

Research Article

Formulation of Sustained-Release Matrix Tablets Using Cross-linked Karaya gum

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Abstract

Purpose: To develop sustained release matrix tablets of diltiazem hydrochloride (DTZ) using modified karaya gum (MK).

Methods: MK was prepared by cross-linking karaya gum with tri-sodium tri-metaphosphate (STMP) which was used as a cross-linker. Matrix tablets of DTZ were prepared using varying ratios of unmodified karaya gum (K) and MK by direct compression. The matrix tablets were evaluated for pharmacotechnical properties and in vitro release, including release kinetics. The optimized formulation was compared with Dilzem SR which served as reference. MK and the formulations were also characterized by scanning electron microscopy (SEM), Fourier transform infra-red spectroscopy (FTIR) and differential scanning calorimetry (DSC).

Results: Tablets with MK showed higher mean dissolution time (MDT) and lower dissolution efficiency than those prepared with karaya gum. Drug release was by water uptake, diffusion and erosion mechanisms. Drug release from tablets formulated with unmodified K at the end of 10 h was 99.9 %, and while for MK tablets, it was 68.2 % at the end of 12h. MK sufficiently controlled drug release unlike K which exhibited poor sustained drug release. Formulation F6 compared well with the reference, Dilzem SR ($p < 0.05$), in terms of release characteristics. Cumulative drug release at the end of 12 h for both test and reference formulations was approx. 85 %. SEM images of the tablets before and after dissolution showed some morphological differences on their tablet surfaces while FTIR and DSC thermogram studies confirmed that there was no chemical interaction between the drug and the polymers in MK formulation.

Conclusion: The results of the study demonstrate that modified karaya gum has good potentials for formulating suitable sustained-release matrix tablets of diltiazem.

Keywords: Karaya gum, Diltiazem hydrochloride, Tri-Sodium Tri-metaphosphate, Crosslinking, Matrix tablets, Sustained release.

Received: 16 February 2011

Revised accepted: 3 December 2011

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INTRODUCTION

Of the approaches used for controlling drug release from solid dosage forms, the compressed matrices continue to attract considerable attention, as such devices low-cost and high levels of drug can be incorporated in them. Hydrophilic polymers are widely used in the formulation of modified release dosage forms because they are low-cost, and usually show reduced risk of systemic toxicity and minimal incidence of dose dumping. Matrix systems can be used to control the release of both water soluble and water insoluble drugs. Although, their drug release behavior appears simple, but in reality, the release pattern is a complex phenomenon. At the molecular level, it involves water penetration, polymer swelling, as well as drug dissolution, diffusion and swelling, and polymer erosion process [1,2].”

In recent years, researchers have become increasingly interested in the utilization of natural biopolymers due to their wide ranging advantages over synthetic polymers. Polysaccharide gums are the materials of choice because they are naturally abundant, biocompatible, biodegradable, and non-immunogenic [3, 4].

Gum karaya, sometimes called as sterculia gum is a complex water-soluble polysaccharide. It is a hydrophilic colloid prepared from the exudates of *Sterculia urens* tree. It is a partially acetylated complex polysaccharide composed of galacturonic acid, beta-D-galactose, glucuronic acid, L-rhamnose, and other residues obtained as the calcium and magnesium salt [5]. As a bulk laxative, gum karaya is second only to psyllium seeds in importance [6]. When used in bulk laxatives, the gum is usually processed to a particle size of 500 μ aperture sieve. These coarse gum particles absorb water and swell 60 to 100 times their original volume, forming a discontinuous type of mucilage. This type of mucilage is very effective as a laxative. The gum has been evaluated as a controlled release-matrix and

has also shown superior mucoadhesion to guar gum [7]. Modification of karaya gum to develop matrix tablets has been reported on extensively in the literature; except for a few works using them as retarding polymers, not much has been done [8].

Tri-sodium tri-metaphosphate(STMP) is a non-toxic cyclic triphosphate, already reported as an effective cross-linker of starches [9], guar gum [10] and hyaluronic acid [11] in order to synthesize gels for pharmaceutical purposes.

Diltiazem hydrochloride (DTZ) is a calcium channel blocker that is widely prescribed for the treatment of hypertension and angina. It is highly water soluble and almost completely absorbed. However, its bioavailability is only 30 to 40 % owing to first pass metabolism, and has an elimination half-life of 3.5 h. Therefore, DTZ requires multiple daily dosing to maintain adequate plasma concentrations. The drug is thus a suitable model candidate for sustained drug delivery [12].

The objective of the present study was to modify karaya gum using STMP as cross linking agent and also to evaluate the modified karaya gum as a suitable, release retardant polymer for the formulation of sustained release tablets of DTZ.

EXPERIMENTAL

Materials

Diltiazem hydrochloride (DTZ) and microcrystalline cellulose (MCC) were obtained free of charge from Micro Lab Ltd, Bangalore, India. Karaya gum (K) and tri-sodium tri-metaphosphate (STMP) were purchased from Sigma Aldrich, Steinheim, Germany, while magnesium stearate, hydrochloric acid, sodium hydroxide, and potassium dihydrogen phosphate were all obtained from Merck, Mumbai, India. All chemicals and reagents used were either of pharmaceutical or analytical grades. The reference diltiazem hydrochloride tablet

formulation used for the study was Dilzem SR (Torrent Pharma Ltd, India).

Synthesis of modified karaya gum(MK)

Karaya gum was cross-linked with tri-sodium tri-metaphosphate (STMP) as follows: STMP (1 g) was dissolved in 50 ml of water and added to 5 ml of 0.1N NaOH in a 200 ml beaker with 1 g of karaya gum in 50 ml of water then added slowly with stirring. The reaction mixture (100 ml) was stirred for 2 h, poured into each of 5 Petri dish (20 ml each) and dried at 60 °C for 24 h. The dried complex (modified gum) was powdered, passed through a 200 μ aperture sieve and used for the formulation of tablets.

Preparation of matrix tablets

Matrix tablets of 90 mg diltiazem hydrochloride were prepared (based on the composition in Table 1) by direct compression method. The excipients (except magnesium stearate) and drug were first passed through a 200 μ aperture sieve and then mixed in geometrical fashion for 10 min. Finally, the magnesium stearate was added and mixed for additional 2 min. The batch size of each formulation was 50 tablets. The tablets were compressed in a tablet machine (Rimek Mini Press I, Mumbai, India) using 12 mm flat-faced punches [13].

Physicochemical characterization of tablets

The mean hardness of 10 tablets determined using a digital hardness tester (Erweka, Mumbai, India) while friability was determined for 20 tablets with a Roche friabilator. Weight variation and uniformity of drug content were assessed for 20 tablets according to Indian Pharmacopoeia (IP) procedures [14]. Twenty tablets were weighed individually and the mean weight determined. The tablets were then powdered in a mortar and a triturate equivalent to 100 mg of the drug was taken in a 100 ml volumetric flask and made up to mark with simulated gastric fluid (SGF, pH

1.2). Ten millimeters of this solution was transferred to another 100 ml volumetric flask and diluted to mark with SGF, 3 ml of which was further diluted to 25 ml, filtered through a 0.45 μm pore membrane filter. The absorbance of the solution was measured spectrophotometrically (model UVPC 1601, Shimadzu, Kyoto, Japan) at 237 nm.

Scanning electron microscopy (SEM)

The surface morphology of the matrix tablets was analyzed with a scanning electron microscope (model JSM-840A, Jeol, Japan) before and after hydration 6 h.

Water uptake and erosion studies

Water uptake and mass loss were computed gravimetrically according to Eqs 1 and 2. Three tablets were used per time point. At predetermined times, the tablets were lightly patted with tissue paper to remove excess surface water. The swollen weight of tablets was determined (T_s) and then the same tablets were dried in a vacuum oven at 40 °C for 48 h, and the dry weight (T_f) measured. The study was carried out in triplicate. Water uptake (%) and erosion (%) were calculated using Eqs 1 and 2, respectively [15].

$$\text{Water uptake (\%)} = (T_s - T) / T \times 100 \dots\dots (1)$$

where T_s is the weight of the swollen tablet and T is the initial of the tablet, i.e., prior to the test.

$$\text{Erosion (\%)} = (T - T_f) / T_f \times 100 \dots\dots\dots (2)$$

where T is the initial weight of the tablet and T_f is the weight of the tablet after the erosion test.

FT-IR spectroscopy

FT-IR studies were carried out using Shimadzu FTIR 8400S. The pellets were prepared with KBr using pure drug, polymers and crushed tablet formulations, and the

spectra recorded in the range of 400 - 4000 cm^{-1} .

Thermal analysis

Thermal analysis of samples were carried out with a Perkin-Elmer, Pyris-1 DSC. The test was performed on 2 - 4 mg samples of drug, polymer and mixture of drug and polymer in the temperature range of 0 – 400 °C. The samples were sealed in a perforated aluminium pan, under nitrogen atmosphere and at a heating rate of 10 °C/min.

In vitro release studies

Dissolution test was carried out using a USP type I apparatus (model TDT-08I, Electrolab, Mumbai, India) at 100 rpm and 37 °C for the first 2 h in 900 mL of simulated gastric fluid (0.1M HCl) and then continued in 900 mL of phosphate buffer (pH 7.4). Five ml of the dissolution fluid was withdrawn at regular time intervals during the studies and replaced with an equal volume of drug-free dissolution fluid to maintain sink conditions. The samples were suitably diluted with fresh dissolution fluid and analyzed for drug release spectrophotometrically at 237 nm.

Kinetic analysis of dissolution data

To study the mechanism of drug release from the matrix tablets, the release data were fitted to zero-order, first-order, and Higuchi models. The data were also subjected to the Korsmeyer-Peppas exponential equation (Eq 3) which is often used to describe drug release behavior from polymeric systems.

$$\text{Log}(M_t/M_f) = \text{Log}k + n\text{Log}t \dots\dots (3)$$

where M_t/M_f is fractional release of drug, k is a constant, n is the diffusional exponent and t = time.

The diffusional exponent “n”, which is indicative of the mechanism of drug release, was obtained by plotting the log value of percent drug released against log time for each batch (Eq 3). A value of n = 0.45 indicates Fickian (case I) release; > 0.45 but < 0.89 is non-Fickian (anomalous) release;

and > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain while anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release. Dissolution efficiency (DE), defined as the area under the dissolution curve up to a certain time t, and expressed as a percentage of the area of the rectangle described by 100 % dissolution in the same time, and mean dissolution time (MDT), were used to translate the profile differences into a single value as shown in Eqs 4 and 5 [16,17].

$$DE_{12\%} = \frac{\int_0^t y dt}{y \times 100} \times 100 \dots\dots\dots (4)$$

MDT is a measure of the dissolution rate: the higher the MDT, the slower the release rate.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M} \dots\dots\dots (5)$$

where i is the dissolution sample number, n is the number of dissolution sample time, t_{mid} is the time at the midpoint between i and i-1, and ΔM is the amount of drug dissolved between i and i-1. The similarities between two dissolution profiles were assessed by a pair-wise model-independent procedure, similarity factor (f_2).

$$f_2 = 50 \text{Log} \left\{ \left[1 + \frac{1}{n \sum_{i=1}^{n=i} (R_i - T_i)^2} \right]^{-0.5} \times 100 \right\} \dots (6)$$

where n is the number of pull points, R_t is the reference profile at time point t, and T_t is the test profile at the same time point; the value of f_2 should be between 50 and 100. An f_2 value of 100 suggests that the test and reference profiles are identical and, as the value becomes smaller, the dissimilarity between release profiles increases [18].

Statistical analysis

Comparison among the developed formulation and the reference formulation (Dilzem-SR) was carried out by Student t-test at 95 % level of confidence using GraphPad.Prism.Ver.5.0.4.

RESULTS

Characterization of tablets

The drug content of the formulations was uniform, being more than 97 % and with less than 1.0 % relative standard deviation. Hardness ranged from 4 - 6 kg/cm² while friability was < 1 %. Thus, all the tablet formulations showed acceptable physical characteristics.

In vitro drug release and kinetics

The *in-vitro* release results are shown in Figure 1. Drug release of diltiazem hydrochloride from all the formulations in the first hour ranged from 16.8 to 86.6 % while after 12 h, it was between 68.2 and 100.0 %. Increase in the content of polymer decreased drug release at the 12th hour.. Burst effect was observed at the 1st hour only in formulations containing low polymer concentration. Formulations containing unmodified karaya gum showed complete drug release in < 12 h whereas those formulated with modified karaya gum exhibited extended drug release over the 12 h period. The formulation containing modified karaya gum was compared with the reference standard, i.e., Dilzem SR, in terms of drug release.

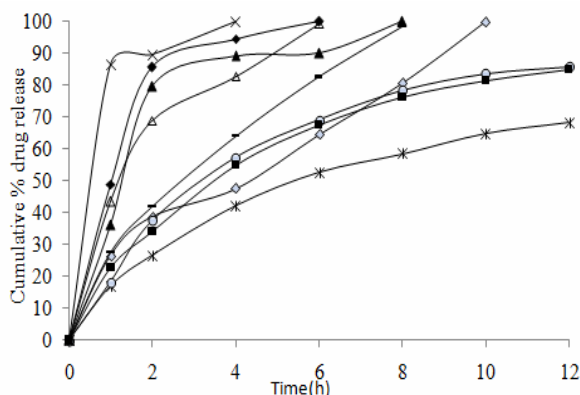


Figure 1: Dissolution profiles of formulations
Key: ◇ = F1; ▒ = F2; △ = F3; × = F4; * = F5; ○ = F6; ▲ = F7; ◆ = F8; ■ = reference standard)

The dissolution kinetic data, mean dissolution time (MDT) and dissolution efficiency (DE₁₂) of the formulation are shown in Table 1. MDT ranged from 0.55 – 3.36 h while DE₁₂ (at the end of 12 h) was 46.0 – 86.5 %. The drug release data of the tableted formulations did not fit satisfactorily to zero-order, first-order but showed good fit into the Korsmeyer equation ($r^2 = 0.8346$ to 0.9924) and Higuchi equation ($r^2 = 0.860$ to 0.9916), respectively. The value of the release exponent, “n”, for the various matrices ranged from 0.0258 to 0.4935. F6 had MDT and dissolution efficiency (DE₁₂ %) similar to those of the standard product, Dilzem SR. The similarity factor (f_2) was 68.75, suggesting that their dissolution profiles were very similar. Of all the formulations, only F6 did not significantly differ in terms of drug release ($p < 0.05$) from the commercial DTZ product used as standard.

Scanning electron microscopy (SEM)

Figure 2 displays the scanning electron micrographs (SEM) of the surface of tablet formulation F6. The micrographs indicate that the surface of the matrix tablet became highly porous after dissolution.

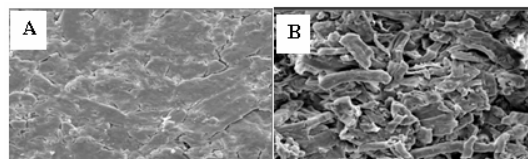


Figure 2: Scanning electron micrographs of tablet formulation F6 (A) before and (B) 6 h after dissolution

Water uptake and erosion

Figure 3 shows the water uptake and erosion profiles for the optimized formulation F6 contained modified karaya gum and the reference (standard) tablets. At the end of 12 h water uptake for the test formulation and reference standard was 165.5 and 250 %, respectively, while erosion was 36.75 and 33.4 %, respectively.

Table 1: Composition of DTZ (90 mg) matrix tablets and kinetic parameters of dissolution data

Formulation code	K	MK	MCC	n	Peppas	Higuchi	MDT(h) ± SD	DE ₁₂ % ± SD
F1	100	-	5	0.4429	0.9924	0.9880	3.3±0.2	60.9±2.3
F2	75	-	30	0.4935	0.9896	0.9916	3.4±0.1	70.5±4.3
F3	50	-	55	0.4859	0.9539	0.9846	1.9±0.2	73.3±5.8
F4	25	-	80	0.0258	0.9442	0.8601	0.6±0.3	86.5±8.9
F5	-	100	5	0.4884	0.9866	0.9855	3.2±0.2	46.1±6.3
F6	-	75	30	0.3956	0.9709	0.9481	2.5±0.1	64.0±4.3
F7	-	50	55	0.4357	0.8974	0.9507	2.0±0.3	80.7±2.6
F8	-	25	80	0.3307	0.8346	0.9168	1.0±0.2	81.3±7.2
Standard	DilzemSR			0.5531	0.9918	0.9862	3.5±0.1	59.8±3.1

Note: Talc and Mg stearate (5 mg/tablet) in the ratio of 2:1 was added as glidant-lubricant to all the tablet formulations

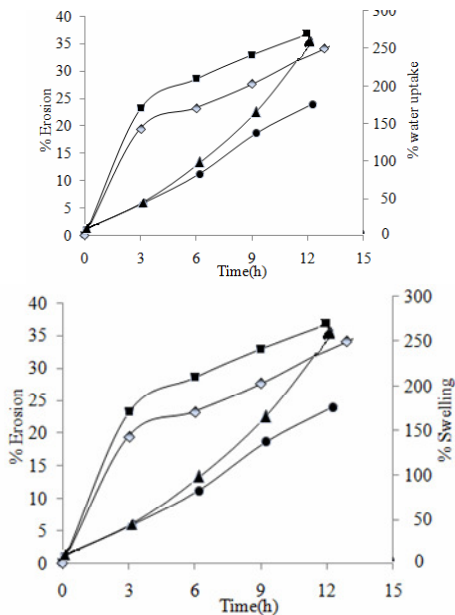


Figure 3: Water uptake and eroding behaviour of test formulation F6 (●, ■) and standard (reference) formulation (▲, ◇)

FT-IR spectroscopy

In Figure 4, pure karaya gum peaks can be associated with OH groups, two of which are indicative of acetyl groups and the other two are due to COO- groups of uronic acid residues. In modified karaya gum, the stunted broadened peak which appeared at 3428 cm⁻¹ is attributed to the overlap of N-H stretching

band of amide group and O-H stretching band. Disappearance of acetyl groups in modified gum was also observed. The appearance of new peaks which were absent in karaya gum are attributed to phosphate-I (-C=O stretching) and phosphate-II (-C-O bending) of the phosphate group of STMP thus confirming the occurrence of cross-linking reaction. The FTIR spectra of the pure drug and formulation F6 showed characteristic peaks for both pure DTZ and DTZ in the test matrix formulation without any significant shift in their positions.

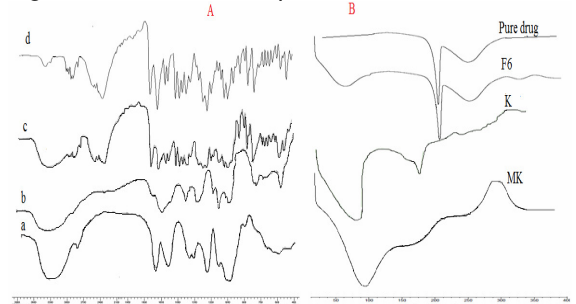


Figure 4: A = FT-IR spectra of a) unmodified karaya gum, b) modified karaya gum, c) F6 and d) pure drug; B = DSC thermograms of unmodified karaya gum, modified karaya gum, F6 and pure drug

Thermal analysis

As Fig 4B indicates, the DSC thermograms of unmodified karaya gum (K) showed endothermic peaks at 85.3 and 186.7 °C,

while modified karaya gum (MK) showed an endothermic peak at 85.3 °C and a new exothermic peak at 259.4 °C. The DSC thermograms of formulation F6 and pure DTZ showed endothermic peaks for the pure drug and the formulation drug at 216.4 and 218.6 °C, respectively.

DISCUSSION

Drug release

The rate of drug release tended to decrease with increase in the amount of polymer. This is in agreement with previous works which suggested that the viscosity of the gel layer around the drug particles in the tablet increases with increase in hydrogel concentration thus limiting the release of the drug [19]. The gel formed during the penetration of dissolution media into the matrix structure, consists of closely packed swollen particles. With further increase in polymer content, thicker gel forms, inhibiting the dissolution fluid penetration and resulting in significant reduction in drug release (compare F5 and F6 with other test formulations). Formulations with low polymer concentrations as well as unmodified karaya gum rapidly hydrated and formed weak matrix systems which accounted for the 'burst' release as well as rapid release.

Furthermore, crosslinking in the modified karaya gum resulted in matrix rigidity, thereby slowing the hydration rate of the gum; this, in conjunction with erosion, resulted in controlled release of drug which was incomplete at the of 12 h. Among the test formulations, F6 was most similar to the standard product, Dilzem SR, with a similarity factor of 68.75. The release data showed close affinity to the Korsmeyer-Peppas model. The release exponent "n" value was characteristic of Fickian diffusion and indicated a combined effect of diffusion and erosion mechanisms for controlled drug release.

The SEM photomicrograph of the tablets after 6 h after hydration commenced showed a highly porous tablet surface which suggest a

porous tablet matrix structure. This confirms that drug release was by diffusion from the tablet core to the surface. Since the gel layer undergoes surface erosion, it is possible that the inner porous network is exposed after the erosion-dissolution of the outer layer of the matrix. The presence of both pores and gel structure on the tablet surface indicates involvement of both erosion and diffusion mechanisms for sustained drug release.

Thus, the matrices underwent both water uptake and erosion simultaneously immediately after placement in the dissolution medium and this continued over the 12 h period of the study. Formulation F6 and the standard DTZ product had overlapping erosion profile but their water uptake behaviour was similar only up to the 6th hour. The plots were almost linear, indicating a balance between water uptake and erosion, and resulting in sustained drug release [20]. FTIR spectra indicate that similar characteristic peaks appeared with minor differences for the drug and the formulations. Hence, it seems that no chemical interaction occurred between the drug and the tablet excipients (including the polymer) used. The DSC thermograms of MK when compared to pure karaya showed a broad endothermic peak. However, the other peak which appeared at 186.7°C disappeared while a new exothermic peak appeared. This suggests that a change in the structure of karaya gum occurred as a result of crosslinking. The DSC endothermic peaks for the pure drug and the drug in formulation F6 showed only a negligible shift in their positions with some peak broadening in the latter. Thus, both FT-IR and DSC indicate that karaya gum structure was modified by crosslinking, and that there was no likelihood of any chemical interaction between the drug and the polymers.

CONCLUSION

This study demonstrates that the crosslinking of karaya gum enhances matrix rigidity, thereby sustaining drug release rate when

compared to the natural (unmodified) gum. Although karaya gum structure was modified by crosslinking, there was no chemical interaction between the drug and the polymer. Overall, the results of the study indicate that modified karaya gum should be suitable for formulating sustained-release matrix tablets of diltiazem.

ACKNOWLEDGEMENT

The authors acknowledge J.S.S. Mahavi-dyapeetha, Mysore and JSS University, Mysore, India, for their invaluable support during this work. The authors also wish to thank IISC, Bangalore, India for providing facilities for SEM and DSC studies.

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