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Research Article

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Preliminary Investigation on the Development of Diltiazem Resin Complex Loaded Carboxymethyl Xanthan Beads

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Abstract. The objective of this study was to develop a multiunit sustained release dosage form of diltiazem using a natural polymer from a completely aqueous environment. Diltiazem was complexed with resin and the resinate-loaded carboxymethyl xanthan (RCMX) beads were prepared by interacting sodium carboxymethyl xanthan (SCMX), a derivatized xanthan gum, with Al^{+3} ions. The beads were evaluated for drug entrapment efficiency (DEE) and release characteristics in enzyme free simulated gastric fluid (SGF, HCl solution, pH 1.2) and simulated intestinal fluid (SIF, USP phosphate buffer solution, pH 6.8). Increase in gelation time from 5 to 20 min and $AlCl_3$ concentration from 1 to 3% decreased the DEE respectively from 95 to 79% and 88.5 to 84.6%. However, increase in gum concentration from 1.5 to 2.5% increased the DEE from 86.5 to 90.7%. The variation in DEE was related to displacement of drug from the resinate by the gel forming Al^{+3} ions. While 75–82% drug was released in 2 h in SGF from various beads, 75 to 98% drug was released in 5 hour in SIF indicating the dependence of drug release on pH of dissolution media. Although the beads maintained their initial integrity throughout the dissolution process in both media, as evident from scanning electron microscopic studies, the faster release in SGF was accounted for higher swelling of the beads in SGF than in SIF. When release data (up to 60%) was fitted in power law expression, the drug release was found to be controlled by diffusion with simultaneous relaxation phenomena.

KEY WORDS: carboxymethyl xanthan beads; diltiazem; entrapment; release; resinate.

INTRODUCTION

Formulation of multiunit sustained release dosage forms like microcapsules, microbeads with synthetic polymers require organic solvents. Currently, there is a trend to restrict or even to eliminate the use of organic solvents in pharmaceutical formulations for various reasons (1). Consequently, extensive research efforts have been concentrated on natural polymers as encapsulating materials as they are derived from natural sources, easily available, qualified for a number of chemical modifications and do not require organic solvents for processing (2). Among the various natural polymers, sodium alginate, a hydrophilic biopolymer obtained from marine brown algae, appeared to be highly promising owing to its non-toxic and biocompatible nature and has been investigated in details. Its unique property of forming water-insoluble calcium alginate gel through ionotropic gelation with Ca^{+2} ions in a simple, mild and ecofriendly condition has been utilized to encapsulate low molecular weight therapeutic agents like imipramine (3), indomethacin (4), nifedipine (5), nitrofurantoin (6), and propranolol (7). One of the major disadvantages of sodium alginate as encapsulating material is the substantially low entrapment efficiency of water soluble drugs though some improvement in the same property may be achieved with water insoluble drugs (8,9). The low drug entrapment efficiency of alginate beads has been related to the large gel porosity of alginate beads that causes leakage of the drugs (10). Another disadvantage of alginate beads is the rapid release of the encapsulated drugs. Although alginate beads do not swell appreciably in acidic fluid (11), the beads swell and erode/disintegrate rapidly in SIF leading to quick release of the loaded drugs within a few minutes (12) to few hours (13). Recently it has reported that although the entrapment efficiency of even highly water soluble drugs like diltiazem (14) and propranolol (15) could be considerably increased if the drugs are incorporated in the form of resinate in calcium alginate beads, rapid release of the drugs (more than 90% in 1.5 hour) in SIF could not be prevented even when the drugs were embedded in the form of resinate.

Xanthan gum is a high molecular weight exopolysaccharide produced by *Xanthomonas campestris.* In addition to its use in food products without specific quantity limitations, it is being widely used in pharmaceutical products because of its safety reports (16,17). Besides its application as thickening, suspending and emulsifying agents in pharmaceutical formu-

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lations (18) its application in drug delivery systems like hydrophilic matrix for controlled drug release (19,20), multiunit floating drug delivery for prolonging the residence time in stomach (21) and in enzyme and cell immobilization as supporting material (22,23) is widening. A recent report indicated that if xanthan gum is derivatized to sodium carboxymethyl xanthan (SCMX) gum, it could be used to formulate carboxy methyl xanthan (CMX) beads through interactions with Al^{+3} ions (24). However, hitherto there is no report on the formulation of resinate-loaded CMX beads using SCMX gum.

This research was undertaken to judge the ability of SCMX gum to form RCMX beads having high drug entrapment efficiency and to provide prolonged release of the drug specially in SIF. Diltiazem hydrochloride has been used as a model drug in this study. It has been reported that diltiazem hydrochloride, a calcium channel blocker is widely used for the treatment of angina pectoris (25,26), arrythmias and hypertension. Its short biological half life and thus frequent administration (usually three to four times a day) makes it a potential candidate for sustained release preparation (27,28).

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride(Stadmed, Kolkata, India), Sulfonic acid cation exchange resin in Na^+ form (Indion 254^R,Ion Exchange (India) Pvt Ltd, Mumbai, India) and Xanthan gum (Sun Pharma, Gujrat, India) were obtained as gift samples. All other analytical grade reagents were obtained commercially and used as received.

Preparation of Resin

Sulfonic acid cation exchange resin was stirred in 200 ml deionized water with a magnetic stirrer for 1 hour and left aside to settle down. The resin was separated by decantation and washed consecutively with methanol (2×50 ml) to remove organic impurities and colouring matter present, if any (29) The resin was then activated by recycling alternately thrice with 1 M NaOH (60 ml) and 1 M HCl (60 ml) and washing after each treatment with deionized water. Finally, the resin in hydrogen/acid form was washed with deionized water until the elute was neutral. The resin was then vacuum dried at 50°C to constant weight. The dried resin was passed through a nest of 240, 300, 350 mesh British Standard sieves and fraction retained on 350 mesh sieve was used to prepare drug-resin complex.

Preparation of Resinate

Weighed amount of resin (100 mg) was stirred in 75 ml of deionized water containing 0.80 mg/ml diltiazem-HCl at 30°C. The resinate was separated after 3 h by vacuum filtration and washed with deionized water until the drug concentration in the filtrate became negligible (below 0.1 μg/ml). The resinate was dried at 50°C in vacuum to constant weight.

Preparation of Resinate Loaded Carboxy Methyl Xanthan (RCMX) Bead

Derivatization of xanthan gum to SCMX gum and preparation of RCMX beads using SCMX gum were adapted from the methods for the preparation of drug loaded CMX beads reported elsewhere (24). Required amount of resinate (30% *w/v*) was dispersed in 10 ml aqueous solution of SCMX gum (2% *w/v*, unless otherwise mentioned) and homogenized for 10 min. Bubble free dispersion was extruded through a 22 bore glass syringe in a gently agitated $AlCl_3$ solution. Following gelation for predetermined times, the gelled beads were separated by filtration, washed with 3×50 ml deionized water, air dried and finally vacuum dried for 24 h to constant weight. The following experimental parameters were varied:

1) Concentration of SCMX gum
   1.5, 2, 2.5% *w/v*
2) Concentration of $AlCl_3$ solution:
   1%, 2%, 3% *w/v*
3) Gelation time:
   5, 10, 20 min

Drug Entrapment Efficiency (DEE)

Accurately weighed amount (20 mg) of RCMX beads were shaken for 24 h in 250 ml USP phosphate buffer solution (pH 6.8) and then filtered. The filtrate, following suitable dilution, was assayed spectrophotometrically (Hitachi2002, Japan) at 236 nm.

DEE was determined from the following Eq. 1

$$\%\mathrm{DEE} = (\textit{experimental drug content}/\textit{theoretical drug content}) \times 100 \quad (1)$$

The reliability of the method was judged by recovery analysis using 10 mg of diltiazem hydrochloride with or without SCMX gum. The recovery averaged 98.6±2.07% indicating that the gum did not interfere with the analysis of the drug at 236 nm.

Scanning Electron Microscopy (SEM)

RCMX beads before and after dissolution studies were mounted onto stubs using double sided adhesive tape and vacuum coated with gold film using sputter coater (Edward S150, UK). The coated surface was observed under SEM (Jeol, SM-5200, Japan) for surface appearance.

Drug Release Study

In vitro release of diltiazem from RCMX beads were monitored in SGF (HCl solution, pH 1.2, without enzyme) and in SIF (USP phosphate buffer solution pH 6.8, without enzyme) at 37±1°C using programmable dissolution tester (Paddle type, Electrolab, model TDT-06P (USP), Mumbai, India). Beads, 100 mg, were immersed in 900 ml of the respective medium and stirred at 50 rpm. Aliquots were removed at predetermined times and were replenished immediately with the same volume of fresh media. The aliquots, following suitable dilution, were assayed spectrophotometrically at 236 nm.

Measurement of Drug Displacement by Various Cations

Accurately weighed amount (10 mg) of resinate was incubated in different solutions (100 ml) containing equimolar

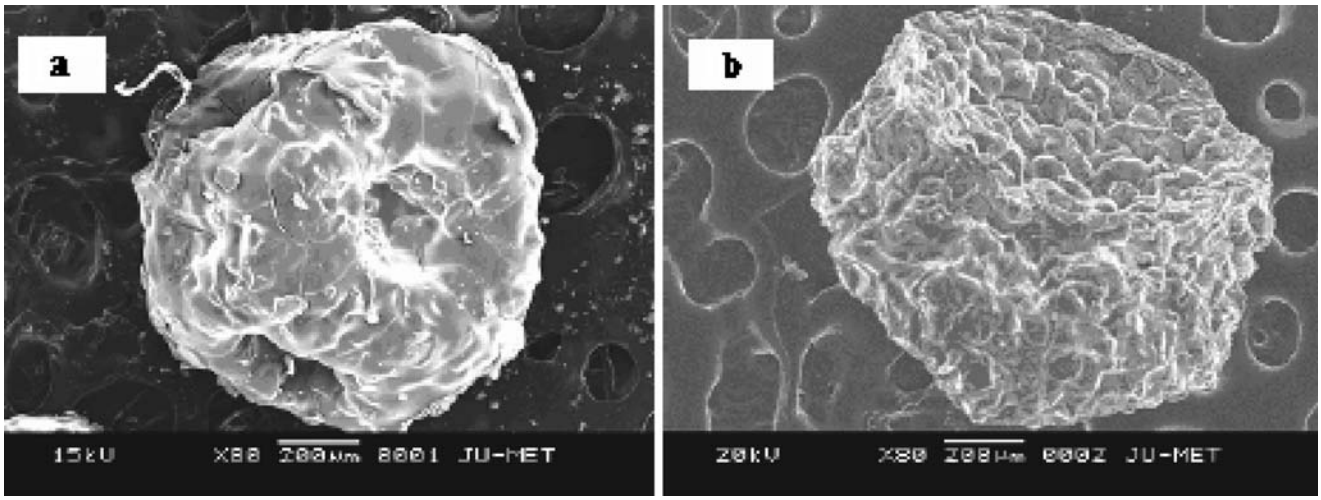

Fig. 1. Scanning electron micrographs of **a**) RCMX bead and **b**) RCMX bead after dissolution

amount (0.1 M) of $AlCl_3$,$CaCl_2$ and NaCl. After 30 min, the solutions were filtered and amount of diltiazem present in the filtrate was measured spectrophotometrically following suitable dilution.

In another experiment weighed amount (10 mg) of resinate was incubated in 100 ml of $AlCl_3$ (1%, 2 or 3% *w/v*) solution (100 ml) for different periods of time (5, 10, 30 min). Then the solutions were filtered and the amount of diltiazem present in the filtrate was measured spectrophotometrically following suitable dilution. Diltiazem content (%) of the resinate after drug displacement studies was determined from Eq. 2.

$$\text{Diltiazem content}(\%) = \frac{(\text{amount of drug in resinate} - \text{amount of drug in elute})}{\text{amount of drug in resinate}} \times 100 \quad (2)$$

Kinetics of Drug Release

Release of a drug from a simple swellable polymeric matrix can be described by the power law expression $M_t/M_\alpha = k\ t^n$ where M_t and M_∞ are respectively the amount of drug released at time t and at infinite time, k represents a constant incorporating structural and geometrical character of the dosage form and n values denotes the diffusion exponent indicative of the mechanism of drug release (30). In case of Fickian release (diffusion-controlled release) from spherical martices, *n* has a limiting value of 0.43. In the case of Case II transport or relaxation-controlled release, the exponent *n* is 0.85. The non-Fickian release or anomalous transport of drug occurs when the *n* values fall between the limiting values of Fickian and Case II transport. The non-Fickian kinetics corresponds to coupled diffusion/polymer relaxation (31).

To evaluate the mechanism of drug release from different RCMX beads, the release data (up to 60%) were fitted in the logarithmic form of the power law Eq. 3;

$$\log\left[\frac{Mt}{M_\infty}\right] = log\ k + n\ \log t \quad (3)$$

and the values of n were calculated from the slopes of the straight line.

Statistical Analysis

Each formulation was prepared in duplicate or triplicate and each analysis was duplicated. Statistical analysis of the data were performed using analysis of variance (ANOVA: single factor) with the aid of Microsoft Excel 2002. Difference was considered significant when $p<0.05$.

Table I. Effect of Gelation Time, $AlCl_3$ Concentration and Initial Gum Concentration on Diltiazem Entrapment Efficiency (DEE) of RCMX Beads

Gelation Time (min)[a]	DEE (%; Mean±SD, *n*=6)	$AlCl_3$ Concentration[b] (% *w/v*)	DEE (%; Mean±SD, *n*=6)	Initial Gum Concentration[c] (% *w/v*)	DEE (%; Mean±SD, *n*=6)
5	95.00±2.05	1.0	88.58±1.94	1.5	86.51±0.53
10	88.58±1.94	2.0	86.27±0.20	2.0	88.58±1.94
20	79.00±3.15	3.0	84.64±1.45	2.5	90.72±3.12
	$p<0.05$		$p<0.05$		$p>0.05$

[a] Preparative condition: 2.0% SCMX gum, 1.0% $AlCl_3$
[b] Preparative condition: 2.0%, SCMX gum, 10 min gelation time
[c] Preparative condition: 1.0% $AlCl_3$, 10 min gelation time

Table II. Residual Diltiazem Content in the Resinate After Incubation for Different Periods of Time in $AlCl_3$ Solution (1.0% *w/v*) and After Incubation for 30 min in $AlCl_3$ Solution Having Different Concentration

Incubation time (min)	Residual Diltiazem Content in Resinate (%±SD, $n=3$)	$AlCl_3$ Concentration (% *w/v*)	Residual Diltiazem Content in Resinate (%±SD, $n=3$)
5	89.23 (±0.98)	1.0	79.08 (±0.46)
10	84.25 (±0.42)	2.0	77.67 (±0.07)
30	79.08 (±0.46)	3.0	75.15 (±0.45)

RESULTS AND DISCUSSION

Formation of Resinate Loaded Carboxy Methyl Xanthan (RCMX) Beads

Preliminary investigation revealed that formation of isolatable RCMX beads having spherical shape depends on the concentration of SCMX gum and the ability of Al^{+3} ions to cross link with SCMX gum. The degree of cross-linking depends on both the concentration of $AlCl_3$ solution and the time of contact of the beads with this solution. When SCMX gum solution having a concentration below 1.5% *w/v* was dropped in 1–3% *w/v* $AlCl_3$ solution, the droplets became flat. Increase in gum concentration above 2.5% *w/v* produced beads having tail. On the other hand, extrusion of SCMX gum solution (1.5–2.5%) in $AlCl_3$ solution having less than 1%w/v concentration produced beads which collapsed after drying and were difficult to isolate. Similarly, beads collapsed and were not isolatable when the gelation time was less than 5 min. Hence, RCMX beads were prepared using 1.5–2.5% *w/v* SCMX gum, 1–3% $AlCl_3$ solution and 5–20 min gelation time. Under the specified conditions, when a dispersion of the resinate in SCMX gum solution was extruded in the form of droplets in $AlCl_3$ solution, isolatable RCMX beads having spherical shape were formed. It has been reported that as soon as a droplet of SCMX gum solution comes in contact with $AlCl_3$ solution, Al^{+3} ions bind with the carboxyl groups of SCMX gum displacing the Na^+ ions and results in the formation of beads having gel structure of insoluble aluminium carboxy methyl xanthan (32) It has also been reported that increase in the gelation time and the concentration of $AlCl_3$ solution increases the influx of Al^{+3} ions into the beads and moves the gel boundaries inwardly forming a thicker gel structure (32). Figure 1a depicts the gross morphology of a dried RCMX bead which was prepared by gelation for 10 min in 1% $AlCl_3$ solution. No distinct changes in the shape and the surface characteristics of other RCMX beads prepared using different gelation time and $AlCl_3$ concentration were noticeable under SEM.

Drug Entrapment Efficiency (DEE) of RCMX Beads

Diltiazem content of the resinate was found to be 30.28± 0.70%.The drug content of the RCMX beads prepared using a gum/resinate ratio of 7:3 is expected to be 8.97%.However, the actual drug content and hence, the DEE of RCMX beads was found to be less than the theoretical value and appeared to be related with the displacement of the drug by Al^{+3} ions during the gelation process. The effect of processing and formulation variables on DEE of RCMX beads have been presented in Table I. Increase in gelation time from 5 to 20 min significantly ($p<0.05$) decreased the DEE of RCMX beads (prepared using

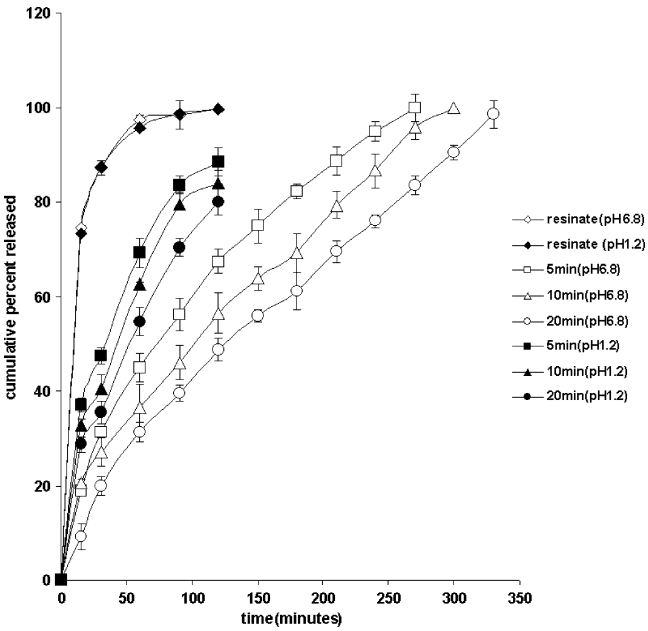

Fig. 2. Release profiles of diltiazem in SGF (*closed symbol*) and in SIF (*open symbol*) from resinate and RCMX beads prepared using different gelation time

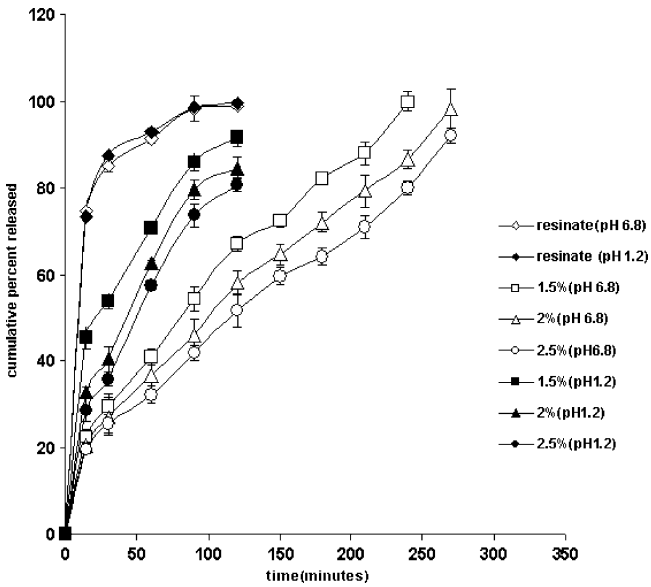

Fig. 3. Release profiles of diltiazem in SGF (*closed symbol*) and in SIF (*open symbol*) from resinate and RCMX beads prepared using different SCMX gum concentration

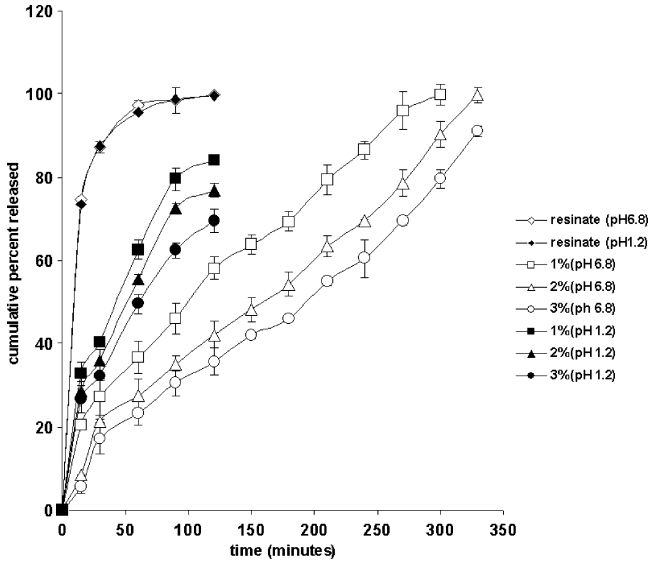

Fig. 4. Release profiles of diltiazem in SGF (*closed symbol*) and in SIF (*open symbol*) from resinate and RCMX beads prepared using different $AlCl_3$ concentration

2% SCMX gum and crosslinked with 1% $AlCl_3$) from 95 to 79%. The DEE of RCMX beads (prepared using 2% SCMX gum and 10 min gelation time) also decreased significantly ($p<0.05$) from 88.5 to 84.64% when the concentration of $AlCl_3$ was increased from 1 to 3% w/v. Although the DEE of the beads prepared by gelling for 10 min in 1% $AlCl_3$ solution increased from 86.5 to 90.7% with increase in SCMX gum concentration from 1.5–2.5% *w/v* statistically no significant difference ($p>0.05$) in the entrapment efficiency was observed. The effect of processing and formulation variables on DEE can be explained on the basis of influx of Al^{+3} ions into the beads and drug displacement from the resinate by the cations present in the gelation medium. When a droplet of SCMX gum solution comes in contact with Al^{+3} ions present in the gelation medium, gelation starts instantaneously at the surface of the droplets. Al^{+3} ions displace Na^+ ions of the gum and form a gel structure of insoluble aluminium carboxy methyl xanthan gum. With time Al^{+3} ions move inwardly into the beads and consequently gel boundary moves inwardly until the crosslinking between Al^{+3} ions and carboxyl group of gum is complete. During their passage inside the beads, Al^{+3} ions also bind with sulphonic acid groups of the resin displacing the already bound weak cation diltiazem. Subsequently, the free diltiazem diffuses out through the gel structure into the aqueous gelation medium resulting in a decrease in DEE. The longer the exposure time of the beads in the gelation medium, the greater the amount of Al^{+3} ions into the beads. This results in larger displacement of the drug and consequently the DEE decreases considerably with increasing gelation time. When the concentration of $AlCl_3$ in the gelation medium is increased, cross linking of the gum and hence, the compactness of the gel structure near the surface of the beads is increased. This slows down the influx of Al^{+3} ions inside the beads. As a result the amount of drug displaced from resinates becomes less. That is why the decrease in DEE becomes less when compared to that produced by the gelation time. On the other hand, as the concentration of the gum is increased, the compactness of the gel structure near the surface is increased due to greater availability of active aluminium-binding sites in the gum. As a result higher DEE is achieved. Similar effects of process and formulation variables on the entrapment efficiency of diltiazem (14) and propranolol (15) in resinate loaded calcium alginate beads have been reported.

To substantiate that gelation time had a more pronounced effect in decreasing the DEE of RCMX beads than the concentration of Al^{+3} ions, uncoated resinate was incubated in $AlCl_3$ solution for different periods of time and the concentration of the eluted drug was measured. Table II shows that the amount of drug in the resinate which were incubated in 1% $AlCl_3$ solution decreased from 89.23 to 79.08% as the incubation time was increased from 5 to 30 min. On the other hand, keeping the incubation time constant at 30 min, increase in $AlCl_3$ concentration from 1 to 3% *w/v* decreased the diltiazem content in the resinate from 79.08 to 75.15%. In view of this phenomenon, it can be said that concentration of $AlCl_3$ has a less pronounced effect in decreasing the DEE than gelation time.

Drug Release from RCMX Beads

The release profiles of diltiazem in SGF and in SIF from the resinate and the RCMX beads which were prepared under different conditions have been represented in Figs. 2, 3, 4. The drug release from the resinate was rapid and complete in about 1.5 h and appeared to be independent of the pH of the dissolution media. Although the release of the drug in SGF from RCMX beads was slower than that from the uncoated resinate, the beads could not provide prolonged release since 75 to 82% drug was released in 2 hour depending upon the formulations. Moreover, the release profiles exhibited a burst release of 28–38% in 30 min. On the other hand, the release of the drug in SIF from the beads was found to be prolonged in comparison to that in SGF. From the Figs. 2, 3, 4 it was

Table III. Effect of Processing and Formulation Factors on the Time Required for 50% Release ($t_{50\%}$) of Diltiazem from RCMX Beads in (a) Simulated Gastric Fluid (b) Simulated Intestinal Fluid

Gelation time (min)	$t_{50\%}$ (min) (Mean±SD, n=4)	$AlCl_3$ Concentration (% *w/v*)	$t_{50\%}$ (min) (Mean±SD, n=4)	Initial Gum Concentration (% *w/v*)	$t_{50\%}$ (min) (Mean±SD, n=4)
5	a) 35±0.91	1.0	a) 48±0.75	1.5	a) 40±0.61
	a) 73±0.61		a) 100±0.71		a) 80±0.61
10	a) 48±0.75	2.0	a) 55±0.53	2.0	a) 48±0.75
	b) 100±0.71		b) 160±0.36		b) 100±0.71
20	a) 60±0.61	3.0	a) 64±0.43	2.5	a) 58±0.42
	b) 115±0.51		b) 195±0.53		b) 115±0.42

Preparative condition as shown in Table I

evident that 75–98% drug was released in SIF in 5 h and the magnitude of the burst release was also less than that in SGF.

Drug release from resinate-loaded beads involves a series of events like swelling of the beads, influx of dissolution media into the swollen beads, elution of the drug from the resinate by the cations present in the dissolution media and finally efflux of the eluted drug from the beads. The faster drug release in SGF could be related to the higher swelling of the beads in SGF and to the higher capacity of H^+ ions present in SGF to displace diltiazem from the resinate. The swelling study of the beads containing drug free resin demonstrated that the swelling of the beads in SGF was higher than that in SIF (data not shown). In order to ascertain that H^+ ions present in SGF had higher drug displacement capacity than Na^+ ions present in SIF, known amount of resinate was incubated for 30 min in equimolar concentration of different cations. It was found that the drug displacement capacity of various cations decreased in the following order: H^+ (32.92%)>Na^+ (27.62%)>Ca^{2+} (20.03%)>Al^{3+} (18.96%). This result shows that exchange rate is quite rapid with small univalent cations and the rate of displacement decreases to a great extent as the valency of the exchanging ions is increased. The faster drug release accompanied by an initial burst effect in SGF were, thus, the combined effect of swelling of the beads and higher drug displacement capacity of H^+ ions.

Rapid swelling and erosion of calcium alginate beads in phosphate buffer solution of pH 6.8 occurs through ion exchange with phosphate buffer and degrades the alginate backbone into smaller molecules leading to rapid drug release (33,34) It has also been reported that even the resinate-loaded calcium alginate beads released about 90% diltiazem only in 1.5 hour in phosphate buffer solution (14). On the contrary, 100% diltiazem was released in SIF from RCMX beads in 5 hour. Unlike calcium alginate beads, RCMX beads did not disintegrate/ erode during the dissolution process and the gross morphology of the beads under SEM was not significantly different from that of the beads before the dissolution study (Fig. 1b).Thus prolonged release of the drug in SIF could be due to the combined effect of the maintenance of the initial integrity of the beads, low swelling ratio of the beads in SIF and lower drug displacement capacity of Na^+ ions present in SIF.

When the time required for 50% drug release ($t_{50\%}$) from various RCMX beads in SGF were compared, it was found that $t_{50\%}$ increased significantly ($p<0.05$) and, hence, the drug release decreased when either the gelation time, the concentration of $AlCl_3$ solution or the concentration of SCMX gum to prepare the beads was increased (Table III). Similar increase in $t_{50\%}$ and hence decrease in drug release in SIF were noted when the magnitude of the processing and formulation variables were increased (Table III).

The release data up to 60% were fitted in Eq. 3 and the values of n and k were determined from the slope and y intercept. At both pH levels, n values varied from 0.47–0.68 (R^2=0.96–0.98) for the beads which were prepared with increasing concentration of $AlCl_3$, from 0.45–0.52 (R^2=0.95–0.99) for the beads prepared with increasing gum concentration and from 0.43–0.68 (R^2=0.96–0.99) for the beads prepared with increasing gelation time. The *n* values indicated that the drug release from the beads prepared under different conditions followed anomalous or non-Fickian transport mechanism and the release was controlled by diffusion with simultaneous relaxation phenomena. Since the n values were less than 0.85, the beads did not undergo disintegration/ erosion and this was confirmed by SEM study (Fig. 1b).

CONCLUSION

SCMX gum appeared to be a suitable polymer for the formulations of highly water soluble drug-loaded beads from a completely aqueous environment. High drug content of the beads was achieved by incorporating the drug in the form of resinate. Though the resulting beads discharged the drug rapidly in SGF, prolonged release was achieved in SIF. Once the release is reduced in SGF through further modifications, the RCMX beads could be useful as a carrier for oral sustained release of diltiazem.

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