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Research Article

Formulation of Sustained-Release Diltiazem Matrix Tablets Using Hydrophilic Gum Blends

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Abstract

Purpose: To develop sustained release matrix tablets of diltiazem hydrochloride (DTZ) using karaya gum (K) alone or in combination with locust bean gum (LB) and hydroxypropyl methylcellulose (H).

Methods: Matrix tablets of DTZ were prepared at different ratios of drug:gum (1:1, 1:2, and 1:4) and of the gum blends (K, K/LB, K/H and K/LB/H) by direct compression. The matrix tablets were evaluated for hardness, friability, in vitro release and drug content. The formulations were also characterised by scanning electron microscopy (SEM), Fourier transform infra-red spectroscopy (FTIR) and differential scanning calorimetry (DSC). A commercial diltiazem hydrochloride product Dilzem SR, was used as a reference for comparison

Results: Tablets with only K or K/H had the highest mean dissolution time (MDT), the least dissolution efficiency (DE, 12 %), and released drug by swelling, diffusion and erosion mechanisms. Karaya gum or combinations with locust bean gum sufficiently controlled drug release, while combinations of KH and KLBH exhibited high and low drug release efficiency, respectively. SEM images of the tablets before and after dissolution showed morphological changes on the tablet surface while FTIR and DSC studies indicate that there was no chemical interaction between the drug and the polymers. Three of the formulations compared well with the reference ($p < 0.05$) in terms of release characteristics.

Conclusion: The results of the study demonstrate that karaya gum alone or in suitable combination with locust bean gum and hydroxypropyl methylcellulose is suitable for formulating sustained-release matrix tablets of diltiazem.

Key words: Karaya gum, Locust bean gum, Diltiazem hydrochloride, Sustained release, Hydroxypropyl methylcellulose

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INTRODUCTION

Hydrophilic matrix tablets have long been used as a drug delivery system. This is due to their simplicity, cost-effectiveness, reduced risk of systemic toxicity, and minimal chance of dose dumping. Matrix systems can be used to control the release of both water soluble and water insoluble drugs. On the surface, their drug release behavior appears simple, but the drug release pattern is a complex phenomenon. At the molecular level, it involves water penetration, polymer swelling, as well as drug dissolution, diffusion, swelling, and polymer erosion process [1-3].

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 [4,5]. Gum karaya, sometimes known as *Sterculia* gum, is the dried exudate of the *Sterculia urens* tree and other species of *Sterculia*. It is a complex polysaccharide of high molecular weight which, on hydrolysis, yields galactose, rhamnose and galacturonic acid. It occurs as a partially acetylated derivative and is compatible with other plant hydrocolloids as well as proteins and carbohydrates. Few works on karaya gum have been reported [6-8].

Locust bean gum (LB), also known as galactomannan, is obtained from the seed of the Locust bean plant, and composed of a 1, 4-linked β -D-mannan backbone with 1, 6-linked α -D-galactose side groups. It is a non-ionic molecule consisting of 2,000 residues; the ratio of mannose to galactose in the molecule is 4:1. The physicochemical properties of galactomannan are strongly influenced by the galactose content and the distribution of the galactose units along the main chain. The structure contains long stretches of bare mannose backbone (up to 80 D-mannose units long) which is

responsible for synergistic interaction with other polymers and its great functionality [9-11].

HPMC (H) is a widely used semi-synthetic hydrophilic matrix polymer that has been employed in the design of sustained release formulations due to its rapid hydration, good compression and gelling characteristics as well as its ease of use, availability and very low toxicity [12].

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 30 to 40 % owing to first pass metabolism, and it has an elimination half-life of 3.5 h. Therefore, DTZ requires multiple daily drug dosage in order to maintain adequate plasma concentrations, and is thus a suitable model candidate for sustained drug delivery [13].

The present study investigates karaya gum as a suitable, natural, low-cost hydrophilic matrix material for the formulation of sustained release tablets. Modulation of DTZ release from its matrix tablet using LB and H as well as release mechanism were also assessed.

EXPERIMENTAL

Materials

Diltiazem hydrochloride (DTZ), micro-crystalline cellulose (MCC), and hydroxyl-propyl methylcellulose (HPMC K4M) were obtained free of charge from Micro Lab Ltd, Bangalore, India. Locust bean gum (LB) and karaya gum (K) were purchased from Sigma Aldrich, Steinheim, Germany while magnesium stearate, hydrochloric acid, sodium hydroxide, and potassium phosphate monobasic were all obtained from Merck, Mumbai, India. All chemicals were either of pharmaceutical or analytical grade. The reference diltiazem hydrochloride tablet used

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

Preparation of matrix tablets

Matrix tablets of 100 mg diltiazem hydrochloride were prepared by direct compression method based on the composition shown in Table 1. The excipients (except magnesium stearate) and drug were first passed through 200 μ aperture sieve and then mixed in geometrical dilution 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) using 12 mm flat-faced punches.

Characterization of tablets

The hardness, friability, weight variation, and content uniformity of the compressed matrix tablets were determined. Briefly, hardness was determined using a digital hardness tester (Inwika, Ahmedabad, India) while friability was assessed with a Roche friability testing apparatus. Weight variation and uniformity of drug content were assessed according to Indian Pharmacopoeia (IP) procedures [14]. Twenty tablets were weighed individually and average weight was determined. Not more than two tablets should show a deviation \pm 5% of the mean weight. For content uniformity, 10 tablets were selected at random and the mean weight was calculated. The tablets were then powdered and a sample containing 100 mg of the drug was taken in a 100 ml volumetric flask. The volume was made up to mark with simulated gastric fluid (SGF, 0.1M HCl, pH 1.2). A portion of this solution (7.5ml) was transferred to 100 ml volumetric flask and diluted up to the mark with SGF; 3ml of this mixture was diluted to 25 ml with SGF, filtered through 0.45 μ m pore membrane and the absorbance measured spectrophotometrically (model UVPC 1601, Shimadzu, Kyoto, Japan) at 237 nm.

In vitro drug release studies

Drug release studies were performed 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 SGF and then at pH 7.4 in 900 mL of phosphate buffer for another 10 h. Two millilitres of the dissolution samples were taken at different time intervals and replaced with an equal volume of drug-free dissolution fluid to maintain sink conditions. The samples were suitably diluted with blank dissolution fluid and analyzed for DTZ spectrophotometrically at 237 nm [15].

Scanning electron microscopy (SEM)

The surface morphology of the matrix tablets was analyzed with a scanning electron microscope (JEOL-JSM-840A, Japan).

Water uptake and erosion studies

Erosion and water uptake of the tableted formulations were determined under conditions identical to those described for dissolution testing using SGF as the medium. Three tablets were used at each time interval. At the predetermined times, the tablets were lightly patted with tissue paper to remove excess surface water. The swollen weight of the tablets was determined (T_s), The tablets were then dried in a vacuum oven at 40 °C for 48 h and their dry weight (T_f) was determined. The study was carried out in triplicate. Swelling (%) and erosion (%) was calculated using Eqs 1 and 2, respectively [19].

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

where T_s is the weight of the swollen tablet and T is the initial weight 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 Tf is the weight of the tablet after the erosion test.

FT-IR spectroscopy

In order to evaluate the compatibility of the drug and the polymers used, FT-IR studies were carried out with a Shimadzu FTIR 8400S facility using KBr pellet to hold the sample.

Thermal analysis

Thermal analysis was carried out with a differential scanning calorimeter (DSC, Perkin-Elmer, Pyris-1). Scanning was performed at a temperature ranging from 40 to 280 °C at a heating rate of 10 °C/min under an atmosphere of nitrogen. The sample weight was 2 - 4 mg and it was sealed in a perforated aluminium pan.

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 equations. The dissolution data were also fitted to the well-known Korsmeyer exponential equation, which is often used to describe drug release behavior from polymeric systems.

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

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 according to 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, and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release. Model-independent

approaches, i.e., dissolution efficiency (DE) which is defined as the area under the dissolution curve up to a certain time t, expressed as a percentage of the area of the rectangle described by 100 % dissolution in the same time range, and mean dissolution time (MDT), were used to translate the profile differences into a single value as shown in Eqs 3 and 4 [16, 17].

$$DE_{12\%} = \frac{\int_0^t y dt}{y100} t \times 100 \dots\dots\dots (4)$$

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 (f₂).

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

where n is the number of pull points, R_i is the reference profile at time point t, and T_i is the test profile at the same time point; the value of f₂ should be between 50 and 100. An f₂ 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 formulations and the reference formulation (Dilzem SR) were made by Student t-test at

95 % level of confidence using Microsoft Office Excel 2007.

RESULTS

Characterization of tablets

The compositions of the matrix tablets and the results of the physical characterization of tablets are summarized in Table 1. Tablet

friability was less than 1 % while hardness ranged from 4 - 6 kg/cm². Good uniformity in drug content was found among the various formulation batches as drug content was more than 96 % in all cases with less than 1 % standard deviation. Thus, all the tablet formulations showed acceptable physical characteristics.

Table 1: Composition and physical characteristics of diltiazem hydrochloride (100 mg) matrix tablets

Formulation & code (drug:polymer)	K	LB	H	MCC	Hardness (kg/cm ²) ±SD	Friability (%)	Assay (%) ±SD
K(1:1) F1	100	-	-	390	5.7±0.6	0.35	97.0±0.7
K(1:2) F2	200	-	-	290	5.6±0.5	0.31	98.0±0.6
K(1:4) F3	400	-	-	90	5.3±0.6	0.46	99.0±0.7
KLB(1:1) F4	50	50	-	390	5.3±0.4	0.49	99.0±0.6
KLB(1:2) F5	100	100	-	290	5.1±0.6	0.59	101.0±0.8
KLB(1:4) F6	200	200	-	90	4.8±0.7	0.65	97.0±0.5
KH(1:1) F7	50	-	50	390	5.7±0.4	0.30	98.0±0.6
KH(1:2) F8	100	-	100	290	5.7±0.4	0.36	98.0±0.5
KH(1:4) F9	200	-	200	90	5.8±0.3	0.42	98.0±0.6
KLBH(1:1) F10	50	25	25	390	5.5±0.4	0.45	98.0±0.7
KLBH(1:2) F11	100	50	50	290	5.7±0.5	0.5	99.0±0.4
KLBH(1:4) F12	200	100	100	90	5.6±0.4	0.58	97.0±0.5
Reference	Dilzem- SR				5.8±0.1	0.28	98.0±0.1

Note: Magnesium.stearate (10 mg/tablet) was added as glidant-lubricant to all the tablet formulations

Table 2: Kinetic parameters of the dissolution data

Formulation	n	Peppas	Higuchi	MDT(h) ± SD	DE ₁₂ % ± SD
F1	0.4784	0.998	0.9652	3.56±0.20	55.69±3.02
F	0.4967	0.9929	0.9891	3.69±0.10	45.17±1.47
F3	0.6214	0.9916	0.9898	4.03±0.20	37.67±5.10
F4	0.0679	--	---	0.87±0.30	90.98±6.12
F5	0.5248	0.9808	0.9768	3.52±0.10	58.02±4.15
F6	0.5861	0.981	0.9743	3.82±0.20	49.22±3.17
F7	0.4956	0.9932	0.879	3.07±0.30	52.63±6.14
F8	0.5896	0.9808	0.9856	3.89±0.20	44.03±1.29
F9	0.6321	0.988	0.9874	4.54±0.20	34.37±2.61
F10	0.5335	0.9962	0.9281	3.38±0.20	64.5±9.15
F11	0.5830	0.997	0.9361	3.42±0.20	48.79±2.88
F12	0.6889	0.7755	0.9844	3.80±0.20	39.46±4.51
Reference	0.5531	0.99i9	0.9862	3.54±0.10	59.82±3.12

In vitro drug release and kinetic analysis

The release profiles of the tablets made with K and KLB blend are presented in Figure 1A. The initial drug released in the 1st hour ranged from 13 – 26 % for K formulations but at the end of 12 h, the value rose to between 50 and 81 %, indicating that the tablets extended release for more than 12 h. For matrix tablets formulated with KLB polymer blend in 1:1 (drug: polymer) ratio, the initial release in the 1st hour ranged from 18 – 83 %. At the end of 12 h, the figure was between 75 and 98 %. The release profiles of the tablets made with polymer blends KH and KLBH are presented in Figure 1B. The tablets containing KH blend in 1:1 ratio as the matrix (i.e., formulations F7, F8 and F9) showed 15 – 24 % release in the first hour and a cumulative release of 48 – 71 % at the end of 12 h. On the other hand, the tablets containing the polymer blend K:LB:H (1.0:0.5:0.5) as the matrix showed a cumulative release of 53 – 92 % at the end of 12 h.

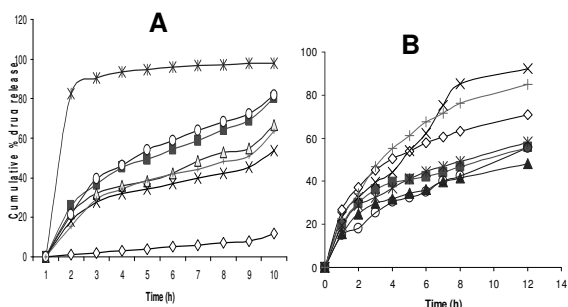


Figure 1: Dissolution profile of formulations. (Note: For A, \diamond = F1; \blacksquare = F2; \triangle = F3; \times = F4; $*$ = F5; \circ = F6, while for B, \diamond = F7; \blacksquare = F8; \blacktriangle = F9; \times = F10; $*$ = F11; \circ = F12; + = DIL)

The results of kinetic analysis of the dissolution data, mean dissolution time (MDT) and DE_{12} of all the formulations are shown in Table 2. MDT values ranged from 0.87 - 4.54 h while dissolution efficiency (DE_{12}) at the end of 12 h was 34 – 91 %. The drug release data of the tablet formulations did not fit satisfactorily to zero-order, first-order, and Higuchi models but showed good

fit to the Korsmeyer model ($r^2 = 0.9652$ to 0.9976) and to some degree the Higuchi model ($r^2 = 0.879$ to 0.9898). The value of the release exponent, “n”, for the various matrices ranged from 0.4700 to 0.6889. F5 had MDT and dissolution efficiency (DE_{12} %) similar to those of the standard product, Dilzem SR. The similarity factor (f_2) was 77.86, suggesting that their dissolution profiles were very similar.

Scanning electron microscopy (SEM)

Figure 2 displays the scanning electron micrographs showing the surface morphology of formulation F5. The SEM photos show that the surface of the matrix tablet was highly porous.

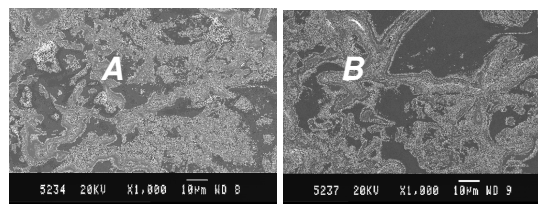


Figure 2: SEM photographs of formulation F5 before (A) and after dissolution (B)

Water uptake and erosion

Figure 3 shows the water uptake and erosion profiles of optimized formulation F5 and reference. Tablet swelling and erosion at the end of 12 h was 172, and 250 %. 33.4 and 33 %, respectively.

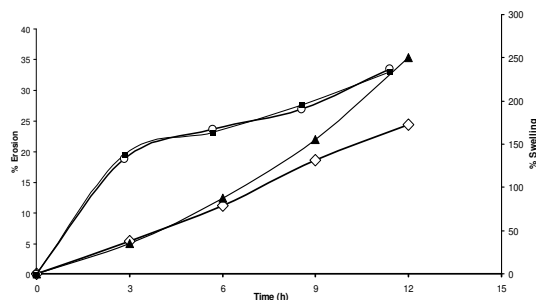


Figure 3: Swelling and eroding behaviour of formulation F5 (\diamond, \circ) and reference formulations (\triangle, \blacksquare)

FT-IR spectroscopy

The FTIR spectra of both the pure drug and one of the matrix formulations (not presented here) showed characteristic peaks at 3433.13 cm^{-1} (aliphatic C-H stretching), 2931.90 cm^{-1} (O-CH₃, C-H stretching), 2387.93 cm^{-1} (amine HCl, N-H stretching), 1741.78 cm^{-1} (acetate C=O stretch), 1678.13 cm^{-1} (lactam C=O stretch), 831.33 cm^{-1} (O-substituted aromatic C-H out of plane-deformation), 773.48 cm^{-1} (p-substituted aromatic C-H out of plane-deformation) thus indicating that there was no drug-polymer interaction in the formulation.

Thermal analysis

The DSC thermograms of one of the formulations and pure DTZ showed endothermic peaks for the pure DTZ and the DTZ in the formulation at 217.4 and 218.9 °C, respectively.

Release analysis

Of all the formulations, only F1, F5, and F10 did not significantly differ in terms of drug release ($p < 0.05$) from the commercial DTZ product used as standard.

DISCUSSION

The matrix tablets exhibited satisfactory mechanical characteristics based on the friability and hardness data presented. Content uniformity was also good. The slower and more sustained drug release from khaya (K) formulation (F3), compared to the control, can be attributed to high gum hydration with concurrent swelling, followed by gradual erosion. This appears to be confirmed by higher MDT and lower dissolution efficiency. In matrix tablets containing a mixture of polymers K and LB in a ratio of 1:1, drug release increased as the amount of polymer blend decreased. Formulations F5 and F6 showed extended drug release over a period that exceeded 12 h. Formulation F4 (K:LB in 1:1 ratio) showed the most rapid release (83

% in 1 h), the least MDT (0.8 h) and highest dissolution efficiency (99 % after 12 h) thus indicating that this polymer mixture was unable to sustain drug release. This may be explained as follows. Studies have shown that LB gum is less soluble and viscous than khaya gum as it has fewer galactose branch points. Thus, the hydrated matrix lacked gel integrity, resulting in higher erosion. An earlier study indicates that LB displayed a high erosion rate and low swelling than K [20]. The matrices containing a mixture of K and H in 1:1 ratio (F7, F8 and F9) showed more pronounced sustained release than those containing K alone and K/LB blend when compared to HPMC. This is probably due to the fact that K and LB gums are more hydrophilic, and, therefore showed greater water uptake and erosion than H (i.e., HPMC). Thus, the HPMC in the blend increased the integrity and resistance of the matrix to erosion. Furthermore, the high viscosity of the gel formed resulted in longer diffusional path length, thus retarding drug diffusion and resulting in high MDT values. Therefore, there is synergism between khaya gum and HPMC to effect sustained release. This is in agreement with earlier results obtained for karaya gum [15] and LB matrices [11]. Formulation of triple mixtures is capable of sustaining drug release considering their MDT. However, the 2 polymer blends or K alone, showed release profiles similar to the reference commercial formulation, indicating there was no synergism between the 3 polymers [19].

The release data showed high linearity with the Korsmeyer model. The values of release exponent "n" were characteristic of anomalous kinetics (non-Fickian) and indicate a combined effect of diffusion and erosion mechanisms for controlled drug release. For all the formulations, there was contribution from polymer relaxation to the dissolution process as "n" value approaches anomalous transport. Relaxational contribution was higher for the formulations with higher "n" values [10].

The SEM photomicrograph of the tablets 8 h after hydration commenced showed a highly porous tablet surface which probably also reflects a porous tablet matrix structure. This would facilitate diffusion of drug 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 dissolution of the outer layer of the matrix. The formation of both pores and gel structure on the tablet surface indicates involvement of both erosion and diffusion mechanisms for sustained drug release [16].

Thus, the matrices underwent both swelling and erosion at the same time immediately after placement in the dissolution medium, and this continued over the 12 h period of the study. Formulation F5 and the reference DTZ had overlapping erosion profiles throughout the study period but their swelling behaviour were similar only up to the 6th hour. However, the swelling profile of F5 was similar to those reported earlier for K, LB and xanthan matrices containing a different water soluble drug [20].

The FTIR spectra of the pure drug and the test formulation showed characteristic peaks for both pure DTZ and DTZ in the test formulation without any significant shift in their positions. Also, the DSC endothermic peaks for the pure drug and the drug in the test formulation showed only a negligible shift in their positions with some peak broadening in the latter. Thus, the likelihood of any chemical interaction between the drug and the polymers used can be ruled out.

CONCLUSION

Previous studies have shown locust bean gum alone cannot efficiently control drug release. This study demonstrates that its combination with khaya gum is synergistic in controlling diltiazem release. Combination of khaya gum with HPMC led to even greater sustained than khaya gum or its combination with locust bean LB gum. Based on a derived dissolution parameter, f_2 , the formulation

containing khaya and locust bean gums in a ratio of 1:2 (i.e., F5) was closest to the commercial diltiazem tablet used as standard. Thus, a suitable combination of the two natural gums (khaya and locust bean gums) may be successfully employed for formulating sustained-release matrix tablets of diltiazem.

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