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FORMULATION DEVELOPMENT AND EVALUATION OF AQUEOUS POLYMER DISPERSIONS (PELLETS) FOR EXTENDED RELEASE DOSAGE FORMS OF GALANTAMINE HYDROBROMIDE

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ABSTRACT

In this study, a novel approach for compression of matrix pellets into matrix tablets has been studied in an attempt to overcome the issues pertaining to rupture of polymer coat during compression of reservoir type pellets. Extended release matrix pellets were prepared by the extrusion/spheronization technique using commercially available aqueous dispersions of ethyl cellulose, acrylic polymers and sodium alginate at 10 %, 20 % and 30 % w/w levels. Galantamine Hydrobromide was used as the model drug and an *in vitro* release profile of 12 h was targeted. Tablets containing matrix pellets were prepared by the direct compression process. Acceptance Value, a pharmacopeial test, was applied to study the uniformity of drug distribution. Effect of compression force (2-6 kN), extrusion screen aperture size, diluent blend composition and pellet percentage on drug release and acceptance value were studied. As polymer is uniformly distributed within each pellet, the drug release pattern from uncompressed pellets was comparable to compressed tablets. The pellet segregated from the surface of the tablet was found to be flattened in the direction of applied compression force with minor deformities. In conclusion, matrix pellets can constitute an alternative approach to reservoir-type pellets in obtaining matrix tablets for extended delivery of drugs.

Keywords: Pellets, Extended release, evaluation, Compression, Extrusion, Spheronization technique.

1. INTRODUCTION

Extended-release systems provide drug release in an amount sufficient to maintain the therapeutic drug level over an extended period, with the release profiles predominantly controlled by the special technological construction and design of the system itself. The development of oral extended-release systems has been a challenge to formulation scientists due to their inability to restrain and localize the system at targeted areas of the gastrointestinal tract. There are numerous products in the market formulated for both oral and parenteral routes of administration that claim extended or controlled drug delivery. Matrix-type drug delivery systems are one of the interesting and promising options in developing an oral extended-release system. In particular, the interest awakened by matrix type delivery is completely justified because of its biopharmaceutical and pharmacokinetic advantages over the conventional dosage forms [1-5].

Over the past decades, the treatment of acute and chronic illness has been accomplished by many conventional drug delivery systems such as tablets, capsules, pills, creams, ointments, liquids, aerosols, injectables, and suppositories [6-7]. These conventional drug delivery systems are still the primary pharmaceutical products commonly seen today in prescription. The oral route is the most commonly employed route of drug administration. Although different routes of drug administration are used for the delivery of drugs, the oral route remains the preferred route. Even for extended-release systems, the oral route of administration has been investigated the most, because of the flexibility in dosage form design that the oral route offers [8].

The basic goal of drug therapy is to achieve a steady-state blood level or tissue level that will be therapeutically effective and non-toxic for an extended period of time 4. To achieve better therapeutic action various types of drug delivery systems are available, out of which extended-release systems are gaining much

importance because of their wide advantages over others like ease of administration, convenience, and non-invasiveness. The vast majority of traditional dosage forms can be described as dump systems that deliver their active substances in first-order kinetics *i.e.,* release occurs at rates that are highest initially and then decline steadily thereafter. Clinically this peak and valley pattern results in a time-dependent mix therapy. Drug side effects tend to predominate at the high peak concentration in blood, whereas an inadequate therapeutic effect may prevail at the valley level [9-12]. The use of controlled-release systems provides an excellent tool to achieve precise control of rate (and also) at a particular site. Besides, from the biological benefits incurred from the prolonged and predictable drug levels, extended-release systems can allow for a significant reduction in the frequency of drug administration and improved patient compliance, more predominantly for chronic ailments such as high blood pressure, arthritis, asthma, and diabetes. There are also good commercial reasons for the strong trend towards an extended-release system [13].

2. MATERIAL AND METHODS

2.1. Preformulation of galantamine hydrobromide

2.1.1. Description

The drug sample was observed for color and appearance.

2.1.2. Solubility

Solubility of the drug in methanol and water was determined. Galantamine Hydrobromide (1g) was added to a 100mL conical flask containing 50mL of individual mediums. The flask was kept on a mechanical shaker for a period of 24 hrs. The solution was centrifuged, supernatant filtered, and appropriately diluted. The absorbance of the solution was measured at 274nm on a UV spectrophotometer.

2.1.3. Melting point

The drug in the finely powdered and dried state was filled in a glass capillary tube, which was sealed at one end. The range of temperature from the start of melting to the end was recorded. This range was compared with the reported value 110.

2.1.4. Spectral specifications

2.1.4.1. UV Spectroscopy

Absorption of a 6.6 µg/mL methanolic solution was recorded on a UV spectrophotometer using a 1 cm path length quartz cuvette. The solution was scanned from 220 to 500 nm and λ max was recorded.

2.1.4.2. Infrared Spectroscopy

IR spectrum of Galantamine Hydrobromide was recorded on Perkin Elmer IR spectrophotometer using the KBr disc method.

2.1.5. Differential Scanning Calorimetry

The Thermogram of Galantamine Hydrobromide was recorded on the Perkin Elmer DSC instrument. The sample was scanned at 5°C/min with a 20mL/min nitrogen purge using an identical empty pan as a reference.

2.1.6. Particle size analysis

Particle size analysis was carried out using Malvern Mastersizer equipped with 2000 Hydro MU (range 0.02µm-2000µm). All measurements were reported as average of triplicate readings.

2.2. Characterization of pellets and compressed tablets

2.2.1. Density and friability

The bulk density was determined by pouring pellets into a previously weighed 10 ml graduated glass cylinder where the weight of the pellets needed to occupy a 10 ml volume was noted. The bulk density was calculated by the ratio of weight to occupied volume.

2.2.2. Friability

Friability was measured using Electrolab Friability testing apparatus (Electrolab Ltd, Mumbai, India) by tumbling 10g of the pellets for 4 min at 25rpm. The tested pellets were gently tapped on an ASTM # 40 mesh to remove the fines generated and weight loss was measured. For testing the friability of the tablets, ten tablets were initially weighed on an analytical balance, transferred to the friabilator and run for 4 min. The tablets were weighed after removing the powdered dust, and weight lost during testing was calculated.

2.2.3. Sphericity

The sphericity of the pellets was measured using the simplest approach described by Lovgren and Lundberg [14], by measuring the length and width of the two

dimensional image of the pellets on an optical microscope (Olympus BX55TF, Japan). The shape factor was expressed as % Sphericity, where 100 % corresponds to a perfect circle. The longest length and breadth of the pellets were measured accurately when the pellets were rested in their most stable position. A frequency distribution of the percent ratio of length to breadth of 100 pellets was calculated and the Sphericity (S).

2.2.4. Hardness testing

The force required to fracture a tablet was measured using a tablet hardness tester (Dr Schleuniger, Pharmatron 8M). Hardness of at least 10 tablets from each formulation was measured and reported as a range.

2.2.5. Disintegration testing

The disintegration time of the tablet was tested using USP disintegration apparatus on 6 tablets from each composition. (Electrolab Disintegration Apparatus, India). Distilled water was used as the medium at a temperature of 37°C. The time taken until no material from any of the tablets was left on the mesh was recorded.

2.2.6. In vitro dissolution testing

In vitro release study of the pellets and compressed tablets was performed using acetate buffer pH 4.5 in a dissolution test apparatus (Electrolab, Mumbai, India). The test employed 900 mL of the specified buffer at 37°C and a USP Type II apparatus (paddle) rotating at 50 rpm. Samples were collected at 1, 2, 4, 6, 8, 10 and 12 h intervals and analyzed by a UV-Visible spectrophotometer (UV 2450, Shimadzu Corporation, Japan) at 273nm. Dissolution of pellets and MUPS tablets was conducted for 6 representative samples.

2.2.7. Drug content analysis

To determine drug content, an amount of crushed pellets equivalent to 100 mg of Galantamine Hydrobromide was weighed into a flask (1000 mL) and extracted with a minimum quantity of methanol and made up to volume with acetate buffer pH 4.5 then sonicated for around 30 min. UV absorbance of the solution filtered through 0.43µ filters was measured using a UV-Visible spectrophotometer (UV 2450, Shimadzu Corporation, Japan) at 273nm (λmax). To avoid the influence of excipients, the placebo blend was also treated similarly and kept as a blank. Standard solution was prepared by accurately weighing (Mettler Toledo, India) 100 mg of Galantamine Hydrobromide and following a similar dilution procedure. From the absorbance of the test solution, the amount of drug in the solution was calculated.

2.2.8. Stability evaluation of compressed tablets

Accelerated stability studies were carried out on the MUPS tablets prepared using calcium chloride-treated pellets as per ICH recommendation. The tablets were packed in HDPE bottles and charged in a stability chamber for a 3M period at 40°C/75 % RH. After completing the stability period, the tablets were evaluated for their physical and chemical attributes including drug content and drug release profile.

As, the lone Methocel® K15M or Methocel® E4M could not yield the desirable results, grouping of these two polymers was thought. These two polymers were combined in diverse ratio as shown in the table.

Table 1: Composition of extended release matrix pellets using various polymers

Composition (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Methocel® K100M	112	112	112	112	112	112	112	112	112	112	112	112
Avicel® pH 101	166	134	102	166	134	102	166	134	102	176	144	112
Hydroxypropyl cellulose	10	10	10	10	10	10	10	10	10	x	x	x
Aquacoat ECD 30	32	64	96	x	x	X	x	x	X	x	x	x
Eudragit L 30D 55	x	x	x	32	64	96	x	x	x	x	x	x
Eudragit NM 30D	x	x	x	x	x	X	32	64	96	x	x	x
Sodium Alginate	x	x	x	x	x	X	x	x	x	32	64	96
Water	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Total Weight (mg)	**320**	**320**	**320**	**320**	**320**	**320**	**320**	**320**	**320**	**320**	**320**	**320**

a Weight of hydrochloride salt equivalent to 100 mg Galantamine Hydrobromide base. qs-Quantity sufficient

Table 2: Composition of MUPS tablets prepared using calcium chloride-treated pellets

Composition (mg)	TAB #1	TAB #2	TAB #3	TAB #4	TAB #5
Methocel® K100M	320	320	320	320	320
Microcrystalline Cellulose Avicel 102	646	446	446	263	78
Microcrystalline Cellulose Avicel PH101	-	200	-	117	35
Milled Avicel PH 102	-		200	-	-
Polyethylene glycol, 6000	64	64	64	64	64
Crospovidone	31	31	31	31	31
Magnesium Stearate	5	5	5	5	5
Total weight (mg)	**1066**	**1066**	**1066**	**800**	**533**
Percent of pellets (%w/w)	**30**	**30**	**30**	**40**	**60**
Acceptance Value	**18.7**	**12.2**	**14**	**NP**	**NP**

b Composition #F11, NP; Not performed

3. MATERIAL AND METHODS

3.1. Description

Galantamine hydrobromide exists as white to off-white, odorless, amorphous powder.

3.2. Solubility

Galantamine hydrobromide is freely soluble in methanol, practically insoluble in water (19.2 µg/mL).

3.3. Melting point

The melting point of drug was found to be 220-225°C (melts with degradation).

3.4. Spectral analysis

3.4.1. UV Spectroscopy

Absorption spectrum was obtained for a range from 400-200 nm. As seen in the fig. 1, λ max was obtained at 274 nm.

3.4.2. Infra red Spectroscopy

The spectrum was found to be similar to the reference pattern. Major peaks at 3390 and 1672 cm^{-1} corresponding to C-N stretching and carbonyl (COOH) stretching respectively were obtained. Peaks at 1591 and 1323 cm^{-1} corresponding to N-H and S-O stretching were obtained.

3.4.3. Differential Scanning Calorimetry

As seen in figure an exotherm (at 222°C) corresponding to the melting point of galantamine hydrobromide was obtained. Galantamine hydrobromide melts with degradation and thus this explains the appearance of exotherm instead of endotherm in the thermogram.

3.4.4. Particle size analysis

In the Particle side distribution of galantamine hydrobromide sample, the average particle size obtained was 9.52 µm.

3.4.5. Uniformity of content of Galantamine hydrobromide

The uniformity of content (CU) of Galantamine hydrobromide tablet was calculated as per the method described in the experimental.

Galantamine hydrobromide content was found to be well within the acceptance limit (85 % and 115 %) per tablet.

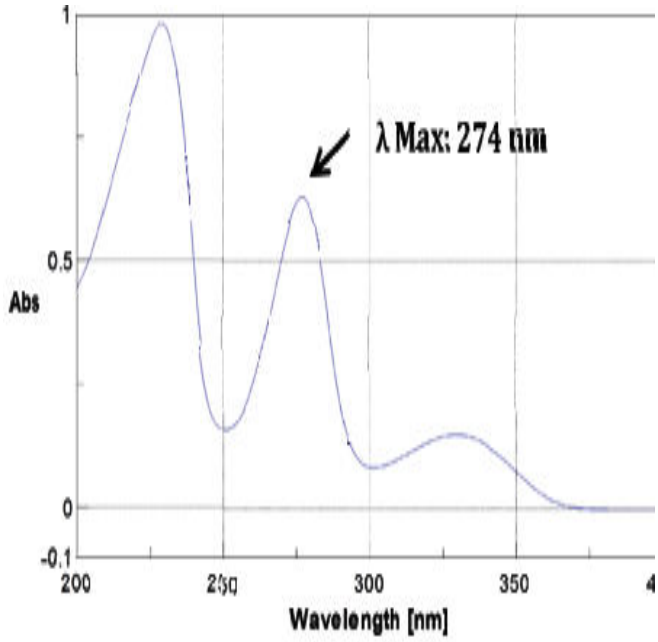


Fig. 1: UV Spectrum of Galantamine hydrobromide

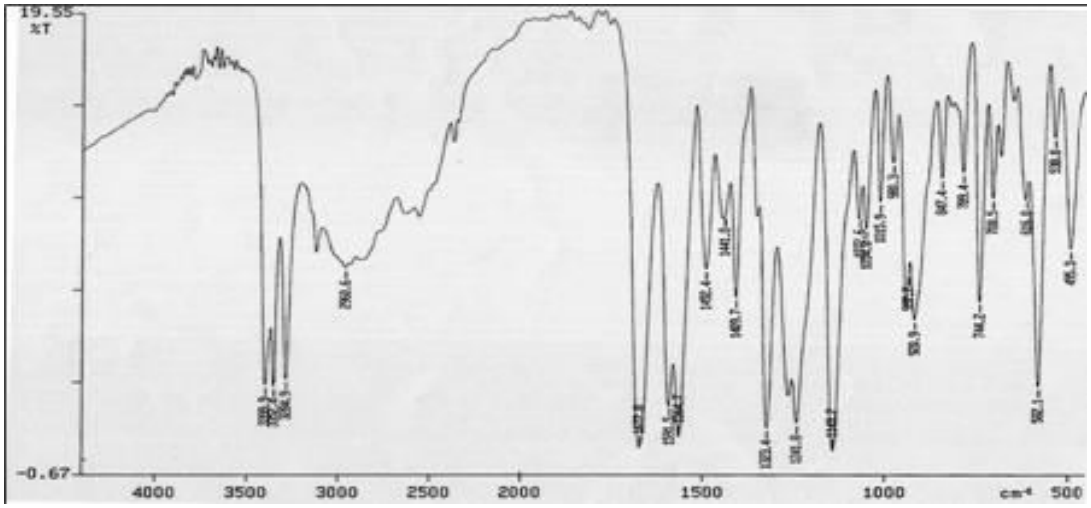


Fig. 2: IR spectra of Galantamine hydrobromide

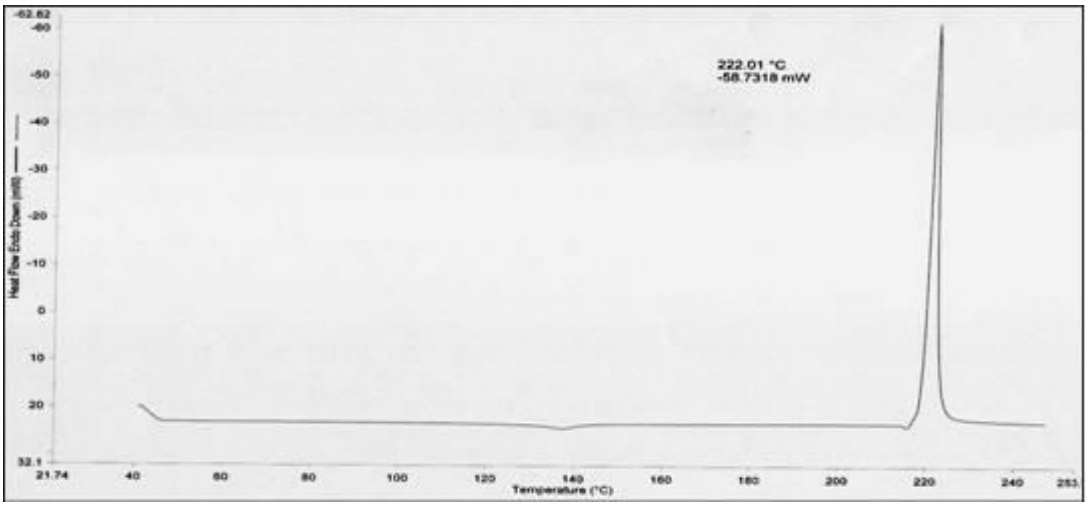


Fig. 3: DSC thermogram of Galantamine hydrobromide

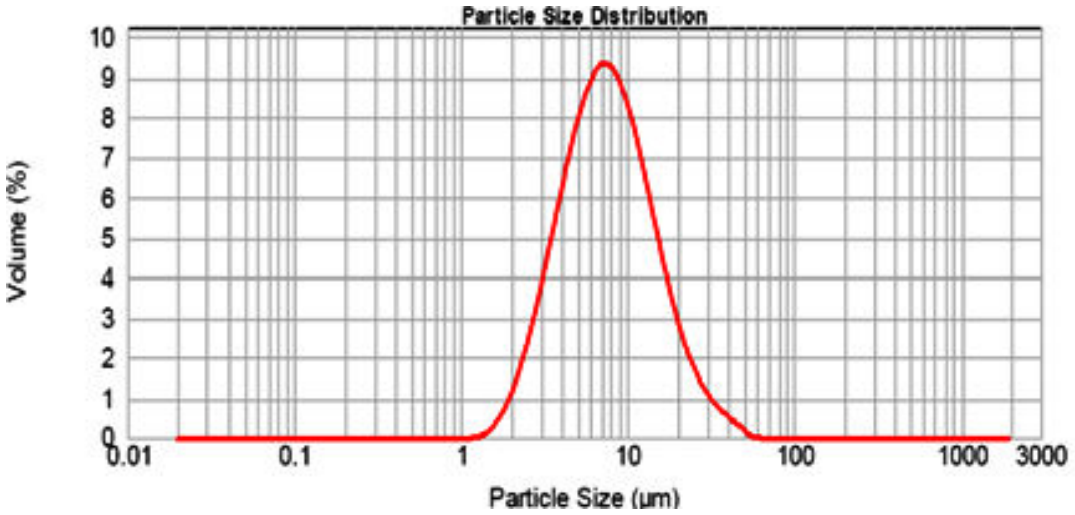


Fig. 4: Particle size distribution curve of Galantamine hydrobromide

Table 3: Content uniformity of the Galantamine hydrobromide tablets

Sample name	Sample area	Standard area	Tablet weight (mg)	Tablet Content (%)
Tablet 1	12149614	11824451	258	103.44
Tablet 2	12118265	11824451	254	101.57
Tablet 3	12047384	11824451	253	100.58
Tablet 4	12214194	11824451	259	104.39
Tablet 5	11863157	11824451	256	100.22
Tablet 6	12040855	11824451	251	99.73
Tablet 7	12205320	11824451	259	104.32
Tablet 8	12193876	11824451	261	105.02
Tablet 9	12134343	11824451	249	99.70
Tablet 10	12267352	11824451	247	99.99
Tablet 11	12267332	11824451	249	99.93
Tablet 12	12267312	11824451	241	99.91

3.5. Preparation of matrix pellets and effect of polymers

The concept of compression of matrix pellets into disintegrating tablet dosage form was derived as a response to issues pertaining to compression of reservoir-type pellets coated with polymers for extended release of drug. In reservoir-type pellets, the nature, type and amount of polymer coating has a significant impact on compression-induced changes in the coating structure. Most of the studies on compression of pellets coated with polymers have shown damage to the coating with loss of the extended release properties due to rupture of the coat [15] resulting in faster drug release. Polymers typically used in the coating of pellets are either cellulosic polymers or acrylic polymers. Hence, in the present study three commercially available aqueous dispersions of ethyl cellulose and acrylic polymers (Eudragit® L 30D; Eudragit® NM 30D) were evaluated in an attempt to develop matrix pellets with an extended drug release profile. For this purpose Galantamine hydrobromide, hydroxypropyl cellulose and microcrystalline cellulose blend was granulated with aqueous dispersions of polymers in a rapid mixer granulator. Considering the aqueous granulation process, a higher level of microcrystalline cellulose was used in the composition to facilitate the extrusion spheronization process due to its unique water absorbing and retaining characteristics [16].

During initial trials of granulation, operational variables such as kneading time and spheronization time were found to have a significant impact on the length of the extrudates and shape/size of the pellets, respectively. The nature of the granules suitable for extrusion was decided based on the preliminary experiments. The process parameters were varied accordingly to obtain pellets with the desired properties. In order to involve minimum process variables while using the different polymers blending time, binder addition time, screw feeder rate and drying temperature were kept constant. Based on the property of the polymer and its quantity in the composition, the spheronization time was varied accordingly to obtain pellets with suitable properties observed visually [17-18].

While preparing pellets using a lower level of polymer, an additional quantity of water was added in order to attain the desired granule mass for extrusion. Extrusion of the blend containing a higher level of polymer (30 % w/w) through the 0.8 mm screen aperture proved difficult leading to an increase in spheronization time (12-15 min). Polymer levels beyond 30%w/w were not evaluated as these were generating lengthy extrudates and leaving tackiness during extrusion. The drug release pattern from the pellets containing ethyl cellulose and acrylic polymer was not satisfactory [19-20].

More than 85 % drug release was observed within 4h from the pellets containing Methocel® K100M and Eudragit NM 30D. However, use of Eudragit L 30D 55 at a 30% w/w level was able to extend the drug release to 6 h. This drug release phenomenon can be ascribed to the erosion of polymer from the surface of the pellets and release of drug from the new surface becoming dissolved in dissolution media. Moreover, these polymers are not soluble in the dissolution media employed (pH 4.5 acetate buffer) for *in vitro* drug release testing. As the desired profile was not obtained in the pellet stage, compression of these pellets into MUPS tablet was not considered further.

Table 3: Physical characterization data of matrix pellets prepared using extrusion/spheronization process

Polymers	Trial	% w/w	Nature of pellets	Process yield (% w/w)	Drug content (%w/w)	Friability (%w/w)	Bulk Density (g/mL)	Sphericity (%)
Methocel ® K100M	F1	10	Spherical + fines	78.6	93.3	0.380	1.125	76±8%
	F2	20	Spherical	86.4	92.1	0.240	1.095	84±5%
	F3	30	Spherical	82.0	90.6	0.236	1.115	80± 5%
Eudragit L 30D 55	F4	10	Spherical + fines	72.2	89.4	0.380	1.186	76±7%
	F5	20	Spherical+ fines	84.5	90.6	0.240	1.182	81±5%
	F6	30	Spherical	86.8	93.4	0.288	1.195	65±8%
Eudragit NM 30D	F7	10	Almost Spherical	80.2	90.0	0.400	1.213	78±9%
	F8	20	Spherical	82.1	92.3	0.380	1.236	82±6%
	F9	30	Dumbbell-Shaped	72.8	91.1	0.385	1.328	65±7%
Sodium Alginate	F10	10	Spherical	78.4	93.2	0.245	0.876	78±4%
	F11	20	Spherical	88.9	92.8	0.210	0.888	86±5%
	F12	30	Dumbbell-Shaped	76.3	91.2	0.220	0.877	72±6%
Calcium Chloride-Treated	F10	20	Spherical	-	91.9	0.180	0.886	88±5%

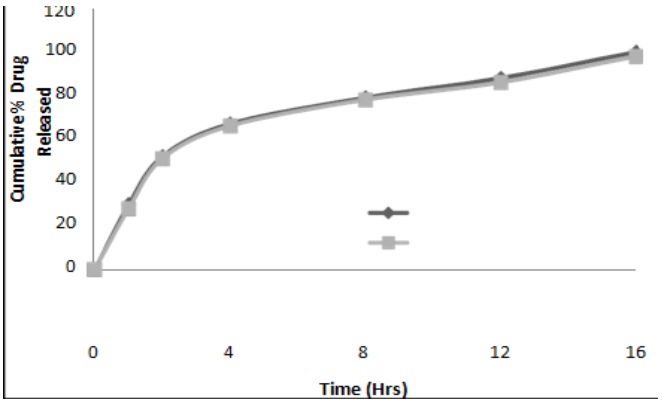
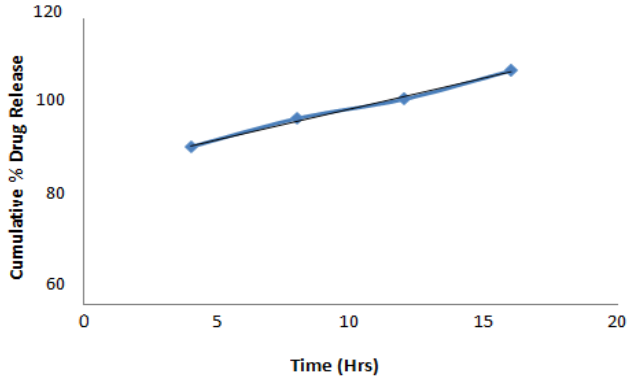


Fig. 5: *In-vitro* release study of optimized formulation

In Zero order plot (fig. 6) the R^2 value obtained was 0.994 and first order gave 0.855, describing the drug release rate relationship independent with concentration of drug.

The fair linearity was found in Higuchi's equation plot (R^2 = 0.986) indicating the release of drug from matrix as a square root of time dependent process based on Fickian diffusion.

The dissolution data was also plotted in accordance with Hixson Crowell cube root law (fig. 9). Correlation of coefficient (R^2 = 0.923) indicated that there was not significant change in surface area and diameter of the tablet during dissolution.



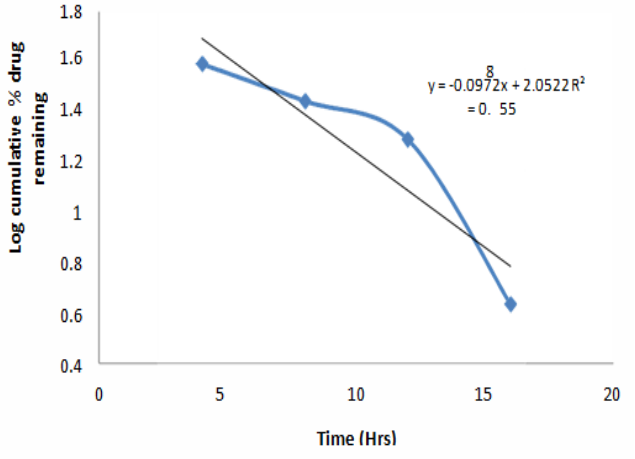


Fig. 6: Zero order release model of galantamine hydrobromide bilayered tablets

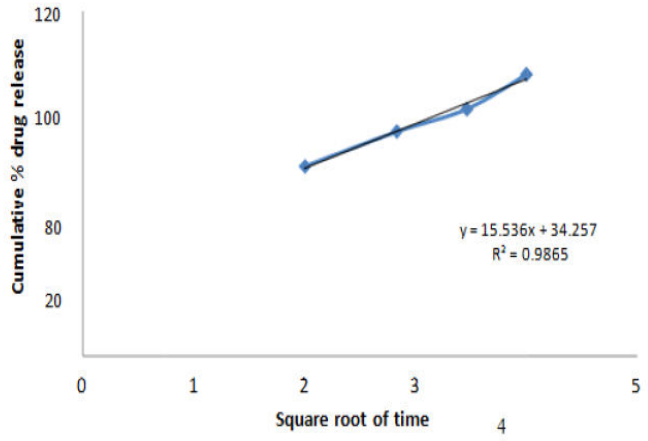


Fig. 7: First order release model of galantamine hydrobromide bilayered tablets

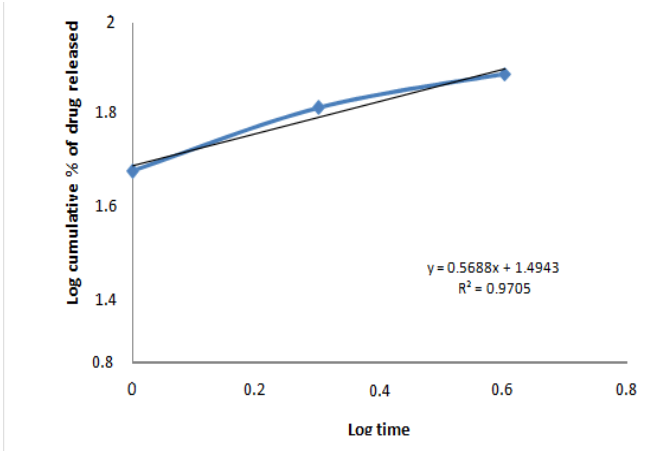


Fig. 8: Koresmeyer-peppas release model of galantamine hydrobromide bilayered tablets

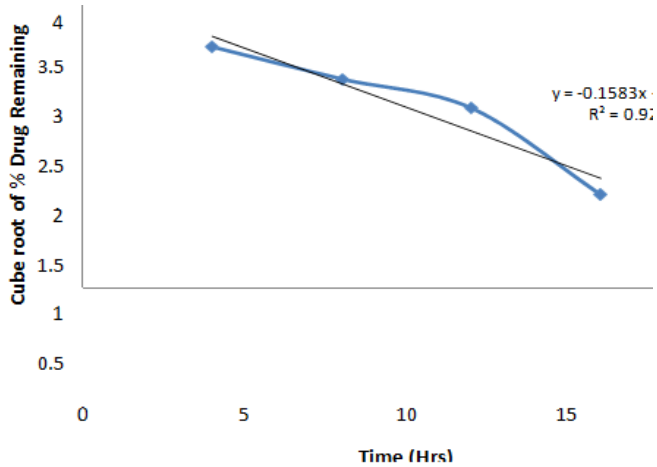


Fig. 9: Hixon-crowell release model of galantamine hydrobromide bilayered tablets

3.6. Kinetics of drug release

Kinetics of drug release was studied by fitting the release data in to zero order release kinetic model. The correlation of coefficient for zero order release kinetics was found to be 0.992, which showed that drug was release at controlled rate independent of concentration gradient. *In-vitro* release data was also fitted to first order release kinetics by plotting log of cumulative percent drug remaining versus time. The correlation of coefficient for first order release kinetics was found to be 0.91, which showed that drug release was independent of concentration gradient across the membrane.

Table 4: Physical characterization data of compressed tablets using optimized composition

Composition	Compression Force (kN)	Hardness (N)	Thickness (mm)	Friability (%w/w)	Disintegration Time (s)
TAB #1-12 (Avg.)	2-3	80-122	6.6±0.1	0.88	45
	3-7	120-184	6.8±0.1	0.33	75
	5-8	180-240	6.3±0.1	0.13	150

3.7. Stability Studies

The study was conducted as per guidelines of ICH. The pellets filled capsules were withdrawn periodically and evaluated for drug content and in-vitro release studies. No significant change was observed in in-vitro release profile and drug content of the formulations after three months and six months of accelerated stability studies. Thus, it was concluded that the in-house developed formulation was stable during six month accelerated stability studies.

4. CONCLUSION

Using various polymers, matrix pellets were successfully prepared. The desired drug release was achieved from the alginate-containing pellets treated with saturated solution of calcium chloride. The drug release from matrix pellets and compressed tablets using these pellets was found to be similar. Acceptance value was easily achieved using a combination of Avicel PH 102 and Avicel PH 101 as fillers in the diluent blend. Further, the extrusion/spheronization technique can be

explored to prepare extended release matrix type pellets which can substitute reservoir-type pellets in preparing the MUPS tablets. Future research could be dedicated to exploring other techniques to obtain greater uniformity of drug content in MUPS tablets.

Conflict of interest

None declared

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