Research Article

Formulation and Evaluation of Galantamine Hydrobromide Floating Matrix Tablet

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ABSTRACT

The aim of the present work was to prepare floating tablets of galantamine HBr using sodium alginate and xanthan gum as matrix forming carriers. Galantamine HBr is used for the treatment of mild to moderate Alzheimer's disease and various other memory impairments, in particular those of vascular origin. The matrix tablet formulations were prepared by varying the concentrations of sodium alginate and xanthan gum. The tablets were prepared by direct compression technique using PVP K-30 as a binder and sodium bicarbonate for development of CO_2. The prepared matrix tablets were evaluated for properties such as hardness, thickness, friability, weight variation, floating lag time, compatibility using DSC and FTIR. *In vitro* dissolution was carried out for 12 hrs in 0.1N HCl at 37±0.5 ℃ using USP paddle type dissolution apparatus. It was noted that, all the prepared formulations had desired floating lag time and constantly floated on dissolution medium by maintaining the matrix integrity. The drug release from prepared tablets was found to vary with varying concentration of the polymers, sodium alginate and xanthan gum. From the study it was concluded that floating drug delivery system for galantamine HBr can be prepared by using sodium alginate and xanthan gum as a carrier.

Keywords: Floating drug delivery system, galantamine HBr, xanthan gum, sodium alginate, *in vitro* dissolution.

INTRODUCTION

Natural polymers and their derivatives are non toxic, less expensive, biodegradable and are widely being used to prepare various pharmaceutical dosage forms[1]. Natural polymers can be modified for preparing various drug delivery systems and thus can compete with synthetic polymers which are abundantly available in the market[2]. Oral administration is the most convenient route and is associated with superior patient compliance compared to other modes of drug administration. However, oral administration has only limited use for important drugs that have poor oral bioavailability due to incomplete absorption or degradation in the gastrointestinal (GI) tract[3]. A gastric floating drug delivery systems (GFDDS) prolongs the retention time of a dosage form in stomach, thereby improving the oral bioavailability of the drug. Controlled release gastroretentive dosage forms (CR-GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of drugs which have a narrow absorption window. Thus, GRDF may improve therapy with clinically used medications, as well as enable oral administration of drugs, or drugs which otherwise had to be administered parenterally[4].
The gastric retention of dosage forms may be achieved by mucoadhesion, floatation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying[5, 6]. In context of the above principles, a strong need was recognized for the development of a dosage form to deliver galantamine in the stomach and to increase the efficiency of the drug, providing controlled release action. In the present study, an attempt was made to develop a GFDDS containing galantamine HBr as a model drug using xanthan gum and sodium alginate as hydrophilic matrix polymer carriers. The present investigation applied a systematic balance between floating lag time, floating duration, and *in vitro* drug release for the development of gastroretentive dosage forms of galantamine suitable for sustained release formulation with improved bioavailability.
The factors influencing the release of drugs from hydrophilic matrices include viscosity of the polymer, ratio of the polymer to drug, mixtures of polymers, compression pressure, thickness of the tablet, particle size of the drug, pH of the matrix, entrapped air in the tablets, molecular size of the drug, molecular geometry of the drug, solubility of the drug, the presence of excipients or additives, and the mode of incorporation of these substances[7, 8].
Xanthan gum is a high molecular weight extracellular polysaccharide produced by the fermentation of gram negative bacteria *Xanthomonas campestris*. It is a hydrophilic polymer, which is used in thickening, suspending, and emulsifying water-based systems. It started gaining appreciation for the fabrication of matrices with sustained/ controlled drug release characteristics[9, 10].

Table 1: Composition of floating galantamine hydrobromide tablets.

Ingredients	Formulation code and weight in mg					
	F1	F2	F3	F4	F5	F6
Galantamine HBr	8	8	8	8	8	8
Sodium alginate	90	120	150	120	120	120
Sodium bicarbonate	30	30	30	30	30	30
Xanthan gum	--	--	--	75	90	120
PVP K-30	9	9	9	9	9	9
Magnesium Stearate	6	6	6	6	6	6
Directly compressible lactose	157	127	97	52	37	7
Total weight of tablet (mg)	300	300	300	300	300	300

Table 2: Evaluation data obtained for prepared tablets.

Formulation code	% weight variation*	Thickness* (mm)	Hardness* (kg/ cm^2)	Friability* (%)	% Drug content*
F1	302±3.1	5.32±0.16	5.7±0.64	0.46±0.11	100.2±2.4
F2	301±2.5	5.27±0.14	6.3±0.56	0.41±0.12	101.8±2.6
F3	297±3.2	5.21±0.17	6.6±0.42	0.33±0.13	100.3±3.1
F4	298±2.7	5.24±0.16	6.7±0.73	0.38±0.12	98.7±1.8
F5	300±3.6	5.21±0.15	6.9±0.48	0.34±0.12	100.5±2.2
F6	298±2.8	5.20±0.18	7.1±0.59	0.27±0.13	101.4±3.2

*Mean ± SD, n = 3

Table 3: Buoyancy results for the prepared formulations.

Formulation code	Onset of Floating* (secs)	Duration of Floating* (hrs)	Water uptake* (%)
F1	44±3.4	20	254±6.4
F2	40±2.7	22	273±5.3
F3	37±2.4	>24	318±6.1
F4	36±3.1	>24	336±5.2
F5	34±3.3	>24	368±6.5
F6	30±2.5	>24	394±6.8

*Mean ± SD, n = 3

Chemically, it is considered an anionic polyelectrolyte, with a cellulosic backbone chain linked to a trisaccharide side chain consisting of two D-mannose units with alternating D-glucuronic acid residues that can be acetylated or pyruvated at different levels, which influences both the chemical and physical properties of xanthan[11]. The release pattern of drug from xanthan gum matrices is preceded by polymer hydration of processing variables that might affect its hydration and would also affect its performance as a controlled release dosage form. Xanthan gum displays high degree of swelling due to water uptake and small degree of erosion due to polymer relaxation[12]. Xanthan gum offers potential utility as a drug carrier because of its inertness and biocompatibility. It is used as an effective excipient for sustained release formulations

Alginic acid, also called algin or alginate, is an anionic polysaccharide distributed widely in the cell walls of brown algae. Alginates mainly consist of mannuronic acid, guluronic acid and mannuronic-guluronic blocks. Sodium alginate is a natural hydrophilic colloidal polysaccharide with an abundance of free carboxyl and hydroxyl groups distributed along its backbone[13-15].

In the present study, galantamine hydrobromide (GAL) was used as a model drug, which is an analkaloid that is obtained synthetically or from the bulbs and flowers of *Galanthus caucasicus*, *Galanthus woronowii* and related genera like *Narcissus*, *Leucojum*, and *Lycoris* including *Lycoris radiate*. It is used is used for the treatment of mild to moderate Alzheimer's disease and various other memory impairments, in particular those of vascular origin[16-18].

The objective of the present work was to prepare a matrix floating tablet using xanthan gum, sodium alginate, drug and excipients. Different formulations were prepared by varying the concentration of gum in the matrix and the prepared tablets were evaluated for hardness, thickness, friability, swelling, buoyancy, compatibility, percentage drug release, diffusion coefficient (n) and stability studies.

MATERIALS AND METHODS

Materials

Galantamine hydrobromide was received as gift sample from Dr. Reddy's Laboratories, Hyderabad, India. It is a white to almost white powder, slightly soluble in water, fairly soluble in hot water, and freely soluble in alcohol, acetone, and chloroform. Directly compressible lactose was obtained as gift sample from Strides Acrolab, Bangalore, India. Xanthan gum and sodium alginate were purchased from Sigma Aldrich, Mumbai, India. Sodium bicarbonate and all other chemicals used were of analytical grade and purchased from Loba Chemie, Mumbai, India.

Fourier Transform Infrared Spectroscopy (FTIR)[19]

FTIR spectra of the pure galantamine HBr and the optimized formulation were recorded. Samples were prepared as KBr disks using a hydraulic pellet press and then scanned from 4000 to 400 cm^{-1} using a Fourier transform infrared spectrophotometer (FTIR 8400, Shimadzu, Japan).

Table 4: Data obtained from Peppas model fitting for the formulations.

Parameters	F1	F2	F3	F4	F5	F6
Constant (A)	1.324	1.257	1.362	1.214	1.278	1.307
Regression coefficient (R^2)	0.9867	0.9836	0.9721	0.9896	0.9941	0.9875

Table 5: Stability study data of optimized formulation F5.

Stability condition	Sampling interval (Months)	Formulation F5	
		Physical appearance	% Drug content
25 ± 2 °C/ 60 ± 5 % RH	0	No change	100.5±2.2
	3	No change	99.6±2.3
	6	No change	99.2±2.2
	12	No change	98.4±2.3
30 ± 2 °C/ 65 ± 5 % RH	0	No change	100.5±2.2
	3	No change	99.7±2.3
	6	No change	98.8±2.2
	12	No change	98.4±2.4
40 ± 2 °C/ 75 ± 5 % RH	0	No change	100.5±2.2
	3	No change	99.6±2.2
	6	No change	98.6±2.3
	12	No change	98.3±2.4

*Standard deviation n=3

Differential Scanning Calorimetry (DSC)[20]
DSC thermograms were recorded for pure galantamine drug and the optimized formulation. Accurately weighed samples were placed on aluminum plates, sealed with aluminum lids and heated at a constant rate of 5°/min over a temperature range of 0–400 °C. All dynamic DSC studies were carried out using DuPont thermal analyzer with 2010 DSC module.

Preparation of floating tablet[21]
The floating tablets containing galantamine hydrobromide were prepared by using direct compression technique. The formulations were designed by varying the concentration of sodium alginate, xanthan gum and sodium bicarbonate in the tablet (Table 1). Accurately weighed quantities of drug, polymers (sodium alginate, xanthan gum), binder (PVP K-30), sodium bicarbonate and other excipients were blended in a mortar and pestle. The resultant homogenous mixture was compressed into tablets in a 10 station rotary tablet machine (Rimek, Mumbai, India) at a speed of 10 rpm and using 9 mm round concave punches and optimum pressure. The prepared tablets were evaluated for properties such as hardness, thickness, weight variation, percent friability and drug content.

UV/Visible spectroscopy[22]
The maximum absorbance (λ_{max}) of the selected drug, galantamine hydrobromide was determined by scanning a known concentration of sample solution in the wavelength region of 200–400 nm by using Shimadzu 1601 UV/ Visible spectrophotometer. The λ_{max} was found to be 221 nm and this wavelength was used for further UV studies.

In vitro buoyancy studies[23]
The *in vitro* buoyancy for the prepared floating matrix tablets was characterized by floating lag time and total floating time. The test was performed using a paddle type USP dissolution apparatus (Electrolab TDL-08L) in 900 ml of 0.1 N HCl at a temperature of 37 ± 0.5°C and 100

rpm. The time required for the tablet to rise to the surface of the dissolution medium and the time duration till which the tablet constantly floated on the dissolution medium were noted as floating lag time and floating duration respectively. The relative matrix integrity of the prepared tablet was determined on the basis of visual inspection after the floating studies.

Water uptake study[24]
The water uptake study for the prepared tablet formulation was performed using a paddle type USP dissolution tester (Electrolab TDL-08L). The study was conducted in 900 ml of 0.1 N HCl, which was maintained at a temperature of 37±0.5 °C. After a specific period of time (8 hrs), the tablets were removed, blotted to remove excess water and weighed. Swelling characteristics of the prepared tablets were expressed in terms of water uptake (WU) using;

$$WU\ (\%) = \frac{wt.\ of\ swollen\ tablet - Initial\ wt.\ of\ tablet}{Initial\ weight\ of\ the\ tablet} x100$$

In vitro dissolution studies
Dissolution studies were carried out in basket type USP type –II (paddle) dissolution apparatus (Electrolab TDL-08L) at 100 rpm and 37±0.5°C using 900 ml of 0.1N HCl for a period of 12 hrs[25,26]. The samples were withdrawn at regular intervals and diluted to a suitable concentration with 0.1N HCl and the absorbance was measured at 221 nm using Shimadzu UV-Visible spectrophotometer.

Peppas model fitting [27, 28]
Koresmeyer-Peppas model is one of the mathematical expression to evaluate the mechanism of drug delivery. The Koresmeyer-Peppas equation is as follows;

$$M_t/ M_\infty = 1- A\ (exp^{-kt}) \qquad (2)$$

$$log\ (1 - M_t/M_\infty) = log\ A – kt/2.303 \qquad (3)$$

where, M_t/M_∞ is the fractional amount of drug released and t is the time in hrs. In this study, the release constant, k and constant, A were calculated from the slopes and intercepts of the plot of In (1- M_t/M_∞) versus time t respectively where, Mt is the amount of drug release at time t; M_∞ is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and A is the diffusional exponent indicative of the mechanism of drug release.

Stability studies[29]
Stability studies for the optimized formulation of galantamine floating matrix tablets was carried out to determine the effect of formulation additives on the stability of the drug in the final formulation and also to determine the physical stability. The optimized formulation was subjected to stability studies according to ICH guidelines by storing at 25 ± 2°C/60 ± 5 % RH and 30 ± 2 °C/65 ± 5 % RH for 12 months, and 40 ± 2 °C/75 ± 5 % RH for 6 months (Thermolab, Mumbai, India). The samples were analyzed and checked for changes in physical appearance and drug content at regular intervals.
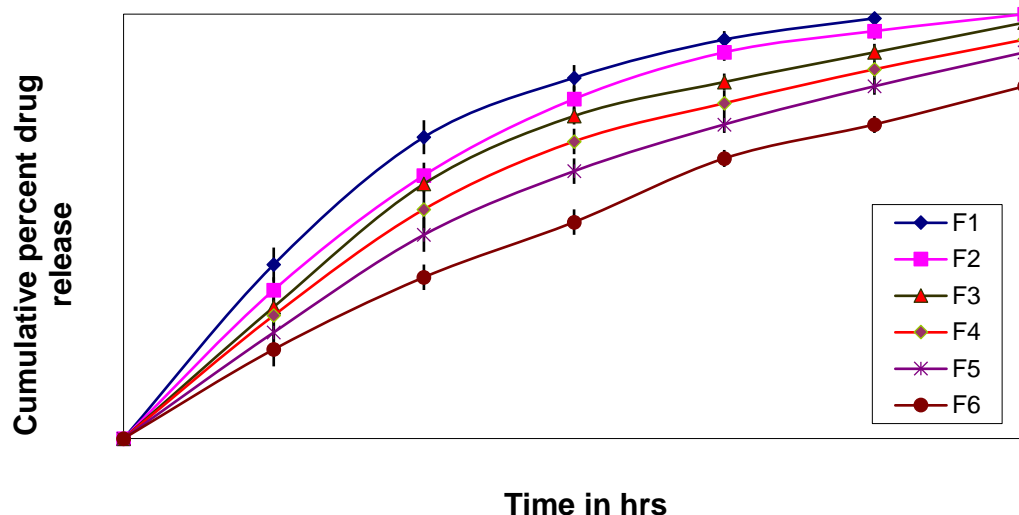
RESULTS AND DISCUSSION

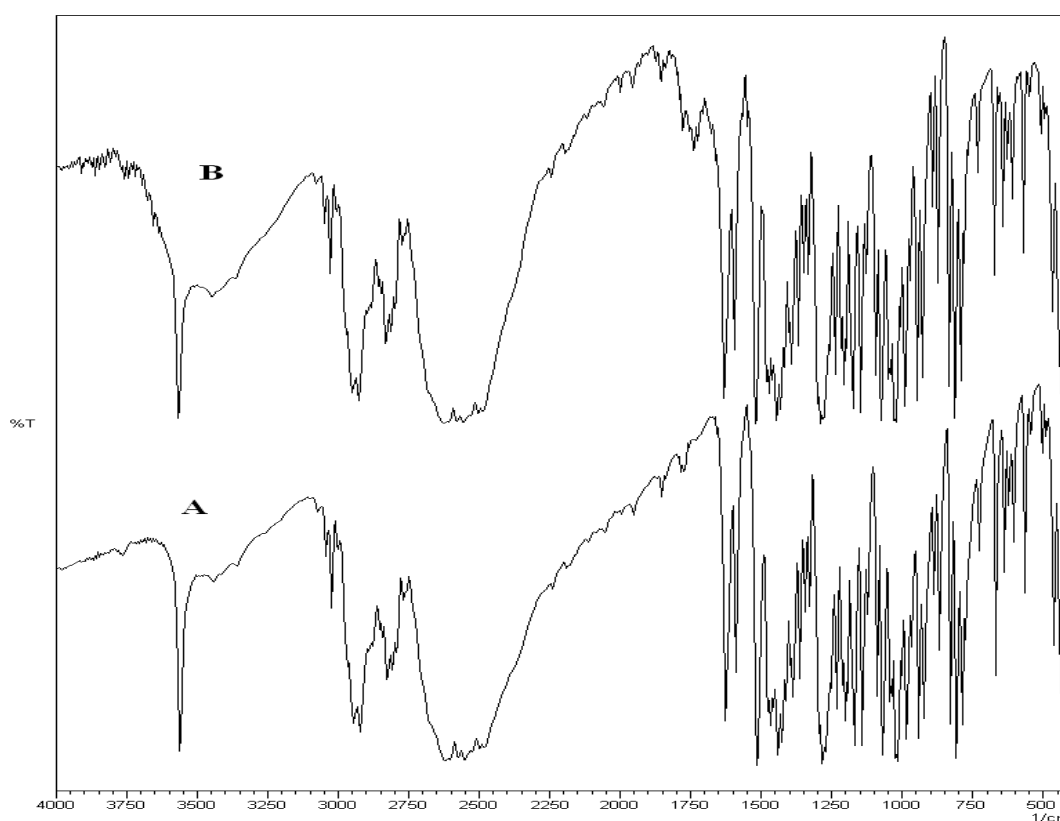Figure 1: *In vitro* drug release profile for the prepared floating tablets.

Figure 2: FTIR chromatogram for pure galantamine (peak A) and formulation F5 (peak).

The FTIR spectra of pure galantamine HBr and the optimized formulation F5 were found to be identical as shown in figure 2. The characteristic IR absorption peaks of galantamine at 3552 (alcoholic –OH group), 3416 (N–CH3), 2931 (C=C), 1612 (aromatic C-H stretch), 1403 (aromatic ether linkage) and 1187 cm^{-1} (O-CH$_3$) were obtained. The FTIR spectra obtained indicated that no chemical interaction occurred between the drug, galantamine, polymers and the excipients used in formulating the floating tablet. But, a slight shift in absorption peaks position was noticed which indicated that physical interaction might have occurred between drug and the polymer/ excipients used.

From the DSC data obtained (Fig. 3), it was evident that the melting point of galantamine HBr has not changed after placing the tablets for stability studies. Hence, it may be inferred that there was no interaction between galantamine and polymers used. From DSC results it can be concluded that the drug maintained its chemical identity throughout the process.

The prepared tablets were evaluated for properties such as hardness (Inweka hardness tester, Ahmedabad, India),
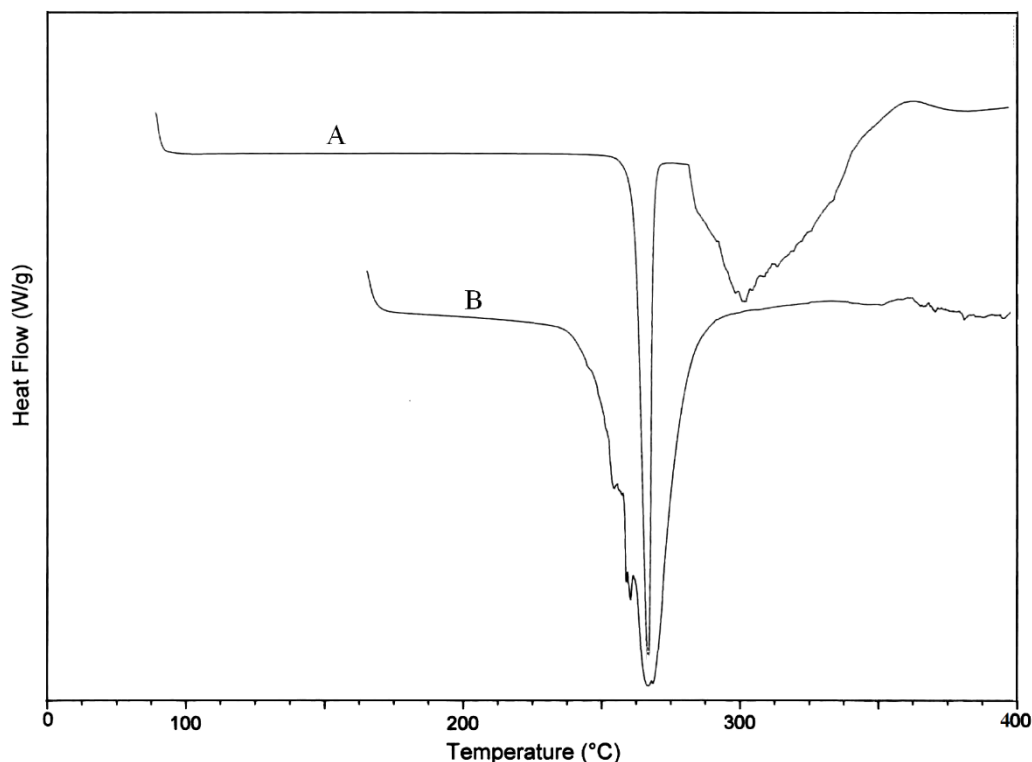
Figure 3: DSC chromatogram for pure galantamine HBr (peak A) and formulation F5 (peak B)

thickness (Mitotoya screw guage, Japan), weight variation (Shimadzu AW 120, Japan), percent friability (Electrolab EF-2 friabilator, Mumbai, India) and drug content (Shimadzu 1702 UV/Visible spectrophotometer, Japan). The percentage weight variation, percent friability and content of active ingredient for all the formulations were found to be well within United States Pharmacopoeia (USP) standards and the data obtained is given in Table 2. From the table, it was clear that the hardness of the prepared tablets had increased as the amount of sodium alginate concentration in the tablet formulation increased (F1-F3). Formulations F3 showed maximum hardness of about 6.6 Kg/cm^2 among the three polymer ratios selected (30%, 40% and 50% w/w sodium alginate). It was clear that addition of xanthan gum had a direct impact on hardness of tablet (increased hardness for formulations F4-F6). Among all the formulations prepared, F6 containing 40% w/w sodium alginate and 40% w/w of xanthan gum showed a maximum hardness of about 7.1 Kg/cm^2. From the table, it was noticed that the percent drug content, thickness and friability lie in the range 98.7–101.4 %, 5.20-5.32 mm and 0.27-0.46% respectively.

In the present study, an effervescent approach using sodium bicarbonate as gas generating agent was employed to make the tablet float. As the dissolution medium (0.1 N HCl) imbibed into the tablet matrix, the interaction of acid with sodium bicarbonate results in the generation of CO_2 gas. The generated gas was entrapped and protected within the gel which was formed due to hydration of polymer viz., sodium alginate and xanthan gum, which decreased the density of the tablet, as a result of which, the tablet float.

The effect of formulation parameters on floating lag time and duration of floating is given in the Table 3. From the table, it was clear that the time taken by the tablet to float (onset of floating) on the dissolution medium decreased with an increase in amount of sodium alginate used. The floating lag time decreased from 44 to 37 seconds indicating that formulation F3 floats faster than F1. It was also noted that, formulations F4-F6 floated more rapidly (36, 34 and 30 seconds) when compared to formulations F1-F3. This phenomenon can be attributed due to the addition of xanthan gum in the tablet formulation. The addition of xanthan gum caused a stable gel, due to which the entrapped CO_2 cannot escape easily from the gel matrix and thus caused a rapid onset of floating. The prepared formulations F3 to F6 floated for a period of more than 24 hrs while the tablet formulations containing 30 and 40% of sodium alginate (F1 and F2) floated only up to 20 and 22 hrs respectively. From the table, it is also clear that formulations F1 to F3 showed 254, 273 and 318% increase in weight after the study period of 8 hrs. A drastic increase in percent water uptake for F4-F6 formulations (336, 368 and 394%) can be attributed to addition of xanthan gum in the concentrations of 25, 30 and 40% w/w, which has better water retention capacity than sodium alginate.

The *in vitro drug* release of galantamine hydrobromide from the prepared hydrophilic floating matrix tablets is shown in Fig. 1. From the release studies, it is clear that the concentration of sodium alginate in the formulation had a remarkable influence on the drug release. Formulations F1 to F3 (30, 40 and 50% w/w sodium alginate) showed drug release of about 35, 31 and 30% at the end of 2 hrs. This decrease in amount of drug release can be directly

attributed to the increase in polymer concentration. Increase in polymer concentration leads to the formation of thick gel barrier, which causes the drug diffusion through the matrix difficult and thus decreases the overall drug release from the tablets. Formulations F1 – F3 formulations showed about 71, 62 and 60% galantamine release at the end of 4 hrs indicating that they are unsuitable for showing 12 hr release profile. On the other hand, formulations F4-F6 showed a drug release of 54, 48 and 38% at the end of 4 hrs study period indicating their suitability for showing 12 hr release profile.

Formulations F4 to F6 showed a drug release of about 29, 25 and 21% at the end of 2 hrs. The decrease in amount of drug release compared to F3 can be attributed to the presence of xanthan gum in the tablet formulation. It is observed from the figure that, formulations containing 30 and 40% w/w of xanthan gum (F5 and F6) showed a marginal decrease in drug release than formulation containing 25% w/w (F4). At the end of *in vitro* dissolution study, F4 and F5 formulations have shown the drug release of 94 and 91% respectively indicating that they are suitable for showing drug release upto 12 hrs.

The data obtained from *in vitro* drug release studies was fit into Peppas model. From the plot of log M_t/ M_∞ versus t, the parameters such as release constant (k), constant (A) and the regression coefficient (R^2) were calculated and are given in Table 4. If A is equivalent to 0.5 indicates Fickian (case I) release; greater than 0.5 but less than 1 for non-Fickian (anomalous) release and A is greater than 1 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain, and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion-controlled drug release. From the table it was concluded that, formulation F5 with R^2 value of 0.9941 is the optimized formulation for 12 hr study period.

The optimized formulation F5 was subjected for stability studies. Stability studies of the drug formulations are performed to ascertain whether the drug undergoes any degradation during its shelf life. The data obtained from the stability studies is tabulated in Table 5. From the stability study data, it was clear that the drug was stable in the optimized formulation for the study period of 6 weeks. DSC thermograms of the pure drug and its formulations before and after stability studies were recorded to evaluate whether the drug has undergone any degradation during the study period.

CONCLUSION

The evaluation data for properties such as hardness, thickness, friability, weight variation, floating lag time and water uptake indicated that the prepared floating tablets were well within the specified standards. The drug release data revealed that the formulation with sodium alginate and xanthan gum (30% w/w) showed a better release rate compared to other formulations. At the end of *in vitro* dissolution study, F4 and F5 formulations have shown the drug release of 94 and 91% respectively indicating that they are suitable for showing drug release upto 12 hrs. The data obtained from the Peppas model fitting indicates that

the mechanism of drug release was by super case-II transport i.e., drug release was by both diffusion and erosion of the polymer. From the stability studies, it was clear that the optimized formulation F5 was stable for six weeks. The DSC thermograms and FTIR spectra for the pure drug and optimized formulation indicated no change in chemical identity of the drug. From the results obtained it can be concluded that sodium alginate and xanthan gum, which are natural and biodegradable polymers can be employed for use as carriers in developing floating drug delivery systems.

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