \frac{WS}{VS} \text{ X DS X } \frac{VT}{WT} \text{ X DT X } \frac{P}{100} \text{ X } \frac{AW}{LC} \text{ X } \frac{M1}{M2} \text{ X } 100$$

$$= \frac{AT}{AS} \text{ X } \frac{WS}{100} \text{ X } \frac{5}{50} \text{ X } \frac{100}{WT} \text{ X } \frac{50}{5} \text{ X } \frac{P}{100} \text{ X } \frac{AW}{LC} \text{ X } 0.7803 \text{ X } 100$$

Where,

AT	=	Peak area of Galantamine HBr in Sample solution.
AS	=	Peak area of Galantamine HBr in Standard solution.
WS	=	Weight of Galantamine HBr working standard taken in mg.
VS	=	Volume of mobile phase to dissolve working standard
DS	=	Dilution of the Standard
VT	=	Volume of mobile phase to dissolve sample
WT	=	Weight of Galantamine HBr sample taken in mg
DT	=	Dilution of the Sample
P	=	Purity of Galantamine HBr working standard used
AW	=	Average fill weight of capsules
LC	=	Label claim
M1	=	Molecular weight of the Galantamine

M2 = Molecular weight of Galantamine HBr

Limits: NLT 90% and NMT 110%

4.2.5 4.2.5. In-vitro Dissolution Study [20]

Dissolution parameters

Medium	:	pH 6.50 phosphate buffer.
Volume	:	900mL
Apparatus	:	USP Type-II (Paddle).
RPM	:	50
Temperature	:	37.0°C ± 0.5°C
Sampling Time intervals	:	0, 2, 4, 6, 8, 10 and 12 Hours.

Procedure

Place one capsule in each of the dissolution jars holding 900ml of pH 6.50 phosphate buffer placed in a thermostatically controlled water bath at 37 ± 0.5ºC and run the equipment at 50 rpm for a specific period. Then, withdraw 10ml of the solution from each jar and replace it with an equal volume of fresh dissolution medium at specific time intervals (0, 2, 4...12hrs). Filter the solution through a 0.45-micron membrane filter and analyze the filtrate by using HPLC. Then calculate % of Galantamine HBr released by using the below formula:

$$\% \text{ of Galantamine HBr released} = \frac{AT}{AS} X \frac{WS}{100} X \frac{5}{50} X \frac{900}{LC} X \frac{P}{100} X\ 0.7803\ X\ 100$$

Where,

AT	=	Peak area of Galantamine HBr in Sample solution
AS	=	Peak area of Galantamine HBr in Standard solution
WS	=	Weight of Galantamine HBr working standard taken in mg
LC	=	Label claim
P	=	Purity of Galantamine HBr working standard used
0.7803	=	Molecular weight of Galantamine/ Molecular weight of Galantamine HBr

Dissimilarity factor (f1) = $\{[\Sigma t_{=1}{}^{n}|R_t - T_t|] / [\Sigma t_{=1}{}^{n} R_t]\}. 100$

Similarity factor (f2) = $50. \log \{1 + (1/n) [\Sigma t_{=1}{}^{n} (R_t - T_t)^2]^{-0.5}\}. 100$

Where R_t, T_t are the cumulative percentage dissolved at each of the selected n time point of the reference & test product respectively.

4.2.6 Moisture Permeation test [21]

The degree and rate of moisture penetration can be determined by packaging the dosage unit with a color revealing desiccant pellet. The packaged unit is then exposed to known relative humidity over a specified time. The desiccant pellet is observed for color change, which indicates absorption of moisture. The amount of moisture absorbed can be calculated by measuring the pretest weight and protest weight of the pellet.

4.3 Stability Studies [22]

The optimized formulation batch of Galantamine HBr ER capsules was loaded for accelerated stability studies at 40 ± 2°C/75 ± 5% RH for approximately 6 months. The capsules were evaluated for disintegration, drug content and in vitro

drug release studies at specific time periods (1,2,3 & 6 months) and compared with initial capsules (optimized batch) evaluated immediately after manufacturing.

5 Results and discussion

Table 2 Organoleptic properties

API description	White to off-white, odorless, crystalline powder
Melting point	276.16^{0}C
% LOD	0.05 %
Absorption maxima (λmax)	289 nm
Solubility	Freely soluble in isopropyl alcohol, ethanol and sparingly soluble in water.

5.1 Calibration Curve

Calibration curve of Galantamine HBr was constructed by taking the absorbance on y-axis and concentration on x-axis. The regression coefficient (r^2) was found to be 0.9996.

Table 3 Calibration curve values of Galantamine HBr in phosphate buffer pH 6.5

Concentration (µg/ml)	**Absorbance (289 nm)***
0	0
1	0.08±0.08
2	0.17±0.15
3	0.26±0.03
4	0.35±0.23
5	0.43±0.03

*All the values are expressed as mean ± standard deviation (n=3)

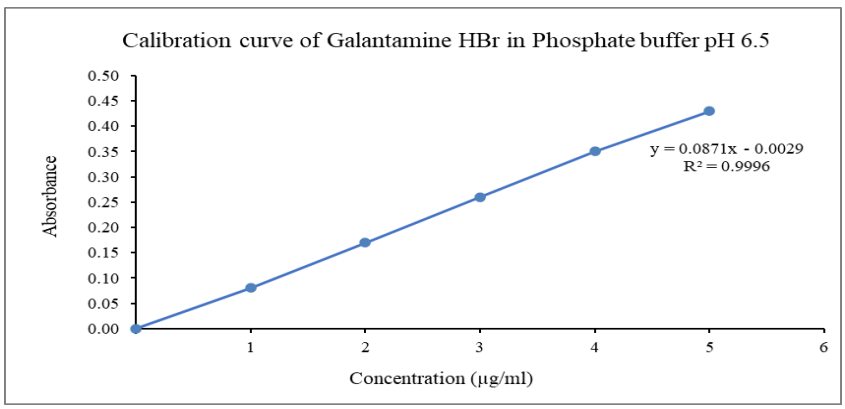

Figure 1 Graphical representation showing calibration curve of Galantamine HBr Phosphate buffer pH 6.5

Table 4 Evaluation Paramaters of Galantamine HBr ER Pellets

Batch No.	% Yield (%)*	Angle of Repose (⁰)*	Bulk density (gm/mL)*	Tapped density (gm/mL)*	Hausner's ratio*	Carr's index (%)*
F1	95.33±0.004	34.21±0.074	0.743±0.047	0.858±0.022	1.154±0.002	13.40±0.007
F2	96.25±0.008	31.83±0.024	0.766±0.016	0.867±0.003	1.131±0.004	11.64±0.045
F3	97.51±0.012	30.82±0.003	0.833±0.027	0.938±0.005	1.126±0.002	11.19±0.035
F4	97.82±0.007	29.68±0.002	0.855±0.002	0.948±0.002	1.108±0.025	9.810±0.025
F5	98.31±0.065	27.52±0.042	0.868±0.007	0.954±0.003	1.099±0.074	9.014±0.003
F6	99.28±0.012	25.22±0.014	0.905±0.003	0.968±0.006	1.069±0.003	6.508±0.006
F7	99.76±0.005	25.08±0.004	0.912±0.005	0.971±0.007	1.005±0.006	6.076±0.003

*All the values are expressed as mean ± standard deviation (n=3)

Table 5 Evaluation Paramaters of Galantamine HBr ER capsules

Batch No.	Wt variation (%)*	Lock length (mm) *	Assay (%)*	Disintegration (min)*	Moisture content (%)*
F1	1.64±0.08	14.35±0.02	99.10±0.07	3.56±0.07	2.27±0.21
F2	1.28±0.02	14.33±0.04	100.70±0.08	3.53±0.04	2.11±0.17
F3	0.02±0.06	14.33±0.55	101.20±0.05	3.48±0.03	1.97±0.02
F4	1.88±0.12	14.28±0.04	100.90±0.03	3.44±0.02	1.63±0.03
F5	0.55±0.34	14.42±0.06	100.20±0.04	3.32±0.07	1.28±0.08
F6	0.08±0.06	14.41±0.07	100.90±0.26	3.27±0.05	1.08±0.03
F7	0.03±0.04	14.40±0.08	100.10±0.08	3.25±0.03	1.03±0.02

*All the values are expressed as mean ± standard deviation (n=3)

Table 6 In-Vitro Dissolution profile of all formulations in pH 6.5 Phosphate buffer:

Time (hrs)	RLD	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0	0
1	28.0±0.03	0.0±0.02	5.0±0.35	7.0±0.33	9.8±0.36	7.8±0.56	21.0±0.05	29.0±0.10
2	38.8±0.11	1.0±0.06	11.0±0.45	15.0±0.22	21.0±0.58	16.8±0.10	33.0±0.44	38.0±0.20
4	57.2±0.02	4.0±0.04	17.0±0.50	23.0±0.40	32.2±0.60	25.8±0.40	52.0±0.42	56.1±0.06
8	72.4±0.02	12.0±0.30	25.0±0.60	33.0±0.30	46.2±0.50	37.0±0.30	68.0±0.11	73.5±0.20
12	83.2±0.25	15.0±0.50	38.0±0.70	51.0±0.20	71.4±0.70	57.1±0.50	80.2±0.27	83.4±0.11
16	90.6±0.03	23.0±0.05	42.0±0.10	56.0±0.26	78.4±0.02	62.7±0.02	87.6±0.50	90.8±0.03
Dissimilarity factor (F1)		85	63	50	30	45	7	1
Similarity factor (F2)		15	22	27	37	29	67	96

*All the values are expressed as mean ± standard deviation (n=3)

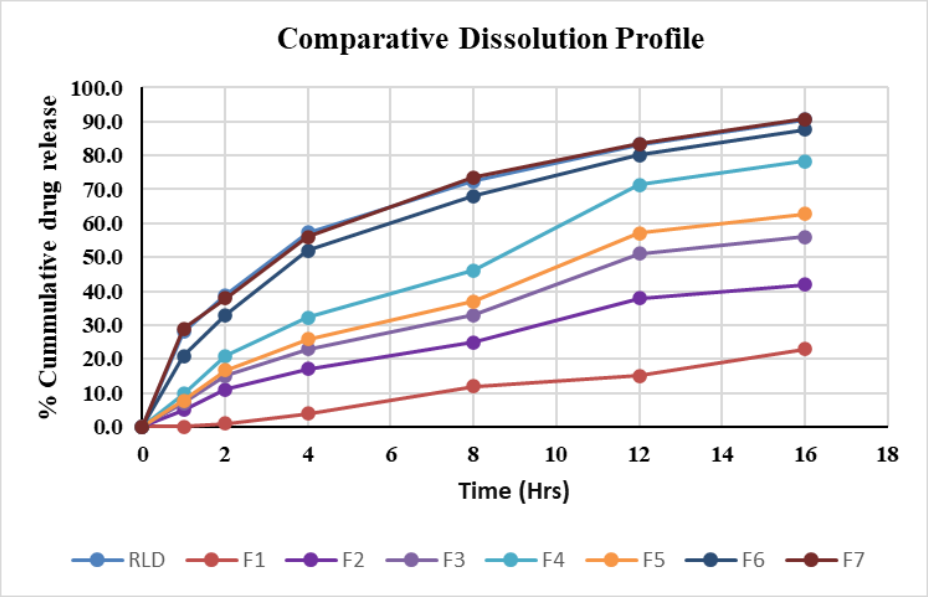

Figure 2 Graphical representation showing comparative in-vitro dissolution profile of all formulations F1-F7 with innovator

- Evaluation parameters of Galantamine HBr pellets of all formulations (F1-F7) shows the good results as shown in the table 4. i.e.,%Yield = 95.33%-99.76%; Bulk density = 0.743 g/mL - 0.912 g/mL; Tapped density = 0.858 g/mL - 0.971g/mL; Hausner's ratio =1.005-1.154; %Carr's index = 6.076%-13.40%.
- Evaluation parameters of Galantamine HBr capsules (8mg) of all formulations (F1-F7) shows the good results as shown in the table 5. i.e., %wt.variation = 0.03%-1.64%; Lock length = 14.40-14.35 mm; Assay = 99.10%-100.10 %; Desintegration time=3.25-3.56 min;Moisture content = 1.03%-2.27%.
- Dissolution studies were conducted for all formulations (F1-F7) and among all the formulation F7 shows the good results as shown in the table 6. i.e., 90.8% of drug was released in 16 hrs.

5.2 Stability studies

The stability study was conducted as per ICH guidelines and no significant changes was observed in disintegration, drug content and invitro drug release profile after 6 months.

6 Conclusion

Galantamine HBr extended release capsules 8mg was prepared and evaluated for physical and chemical parameters. All the evaluation parameters are found to be within the limits. Among all the formulations, F7 shows 90.8% drug release in 16 hours and found to be pharmaceutically equivalent to reference listed drug due to its similarity factor (f2= 96) in drug release profile. The formulation F7 was loaded for stability studies, and no changes were observed, which indicates that the optimized F7 formulation was stable.

References

[1] Hofman, A., Rocca, W. A., & Brayne, C. (1991). The prevalence of dementia in Europe: A collaborative study of 1980–1990 findings. International Journal of Epidemiology, 20(3), 736–748.

[2] Gray, A. M., & Fenn, P. (1993). Alzheimer's disease: The burden of illness in England. Health Trends, 25(1), 31–37.

[3] Small, G. W., et al.(1997). Diagnosis and treatment of Alzheimer disease and related disorders. Consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. JAMA, 278(16), 1363–1371.

[4] Martinez, A. (2010). Emerging drugs and targets for Alzheimer's disease. Royal Society of Chemistry Publishing.

[5] Rattan, S., & Kassem, M. (2006). Prevention and treatment of age-related diseases (7th ed). Springer.

[6] Kumar, A., Prakash, A., & Pahwa, D. (2011). Galantamine potentiates the protective effect of rofecoxib and caffeic acid against intrahippocampal kainic acid-induced cognitive dysfunction in rat. Brain Research Bulletin, 85(3–4), 158–168.

[7] Adewusi, E. A., Moodley, N., & Steenkamp, V. (2011). Antioxidant and acetylcho-linesterase inhibitory activity of selected southern African medicinal plants. South African Journal of Botany, 77(3), 638–644.

[8] Suh, G. H., Yeon Jung, H., Uk Lee, C., Hoon Oh, B., Nam Bae, J., Jung, H. Y., Ju, Y. S., Kil Yeon, B., Park, J., Hong, I., Choi, S., Ho Lee, J., & Korean Galantamine Study Group. (2004). A prospective, double-blind, community-controlled comparison of three doses of galantamine in the treatment of mild to moderate Alzheimer's disease in a Korean population. Clinical Therapeutics, 26(10), 1608–1618.

[9] Vijaykumar, G. (2016). Formulation and characterization of galantamine hydrobromide extended release tablets. ResearchGate. Indo Global Journal of Pharmaceutical Sciences.

[10] David Raja. (2023). Determination of melting point and boiling point experiment. Medium

[11] United States Pharmacopeia (USP): <731> Loss on drying USP31-NF26. (2008). Pharmacopeial Forum, 33(2), 234.

[12] Kaur, D. (2020). Formulation and evaluation of hard gelatin capsules containing Bacopa monnieri. International Journal of Pharmaceutical Education and Research, 1(2), 33–37.

[13] Hitesh, P., Amit, P., & Jayant, D. (2010). UV-spectrophotometric method development and validation for estimation of galantamine hydrobromide in tablet dosage form. Journal of Chemical and Pharmaceutical Research, 2(2), 44–49.

[14] Nidadavolu, A. (2014). Formulation development and in vitro characterization of sustained release pellets of venlafaxine HCl. PharmaciaTutor, 2(1), 129–156.

[15] Shah, R. B., Tawakkul, M. A., & Khan, M. A. (2008). Comparative evaluation of flow for pharmaceutical powders and granules. AAPS PharmSciTech, 9(1), 250–258.

[16] Beakawi Al-Hashemi, H. M., & Baghabra Al-Amoudi, O. S. (2018). A review on the angle of repose of granular materials. Powder Technology, 330, 397–417.

[17] Indian Pharmacopoeia Commission. (2014). Indian pharmacopoeia (7th ed). Indian Pharmacopoeia Commission.

[18] United States pharmacopoeia. 28th Asian Edn, Rockvilne. (2005). United States of America Pharmacopoeial Convention Inc.

[19] United States Pharmacopeia (USP): <621> Assay USP31-NF26. (2008). Pharmacopeial Forum, 33(2), 234.

[20] United States Pharmacopeia (USP): <711> Dissolution revision bulletin. (2016). United States of America Pharmacopoeial Convention Inc.

[21] Allen, L. V., Popovich, N. G., & Ansel, H. C. (2011). Ansel's pharmaceutical dosage forms and drug delivery systems (9th ed).

[22] ICH harmonised tripartite guideline. (2003). Stability Testing of New Drug Substances and Products Q1A, (R2),(4th ed),