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Investigation of Kondagogu Gum as a Pharmaceutical Excipient: A Case Study in Developing Floating Matrix Tablet

Valluru Ravi* and T.M. Pramod kumar

Department of Pharmaceutics, JSS College of Pharmacy, JSS University, Mysore – 570 015, Karnataka, India

***Corres.author: ravivalluru@rediffmail.com; +918212548353**

Abstract: The aim of the present work was to prepare floating tablets of diltiazem HCl using kondagogu gum as matrix forming carrier. Diltiazem HCl, having an elimination half-life of about 3.5 hrs, is a calcium channel blocker used in treatment of several diseases of the cardiovascular system, especially angina and hypertension. The matrix tablet formulations were prepared by varying the concentrations of kondagogu gum and sodium bicarbonate. The tablets were prepared by direct compression technique using PVP K-30 as a binder, hydroxy propyl methyl cellulose (HPMCK4M) was employed in the formulation as a gel forming polymer 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 buffer at 37±0.5 °C using USP basket type dissolution apparatus. *In vivo* studies were done in rabbits to prove the floating lag time by roentgenography. 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 polymer, kondagogu gum. From the study it was concluded that floating drug delivery system can be prepared by using kondagogu gum as a carrier.
Key words: Floating drug delivery system, diltiazem HCl, kondagogu gum, *in vitro* dissolution.

INTRODUCTION

Natural polymers and their derivatives are widely being used to prepare various pharmaceutical dosage forms. Natural polysaccharides hold advantages over synthetic polymers as they are non toxic, less expensive, biodegradable and easily available[1]. Natural polymers can be modified to have tailor-made materials for preparing drug delivery systems and thus can compete with synthetic materials which are widely available in the market[2]. Oral sustained release (SR) dosage forms (DFs) are being developed for the past several decades due to their considerable therapeutic advantages[3,4].

Oral administration is the most convenient mode of drug delivery 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. Some of these drugs are characterized by a narrow absorption window (NAW) at the upper part of the gastrointestinal tract and enhancing the gastric residence time (GRT) of a NAW drug may significantly improve the net extent of its absorption[5].

The gastric floating drug delivery systems (GFDDS) prolong the retention time of a dosage

form in the stomach, thereby improving the oral bioavailability of the drug. Compounding narrow absorption window drugs in a unique pharmaceutical DF with gastroretentive properties would enable easy administration of drug and such a DF would retain in stomach for long time and release the drug in a controlled or prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would be best to achieve the pharmacokinetic and pharmacodynamic advantages of sustained release dosage forms for drugs[6, 7].

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, floatation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying[8, 9]. From the formulation and technological point of view, the floating drug delivery system is considerably easy and logical approach[10]. In the present study, an attempt was made to develop a GFDDS containing diltiazem HCl as a model drug using kondagogu gum as the matrix polymer carrier.

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[11].

Carbohydrate and biodegradable polymers have been extensively used to develop the sustained release (SR) formulations to decrease the release rates of drugs having short plasma life. Responsive polymers, in particular hydrophilic natural carbohydrate polymers, are some of the promising new resourceful carriers for the preparation of oral sustained release (SR) systems[12]. A large number of polysaccharides like amylose, guar gum, chitosan, inulin, pectin, cyclodextrins, dextrans, dextrin chondroitin sulphate, and locust bean gum have been investigated for their use in sustained drug delivery systems. One such responsive polymer is Kondagugu gum[13].

Kondagugu gum [KG] is the dried exudates obtained from tree *Cochlospermum gossypium* which belongs to the family Bixaceae[14]. KG is a high molecular weight complex acetylated polysaccharide consisting mainly of D-galacturonic acid, D-galactose and L-rhamnose[15]. KG has aroused lot of interest in the preparation of hydrophilic matrix tablets because of its high water swellability, nontoxicity, and low cost. Unlike other water soluble gums, it does not dissolve in water but absorbs it to form a viscous colloidal solution[13]. Powdered KG swells in cold water to an extent that a 3% to 4% sol will produce a gel of uniform smoothness and texture.

In the present study, diltiazem hydrochloride (DTZ) was used as a model drug, which is a calcium channel blocker belonging to benzothiazepine family. It is widely prescribed for the treatment of hypertension and angina[16, 17]. DTZ undergoes an extensive biotransformation, mainly through cytochrome P-450 CYP3A, which results in less than 4% of its oral dose in being excreted unchanged through urine. Bioavailability of DTZ is ~30% to 40% owing to an important first pass metabolism. It has an elimination half-life of 3.5 hours and has an absorption zone from the upper gastrointestinal tract. DTZ requires frequent dosage administration in order to maintain adequate plasma concentrations. Therefore, it is a suitable model candidate for formulating into a gastroretentive tablet formulation[18, 19].

The objective of the present work was to prepare a matrix floating tablet using kondagogu gum, 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

Diltiazem Hydrochloride was received as gift sample from Divis Laboratories, Hyderabad, India. It is a white, odourless, crystalline powder, freely soluble in water and methanol. Directly compressible lactose was obtained as gift sample from Strides Acrolab, Bangalore, India. Kondagogu gum was purchased from girijan co-operative society, Govt. of Andhra Pradesh, Hyderabad, India. Hydroxy propyl methyl cellulose (HPMCK4M) was purchased from Sigma Aldrich, Mumbai, India. Sodium bicarbonate and all other chemicals used were of analytical grade and purchased from Loba Chemie, Mumbai, India.

Purification of gum

First the foreign extraneous matter like bark etc was separated from the gum, then powdered and passed through sieve # 80. The powdered gum was dispersed in distilled water to get a 1% solution, kept in sonicator for 10 min until it was clear and added

to equimolar mixture of acetone and ethanol (2:1 v/v) to give precipitation of gum. Precipitated polymer was kept in an oven for drying, powdered and evaluated for its general characteristic properties[15].

Preparation of floating tablets

The floating tablets containing diltiazem hydrochloride were prepared by direct compression technique. The formulations were prepared by varying the concentration of polymers and sodium bicarbonate in the tablet (Table 1). Accurately weighed quantities of drug, polymers (kondagogu gum, HPMCK4M), binder (PVP K-30), sodium bicarbonate for gas-generation and other diluents were blended homogeneously in a mortar and pestle and the resultant mixture was compressed into tablets using 10 station rotary tablet machine (Rimek, Mumbai, India) at 10 rpm and using 9 mm round concave punches at an optimum pressure. The prepared tablets were evaluated for tablet properties such as hardness (Inweka hardness tester, Ahmedabad, India), 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).

UV/Visible spectroscopy

The wavelength of maximum absorbance (λ_{max}) of the selected drug, diltiazem hydrochloride 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 237 nm and this wavelength was used for further UV studies.

In vitro buoyancy studies

The *in vitro* buoyancy for the prepared floating matrix tablets was characterized by floating lag time and total floating time. The test was performed in a basket type USP dissolution apparatus (Electrolab TDL-08L) using 900 ml of 0.1 N HCl buffer at a temperature of 37 $\pm$ 0.5 °C and 100 rpm. The time required for the tablet to rise to the surface of the dissolution medium and the duration till which the tablet constantly floated on the selected dissolution medium were noted as floating lag time and floating duration respectively The relative matrix integrity was determined on the basis of visual inspection after the floating studies.

Water uptake study

The water uptake study of the tablet was done using basket type USP dissolution tester (Electrolab TDL-08L). The study was conducted in 900 ml of 0.1 N HCl buffer, which was maintained at a temperature of 37±0.5 ºC and after a specific period of time (8 hrs), the tablets were withdrawn, blotted to remove excess water and weighed. Swelling characteristics of the prepared tablets were expressed in terms of water uptake (WU) as;

$$W\,U\,(\%) = \frac{[\text{weight of the swollen tablet}] - [\text{Initial weight of the tablet}] \times 100}{[\text{Initial weight of the tablet}]} \quad \ldots..(1)$$

In vitro dissolution studies

Dissolution studies were carried out in basket type USP dissolution apparatus (Electrolab TDL-08L) at 100 rpm and 37±0.5 °C temperature using 900 ml of 0.1N HCl buffer for a period of 12 hrs. The samples were withdrawn at regular intervals and diluted to a suitable concentration with 0.1N HCl buffer and the absorbance was measured at 237 nm using Shimadzu UV-Visible spectrophotometer.

Peppas model fitting [20, 21]

Koresmeyer-Peppas model is one of the mathematical expression to evaluate the mechanism of drug delivery. The Koresmeyer-Peppas equation is as follows;

$$M_t/M_\infty = 1 - A\,(\exp -kt) \quad \ldots\ldots (2)$$

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

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 $(1- M_t/M_\infty)$ 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. To find out the release exponent, the log value of percentage drug dissolved was plotted against log time for each batch according to the above equation. 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.

Fourier Transform Infrared Spectroscopy (FTIR)[22]
FTIR spectra of the pure diltiazem HCl and the optimized formulation were recorded using a Fourier transform infrared spectrophotometer (FTIR 8400, Shimadzu, Japan). Samples were prepared as KBr disks using a hydraulic pellet press and scanned from 4000 to 400 cm^{-1}.

Stability studies
Stability studies of the optimized formulation of diltiazem floating matrix tablets was carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 40 ºC/75% RH for 3 months (Thermolab, Mumbai, India). Formulation was analyzed every 15 days for its hardness and % drug content.

Differential Scanning Calorimetry (DSC)[22]
DSC thermograms were recorded for pure diltiazem drug and the optimized formulation using a differential scanning calorimeter. Accurately weighed samples were placed on aluminum plates, sealed with aluminum lids, and heated at a constant rate of 5 °C/min over a temperature range of 0–300 °C. All dynamic DSC studies were carried out using DuPont thermal analyzer with 2010 DSC module.

RESULTS AND DISCUSSION

Kondagogu gum powder after purification was pale yellow in colour, had ash content of 8.2% and the moisture content in the gum was 14.8%. 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 kondagogu gum concentration in the tablet increased (F1-F3). Formulations F3 showed maximum hardness of about 6.7 Kg/cm^2 among the three polymer ratios selected (40%, 50% and 60%). It was clear that addition of HPMCK4M had a direct impact on hardness of tablet (increased hardness for formulations F4-F6). Among all the formulations prepared, F6 containing kondagogu gum and HPMCK4M at concentration of 50% and 15% w/w respectively showed a maximum hardness of about 7.4 Kg/cm^2. From the table, it was noticed that the percent drug content, thickness and friability lies in the range 98.7–101.3 %, 5.28-5.46 mm and 0.19-0.38% respectively.

In the present study, an effervescent approach using sodium bicarbonate as gas generating agent was adopted to enable the tablet to float. As the dissolution medium (0.1 N HCl buffer) imbibed into the tablet matrix, the interaction of acid with sodium bicarbonate resulted in the generation of CO_2 gas. The generated gas was entrapped and protected within the gel which was formed due to hydration of kondagogu gum and decreased the density of the tablet, as a result of which, the tablet became buoyant.

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 kondagogu gum concentration in the formulation (formulation F3 floats faster than F1). It was also noted that, formulations F4-F6 floated readily when compared to formulations F1-F3. This can be attributed to the addition of HPMCK4M, at concentrations of 5, 10 and 15% w/w for formulations F4, F5 and F6 respectively. The addition of HPMCK4M caused gel formation at a fast rate, due to which the entrapped CO_2 does not escape from the gel matrix and thus caused a rapid onset of floating. The formulations F3 to F6 floated for a period of more than 24 hrs while the formulations containing 30 and 40% of kondagogu gum (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 263, 296 and 358% increase in weight after the study period of 8 hrs. A linear increase in percent water uptake for F4-F6 can be attributed to addition of HPMCK4M in the concentrations of 5, 10 and 15% w/w.

The *in vitro drug* release of diltiazem hydrochloride from the prepared floating matrix tablets is given in Fig. 1. From the figure, it can be noted that the concentration of kondagogu gum in the formulation had a remarkable influence on the drug release. Formulations F1 to F3 showed about 37, 32 and 30% of drug release 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, causing the drug diffusion through the matrix difficult and thus decreasing the overall drug release from the matrix. Formulations F1 – F3 showed about 78, 71 and 62% drug release within 6 hrs. On the other hand, F1 showed a release of about 94% of drug in 10 hrs indicating that it is unsuitable for showing 12 hr release profile. Formulations F2 and F3 showed a drug release of 94 and 91% at the end of 12 hr study

period indicating their suitability for showing 12 hr release profile. The order of drug delivery from the tablets with reference to polymer concentration is; 40 > 50 > 60%.

Formulations F4 to F6 showed a drug release of about 29, 25 and 22% at the end of 2 hrs. The decrease in amount of drug release compared to F3 can be attributed to the presence of HPMCK4M in the tablet formulation. It is observed from the figure that, formulations containing 10 and 15% of HPMCK4M (F5 and F6) showed a marginal decrease in drug release than formulation containing 5% (F4). At the end of *in vitro* dissolution study, F2, F3, F4 and F5 has showed a drug release of 94, 91, 93 and 92% 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. In all the cases, the value of A were found to be more than 1. This result indicated that the release of drug from the polymer matrix formulations was found to be super case-II transport, i.e., drug release by both diffusion and relaxation of polymer chain. From the table it was concluded that, formulation F5 with R^2 value of 0.9964 is the optimized formulation for 12 hr study period.

The IR spectra of diltiazem HCl and optimized formulation, F5 were found to be identical (Fig. 2). The characteristic IR absorption peaks of diltiazem at 2966 (aliphatic C–H stretch), 2837 (O–CH3 stretch), 2393 (amine HCl), 1679 (lactam C=O stretch), 839 (o-substituted aromatic C–H out of plane deformation) and 781 cm^{-1} (p-substituted aromatic C–H out of plane deformation) were obtained. The FTIR spectra obtained indicated that no chemical interaction occurred between the drug, diltiazem, polymers and the excipients used in formulating the tablet. But, a slight shift in absorption peaks position was noticed which indicated that physical interaction might have occurred between drug and the polymer.

The optimized formulation F5 was subjected for 3 months 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. From the DSC data obtained (Fig. 3), it was evident that the melting point of diltiazem hydrochloride is not changed after placing the tablets for stability studies. Hence, it may be inferred that there was no interaction between diltiazem hydrochloride and polymers used. From DSC results it can be concluded that the drug maintained its chemical identity throughout the process.

Table 1: Composition of floating diltiazem hydrochloride tablets.

Ingredients	**Formulation code and weight in mg**					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Diltiazem hydrochloride	60	60	60	60	60	60
Kondagogu gum	120	150	180	150	150	150
Sodium bicarbonate	30	30	30	30	30	30
HPMCK4M	--	--	--	15	30	45
PVP K-30	9	9	9	9	9	9
Magnesium Stearate	6	6	6	6	6	6
Directly compressible lactose	75	45	15	30	15	--
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	328±2.1	5.46±0.14	5.8±0.46	0.38±0.18	100.5±1.7
F2	331±1.5	5.36±0.13	6.4±0.41	0.31±0.12	99.8±2.3
F3	330±2.0	5.37±0.20	6.7±0.45	0.24±0.19	101.3±1.8
F4	332±1.7	5.33±0.17	6.8±0.32	0.29±0.13	98.9±2.1
F5	329±2.2	5.30±0.18	7.1±0.39	0.24±0.14	99.4±1.7
F6	330±1.6	5.28±0.21	7.4±0.34	0.19±0.17	98.7±2.2

*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	45±2.4	20	263±3.6
F2	41±3.0	22	296±4.2
F3	38±2.8	>24	358±4.1
F4	37±3.2	>24	316±3.6
F5	35±2.6	>24	338±4.2
F6	31±1.8	>24	357±3.8

*mean ± SD, n = 3

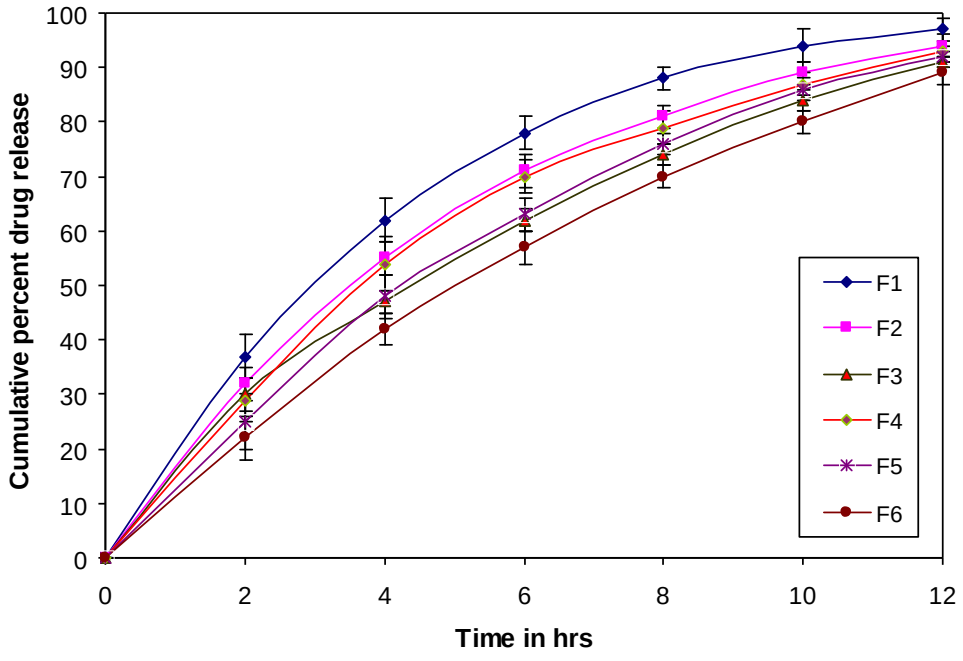

Figure 1: *In vitro* drug release profile for the prepared formulations

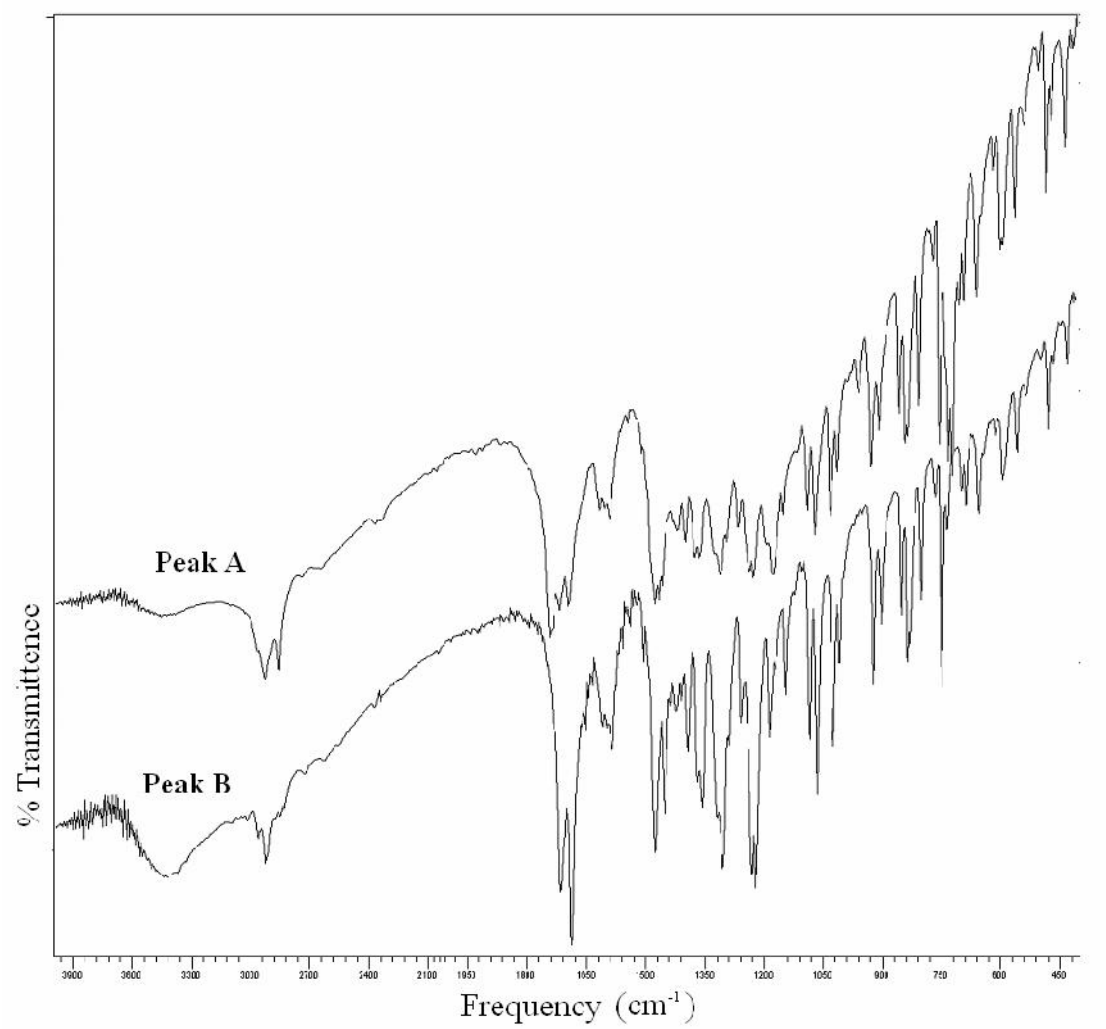

Figure 2: FTIR chromatogram for pure diltiazem hydrochloride (peak B) and formulation F5 (peak A)

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)	0.9844	0.9936	0.9921	0.9839	0.9964	0.9875

Table 5: Stability study data of optimized formulation F5.

Time in days	**Hardness* (kg/ cm^2)**	**% Drug content of F5 mean ï SD* at 40 ï 0.5îC and 75% RH**
0 (Initial)	7.0±0.31	99.64 ± 1.62
15	7.1±0.28	100.81 ± 1.43
30	7.1±0.35	102.15 ± 2.12
45	6.9±0.31	99.72 ± 1.69
60	7.1±0.29	99.86 ± 2.3
75	7.0±0.44	100.45 ± 1.67
90	7.0±0.26	101.28 ± 2.18

*Standard deviation n=3

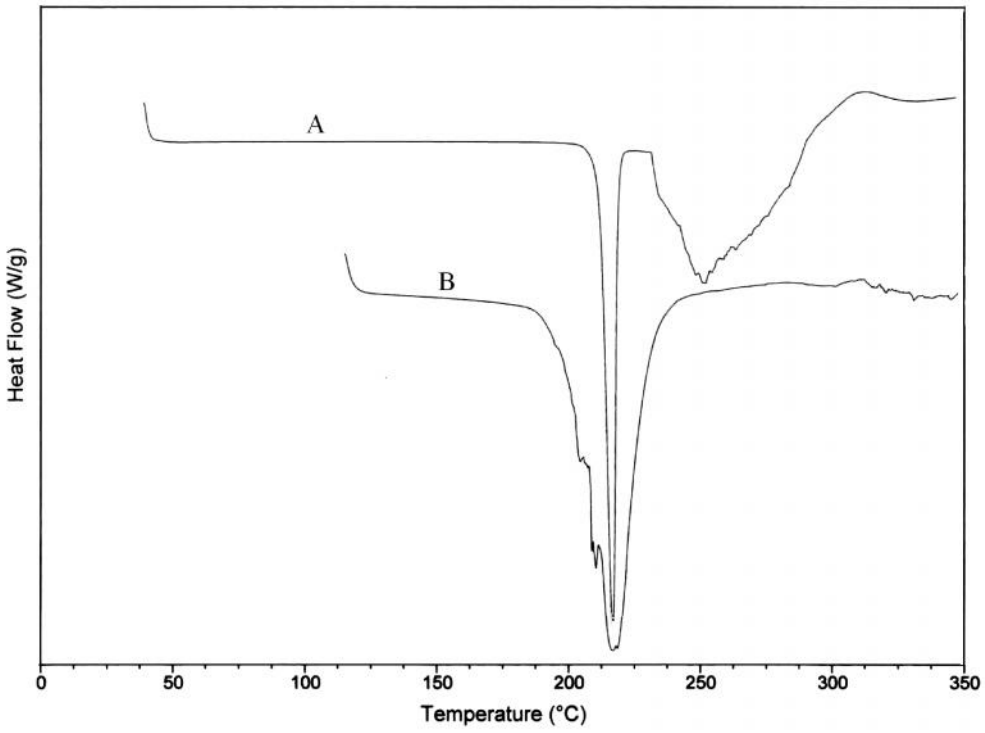

Figure 3: DSC chromatogram for pure diltiazem hydrochloride (peak A) and formulation F5 (peak B)

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 low amount of kondagogu gum (40% w/w) showed a low release rate compared to formulation with higher concentration (50 and 60% w/w). At the end of *in vitro* dissolution study, F2, F3, F4 and F5 has showed a drug release of 94, 91, 93 and 92% 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 formulation was stable for six weeks and the DSC thermograms and FTIR spectra obtained indicated no change in chemical identity of the drug. From the results obtained it can be concluded that kondagogu gum, a natural and biodegradable polymer can be employed for use as a carrier in developing floating drug delivery system.

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