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Original Article

Formulation and Evaluation of Crosslinked-Kondagogu Gum as a carrier in Developing Floating Matrix Tablet

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ABSTRACT

The aim of the present work was to prepare floating tablets of metoprolol succinate using crosslinked-kondagogu gum as matrix forming carrier. The floating matrix tablet formulations were prepared by varying the concentrations of kondagogu gum and cross linked kondagogu gum with $CaCl_2$. The tablets were prepared by direct compression technique using PVP K-30 as a binder, hydroxy propyl methyl cellulose (HPMCK4M) 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 using USP basket 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 polymer, kondagogu gum. From the study it was concluded that floating drug delivery system can be prepared by using cross linked kondagogu gum as a carrier.

Key words: Floating drug delivery system, metoprolol succinate, kondagogu gum, *in vitro* dissolution .

1. INTRODUCTION

Natural polymers and their derivatives are non-toxic, less expensive, biodegradable and are widely used to prepare dosage forms[1]. Natural polymers can be modified physically and chemically for preparing various drug delivery systems and thus can compete with synthetic polymers available in the market[2]. Oral route is the most convenient mode of drug delivery and has better patient compliance compared to other routes of drug administration. However, oral administration

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has limited use for drugs that have poor oral bioavailability or which undergoes 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. These systems improve oral administration of drugs which otherwise had to be administered parenterally[4].

The gastric retention of administered oral dosage form can be achieved either by mucoadhesion, floatation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of drugs that vary in gastric emptying[5, 6]. In the present study, an attempt was made to develop a GFDDS containing metoprolol succinate as a model drug using crosslinked kondagogu gum as hydrophilic matrix polymer carriers.

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].

Kondagogu gum [KG] is the dried exudates obtained from tree Cochlospermum gossypium which belongs to the family Bixaceae[8]. KG is a high molecular weight complex acetylated polysaccharide consisting mainly of D-galacturonic acid, D-galactose and L-rhamnose[9]. Metoprolol succinate is a β1-selective (cardio selective) adrenoceptor blocking agent, which is widely prescribed in diverse cardiovascular diseases such as hypertension, angina, arrhythmia and congestive heart failure. It undergoes extensive first pass metabolism of about 40-50% and a short biological life of 4 hrs and hence a suitable candidate for GFDDS[10, 11].

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, cross-linking agent and the prepared tablets were evaluated for hardness, thickness, friability, swelling, buoyancy, compatibility, percentage drug release, diffusion coefficient (n) and stability studies.

2. MATERIALS AND METHODS

Materials

Metoprolol succinate 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. Kondagogu gum was purchased from Girijan cooperative society, Hyderabad, India. Sodium bicarbonate and all other chemicals used were of analytical grade and purchased from Loba Chemie, Mumbai, India.

Purification of gums[12]

First the foreign extraneous matter like bark etc was separated from kondagogu gum, and then powdered using mixer grinder 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 then added to equimolar mixture of acetone and ethanol (2:1 v/v) to give precipitation of gum. Precipitated polymer was kept in an oven at 40˚C for drying, powdered and evaluated for general characteristic properties.

Preparation of cross-linked kondagogu gum[13, 14]

The powdered gum was dispersed in distilled water to get a 1% solution and the resulting dispersion was extruded through 23 Guage hypodermic needle into $CaCl_2$ solution (3, 5 and 7% w/v) kept under stirring at 800 rpm using a magnetic stirrer. The obtained cross-linked gum was then collected by filtration, washed with deionized water, air dried at room temperature for 12 h and dried at 40°C in a hot air oven to constant weight, powdered and passed through sieve #100 for further use.

Preparation of floating tablets[15]

The floating tablets containing metoprolol succinate were prepared by using direct compression technique. Six formulations were prepared by varying the concentration of gums and cross-linking agent as given in Table 1. Accurately weighed quantities of drug, polymer, 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[16]

The maximum absorbance (λ_{max}) of the selected drug, metoprolol succinate 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 222 nm and this wavelength was used for further UV studies.

In vitro buoyancy studies[17]

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 $\pm$ 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[18]

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 ºC. 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;

$$WU\ (\%) = \frac{\text{weight of the swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100 \quad \text{.....(1)}$$

Fourier Transform Infrared Spectroscopy (FTIR)[19]

FTIR spectra of the pure metoprolol succinate 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).

Differential Scanning Calorimetry (DSC)[20]

DSC thermograms were recorded for pure metoprolol succinate drug and the optimized formulation. Accurately weighed samples were placed on aluminum plates, sealed with aluminum lids and heated at a constant rate of 5º/min over a temperature range of 0-400 ºC. All dynamic DSC studies were carried out using DuPont thermal analyzer with 2010 DSC module.

In vitro dissolution studies[21, 22]

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. The samples were withdrawn at regular intervals and diluted to a suitable concentration with 0.1N HCl and the absorbance was measured at 222 nm using Shimadzu UV-Visible spectrophotometer.

Peppas model fitting [23, 24]

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

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

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

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.

Stability studies[25]

Stability studies for the optimized formulation of metoprolol succinate 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.

3. RESULTS AND DISCUSSION

The prepared tablets were evaluated for 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). 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 formulation increased (F1-F3). Formulations F3 showed maximum hardness of about 7.2 Kg/cm^2 among the three polymer ratios selected (40%, 50% and 60% w/w kondagogu gum). It was clear that cross linking of kondagogu gum had a negative impact on hardness of tablet (decreased hardness for formulations F4-F6). From the table, it was noticed that the percent drug content, thickness and friability lies in the range 99.7–102.4 %, 5.21-5.29 mm and 0.33-0.37% 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 buffer) 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 kondagogu 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 increase in amount of cross linking agent used. The floating lag time increased from 38 to 44 seconds indicating that formulation F4 floats faster than F6. It was also noted that, formulations F1-F3 floated more rapidly (38, 37 and 36 seconds) when compared to formulations F4-F6. All the prepared formulations floated for a period of more than 24 hrs. From the table, it is also clear that formulations F1 to F3 showed 303, 314 and 328% 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 cross linking of kondagogu gum in the concentrations of 3, 5 and 7% w/v, which has better water retention capacity than pure kondagogu gum.

The *in vitro drug* release of metoprolol succinate from the prepared hydrophilic floating matrix tablets is shown in Fig. 1. From the figure, it is clear that the concentration of kondagogu gum in the formulation had a remarkable influence on the drug release. Formulations F1 to F3 (40, 50 and 60% w/w kondagogu gum) showed drug release of about 41, 35 and 31% 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 tablet. Formulations F1 – F3 released about 69, 64 and 58% metoprolol 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 61, 47 and 37% 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 32, 26 and 22% at the end of 2 hrs. The decrease in amount of drug release compared to F1 can be attributed to the degree of cross linking of kondagogu gum in the tablet formulation. At the end of *in vitro* dissolution study, F5 and F6 formulations have shown the drug release of 91 and 86% respectively indicating that they are suitable for showing drug release up to 12 hrs.

The data obtained from *in vitro* drug release studies was fit into Peppas model. From the plot of log Mt/ 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 0.9963 is the optimized formulation for 12 hr study period.

The IR spectra taken of metoprolol succinate drug and the optimized formulation (F5) were found to be identical (Figure 2). The characteristic IR absorption peaks of metoprolol Succinate at 3600-2300 (NH_2, OH Aliphatic and aromatic OH), 1580 (Carboxylic acid salt), 1580, 1515 (Aromatic ring), 1250, 1015 (Aromatic Ether), 1180 (Isopropyl Group) and 1100 cm-1 (Aliphatic Ether, Secondary Alcohol) 820 1,4 (disubstituted Benzene) were obtained. The FTIR spectra of the pure drug as well as coated formulation indicated that no chemical interaction occurred between the metoprolol succinate and the polymers used.

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

4. 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. At the end of *in vitro* dissolution study, F5 and F6 formulations have shown the drug release of 91 and 86% respectively indicating that they are suitable for showing drug release up to 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 kondagogu gum, which is natural and biodegradable polymer can be employed for use as carrier in developing floating drug delivery systems. It can also be concluded that $CaCl_2$ as a cross linker is effective in sustaining drug release.

Table 1: Composition of floating metoprolol succinate tablets

Ingredients	Formulation code and weight in mg					
	F1	F2	F3	F4	F5	F6
Metoprolol succinate (mg)	60	60	60	60	60	60
Kondagogu gum (mg)	120	150	180	120	120	120
Sodium bicarbonate (mg)	30	30	30	30	30	30
Calcium chloride (% w/v)	--	--	--	3	5	7
PVP K-30 (mg)	9	9	9	9	9	9
Magnesium Stearate (mg)	6	6	6	6	6	6
Directly compressible lactose (mg)	75	45	15	75	75	75
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	301±3.3	5.29±0.12	6.7±0.57	0.35±0.12	101.2±2.4
F2	302±2.6	5.27±0.15	6.8±0.39	0.38±0.12	100.8±2.6
F3	299±3.2	5.21±0.13	7.2±0.33	0.33±0.12	102.3±3.1
F4	300±2.5	5.24±0.17	6.6±0.65	0.34±0.11	99.7±1.8
F5	302±3.8	5.25±0.14	6.5±0.72	0.36±0.12	101.5±2.2
F6	301±2.1	5.24±0.16	6.2±0.52	0.37±0.11	102.4±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	38±3.4	>24	303±8.4
F2	37±2.7	>24	314±9.2
F3	36±2.4	>24	328±7.7
F4	38±3.1	>24	336±8.6
F5	40±3.3	>24	368±7.3
F6	44±2.5	>24	394±6.5

*Mean ± SD, n = 3

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)	0.9883	0.9861	0.9833	0.9890	0.9963	0.9910

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	101.5±2.2
	3	No change	100.6±2.6
	6	No change	99.8±2.1
	12	No change	99.1±1.5
30 ± 2 ˚C/ 65 ± 5 % RH	0	No change	101.5±2.2
	3	No change	100.7±2.3
	6	No change	99.4±1.2
	12	No change	98.9±2.1
40 ± 2 ˚C/ 75 ± 5 % RH	0	No change	101.5±2.2
	3	No change	99.6±2.7
	6	No change	98.9±1.3

*Mean ± SD, n = 3

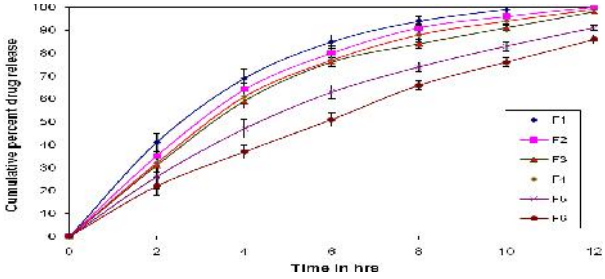

Fig 1: *In vitro* drug release profile for the prepared floating tablets

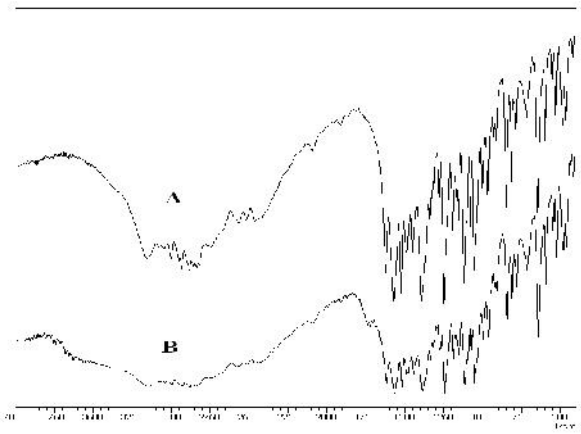

Fig 2: FTIR chromatogram for pure metoprolol (peak A) and formulation F5 (peak B)

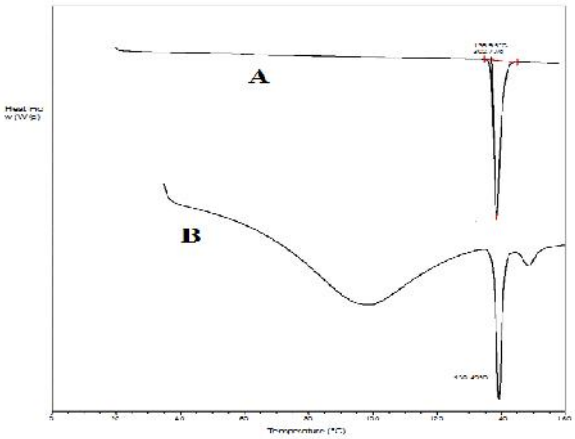

Fig 3: DSC chromatogram for pure metoprolol succinate (peak A) and formulation F5 (peak B)

5. ACKNOWLEDGEMENT

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