

Carboxymethylcellulose – aluminum hydrogel microbeads for prolonged release of simvastatin

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Abstract

Carboxymethylcellulose based hydrogel microbeads loaded with simvastatin were prepared using ionotropic gelation method. The beads were characterized by differential scanning calorimetric (DSC) analysis, and scanning electron microscopy (SEM). DSC studies confirmed the amorphous dispersion of the drug in the hydrogel matrix. The effect of crosslinking agent and polymer concentration on drug release was studied. Increase in concentration of crosslinking agent and polymers decreased the release rate of simvastatin. The release data were fitted to an empirical equation to determine the transport mechanism. Drug release followed anomalous/non-Fickian transport mechanism.

Keywords: Simvastatin, drug release, hydrogel beads, carboxymethylcellulose.

Introduction

Oral controlled release (CR) multiple unit dosage forms such as microparticles, beads and pellets are gaining considerable importance in recent years in view of their advantages over the conventional single unit formulations. The multiple unit dosage forms spread uniformly throughout the gastrointestinal tract (GIT), this will avoid the release of drug at one particular site, thus avoiding the risk of toxicity. Uniform distribution of multiple units in GIT results in more reproducible absorption and will reduce the risk of local irritations when compared to single unit systems. Multiple units can be filled into hard gelatin capsules or they can be compressed into tablets (Galeone et al. 1981).

Polymeric hydrogels are three-dimensional cross-linked networks that have the ability to absorb water and swell without losing their shape (Kulkarni and Sa 2007). Their most remarkable macroscopic property is their high swelling ability, which depends largely on the external conditions (i.e. pH, temperature) and the parameters of the gel (i.e. mesh size) (Siegel 1993, Yao et al. 1994). Hydrogels have been widely used in medicine and pharmacy as controlled delivery devices of various active materials (Kulkarni and Sa 2008a, 2008b, 2008c). The incorporation and the delivery of bioactive materials (e.g. drugs, antibodies or enzymes) can be accomplished by swelling/deswelling of the hydrogel as a result of the environmental changes of the medium. The cross-linked hydrophilic polymers provide a temporary or permanent macromolecular network through which the release of active ingredients occurs.

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Recently, much research has been focused on the development of multi-unit controlled release systems using natural hydrophilic polymers as they are easily available and qualified for a number of chemical modifications. The Carboxymethylcellulose sodium (NaCMC), carboxymethyl ether of cellulose has been used as a matrix material to sustain the release of drugs using ionotropic gelation method by various researchers (Hosny and Al-Helw 1997, 1998). However, there is no report on the NaCMC based hydrogel beads for prolonged release of simvastatin.

Simvastatin is a powerful lipid-lowering drug that can decrease cholesterol levels by 50 %. It is an inhibitor of HMG-CoA reductase, the enzyme that inhibits the biosynthesis of cholesterol; hence it is used in the treatment of hypercholesterolemia. After oral administration, it readily absorbs from GIT and is having a bioavailability of less than 5 % and plasma half life of about 1.9 h (James 2007). A repeated administration of drug is required to maintain constant plasma levels; this may results in accumulated toxicity, therefore it is a suitable candidate for the development of sustained release formulations.

The present work is aimed at the development and evaluation of carboxymethylcellulose based hydrogel beads for the prolonged release of simvastatin by ionotropic gelation method.

Materials and Methods

Materials

Simvastatin was obtained as gift sample from Dr. Reddy's Laboratory, Hyderabad (India). Carboxymethylcellulose sodium salt, high viscosity grade (500-800 cPs) (NaCMC), aluminum chloride hexahydrate and sodium hydroxide (NaOH) were purchased from SD fine Chemicals, Mumbai (India). Double distilled water was used throughout the study. All other chemicals were extra pure reagent grade and were used as received.

Preparation of beads

An accurately weighed quantity of simvastatin was dispersed in an aqueous solution of carboxymethylcellulose sodium (NaCMC) and mixed homogeneously using magnetic stirrer. Twenty milliliters of dispersion was extruded in the form of droplets into 100 ml aqueous solution of $AlCl_3$ solution using 25 ml hypodermic syringe through a needle (number 23). The beads were removed after the gelation period of 15 min and washed with distilled water repeatedly to make free from un-reacted ions and dried at room temperature for 24 h and then at 40°C for 10 h. The composition of beads is given in Table 1.

Table 1. Composition of microbeads

Code	NaCMC (% w/v)	Drug (% w/w of dry polymer)	$AlCl_3$ (% w/v)
M1	3	20	2
M2	4	20	2
M3	5	20	2
M4	5	20	4
M5	5	20	8
M6	5	40	8

Scanning electron microscopic studies (SEM)

The beads were mounted onto stubs using double sided adhesive tape and sputter coated with platinum to make them conducting using sputter coater (Edward S 150, UK). The coated beads were observed under scanning electron microscope (JEOL, JSM-6360, Japan) at the required magnification at room temperature.

Measurement of bead size

The bead size was measured using a digimatic micrometer (MDC-25S Mitutoyo, Japan) having an accuracy of 0.001 mm. The average diameter of the 100 particles per batch was calculated.

Estimation of drug entrapment efficiency (DEE)

Known amount of beads were incubated with 100 ml of phosphate buffer pH 7.4 for complete swelling. Then the beads were crushed in a glass mortar with pestle, the solution was heated gently for 3 h to extract the drug completely and centrifuged to remove the polymeric debris. The clear supernatant solution was analyzed for the drug content using UV-visible spectrophotometer (Model Pharmaspec UV-1700, Shimadzu, Japan) at 238 nm. The entrapment efficiency was calculated using the following equation:

$$\text{Drug entrapment efficiency} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100 \quad (1)$$

Differential scanning calorimetry (DSC)

DSC analysis was performed on simvastatin, drug-free M6 and drug-loaded M6 beads. The samples were heated from 0-300 °C at a heating rate of 10 °C/min under argon atmosphere using a microcalorimeter (DuPont-9900, USA).

Dynamic swelling study

The dynamic swelling behavior of the beads was studied by mass measurement. The beads were incubated with 25 ml phosphate buffer pH 7.4 in a petridish at 37 °C. The beads were taken out at different time intervals using stainless steel grid and blotted carefully without pressing hard to remove the excess surface liquid. The swollen beads were weighed using the electronic microbalance. The studies were performed in triplicate and average values were taken in data analysis.

In vitro drug release

In-vitro drug release study was carried out in triplicate using a USP-23 rotating paddle dissolution tester (Electrolab TDT-06P, Mumbai, India). The dissolution rates were measured at 37.0 ± 0.5 °C and 50 rpm paddle speed. Drug release from the beads was studied in 900 ml phosphate buffer medium (pH 7.4). At predetermined time intervals, 5 ml aliquots were withdrawn and replaced with the same volume of fresh solution. The samples were passed through a 0.45 µm membrane filter and the amount of drug released was analyzed using UV-visible spectrophotometer at a λ_{max} of 238 nm following suitable dilutions.

Results and Discussion

When a dispersion of drug and NaCMC was extruded through the needle into a solution containing Al^{3+} cations, the beads were formed instantaneously. As soon as the trivalent cations (Al^{3+}) are brought in contact with NaCMC, they form ionic cross-links between two polymer molecules and different parts of the same polymer chain. The exchange of Na^+ ions occurs with Al^{3+} . These ions are ionically substituted at the carboxylate site and a second strand of NaCMC can also be connected with Al^{3+} forming a link in which the cations are attached to three NaCMC strands together.

The beads were spherical in shape having rough and dense surface with microscopic cracks on the surface as evidenced by SEM (Figure 1) and they fell in the size range of 982 to 1358 µm (Table 2). As the concentration of AlCl_3 was increased, smaller beads were produced. This suggests that during crosslinking, the hydrogel might have undergone rapid shrinking leading to the formation of smaller and rigid matrix at higher crosslink densities. Also by increasing the polymer concentration in the beads, an increase in size of the beads was observed, which could be attributed to the formation of bigger droplets due to increase in the viscosity of the solution with increasing concentration of polymer during extruding through a needle. On the other hand, increase in amount of simvastatin increased the bead size because simvastatin might have occupied the interstitial spaces between polymer segments (Agnihotri and Aminabhavi 2004).

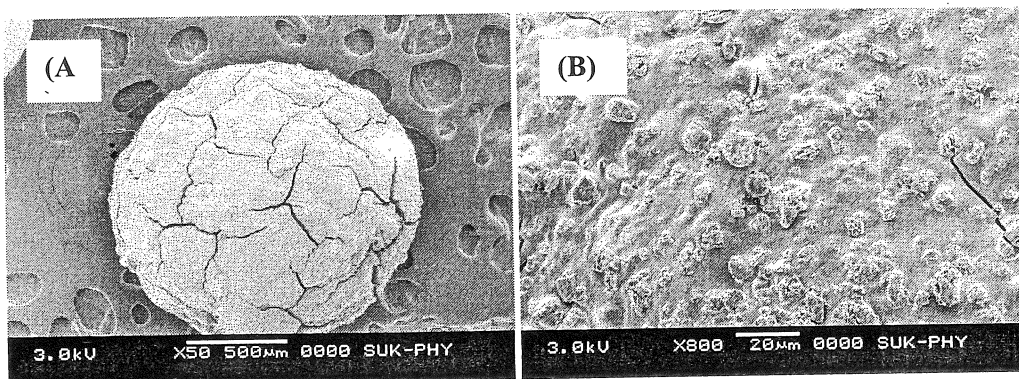


Figure 1. SEM photographs of microbead (A) and its surface morphology (B)

Table 2 shows that DEE of the beads prepared with lower concentration of $AlCl_3$ was lowest as compared to those prepared with higher concentration of $AlCl_3$. At lower concentration of $AlCl_3$, the hydrogel matrix might be loose and have larger pores due to insufficient crosslinking, which results in higher leakage of drug into the gelation medium from polymer matrix during the preparation of beads, this resulted in lower DEE. At higher concentration of $AlCl_3$, the hydrogel matrix is rigid and leakage of drug from the polymer matrix is low resulting in high DEE (Bhopatkar et al. 2005).

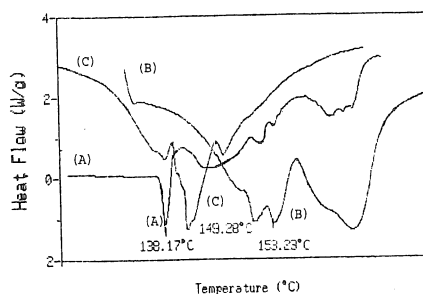
Table 2. Average bead size, drug entrapment efficiency (DEE), release parameter (n) and correlation coefficients (r) of the microbeads

Beads	Average size (μm)	DEE (%)	D (cm^2/s)	N	r^*
M1	982 ± 3.95	62.96 ± 0.010	4.7937×10^{-3}	0.521	0.971
M2	1235 ± 3.87	64.59 ± 0.100	4.6552×10^{-3}	0.536	0.980
M3	1358 ± 3.69	66.79 ± 0.050	3.0308×10^{-3}	0.541	0.974
M4	1242 ± 4.72	70.07 ± 0.008	2.7620×10^{-3}	0.545	0.977
M5	1057 ± 4.72	72.26 ± 0.007	2.3910×10^{-3}	0.587	0.980
M6	1150 ± 3.15	73.91 ± 0.009	2.8962×10^{-6}	0.556	0.986

* Correlation coefficients

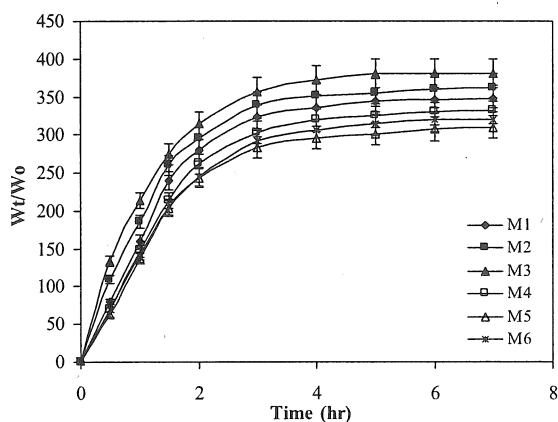
The DSC thermograms for plain simvastatin (A), drug-free M6 beads (B) and drug-loaded M6 beads (C) are presented in Figure 2. The drug-free beads have shown a sharp endothermic peak at $153^\circ C$ indicating melting temperature of the polymer, whereas drug-loaded beads showed an endothermic peak at $149^\circ C$. This decrease in the melting temperature may be due to physical and morphological changes taking place in the beads after entrapment of the drug. The plain simvastatin has shown a sharp endothermic peak at $138^\circ C$ due to melting of the drug, but this peak has not appeared in the drug-loaded beads. This indicates that the drug was uniformly dispersed in an amorphous state in the polymer matrix.

Figure 2. DSC thermograms of simvastatin(A), drug-free M6 beads(B) and drug-loaded M6 beads(C)



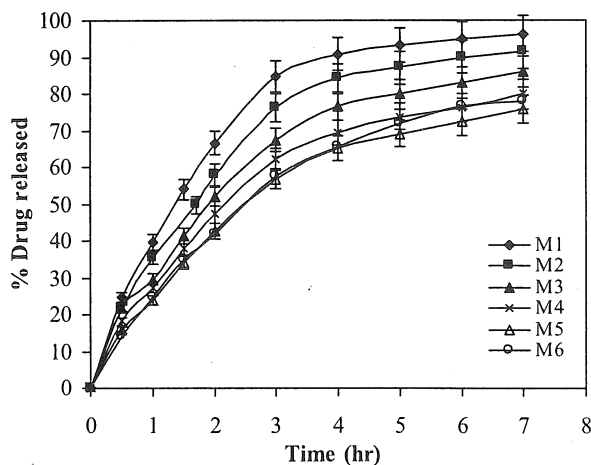
The Figure 3 depicts dynamic swelling behavior of beads expressed as w_t/w_0 (where w_0 is the initial weight of the beads and w_t is the weight of beads at time 't') as a function of time in phosphate buffer pH 7.4. The swelling depends upon the concentration of polymer and extent of crosslinking in the beads. It was observed that swelling of the beads increased with an increasing amount of polymer in the beads and swelling decreased with an increasing amount of $AlCl_3$, due to the formation of more rigid hydrogel network. At low crosslink density, the hydrogel network is loose with a greater hydrodynamic free volume and can absorb more of the solvent resulting in higher swelling.

Figure 3. Effects of formulation variables on swelling behavior of microbeads.



The release profile of simvastatin from microbeads is shown in Figure 4. The beads which were prepared with higher concentration of $AlCl_3$ released the drug more slowly because increase in concentration of the gel forming ions provided increased rigidity of the hydrogel network due to increased cross-link density. On the other hand, increase in concentration of polymer in formulations resulted in decreased drug release, which may be due to increased diffusional path length for drug penetration. Figure 4 also shows the effect of initial drug loading on the release of drug from beads. Keeping all the variables constant, increase in initial drug loading increased the drug release. Increase in initial drug load decreases the proportion of polymer per unit weight and this weakens the gel network structure. Moreover, higher drug loading increases the free volume within the network and creates a more tortuous path for water to penetrate through. Consequently increase in initial drug loading increased the release of drug.

Figure 4. *In-vitro* release profiles of simvastatin from microbeads



The diffusion of solute in a spherically shaped hydrogel matrix can be explained with the help of following mathematical models (Crank 1975, Vergnaud 1991) based on Fick's second law of diffusion given in the form:

$$\frac{dC}{dt} = D \left(\frac{d^2 C}{dr^2} + \frac{2}{r} \frac{dC}{dr} \right) \quad (2)$$

The change in concentration of the solute in the matrix can be expressed by following equations derived from Fick's second law using Laplace transformations to give:

$$\frac{Mt}{M_\infty} = 6 \sqrt{\frac{Dt}{\pi^2}} \left(\frac{1}{\sqrt{\pi}} + 2 \sum_{n=1}^{\infty} \text{ierf} \frac{nr}{\sqrt{Dt}} \right) - 3 \frac{Dt}{r^2} \quad (3)$$

In the above equation, M_t is amount of solute released at time t , M_∞ is total amount of solute in the bead and D is diffusion coefficient of the solute in hydrogel network. However, above equation is too complex to calculate the values. Hence, Baker and Lonsdale (Baker and Lonsdale 1974) have derived the following approximations, considering following initial and boundary conditions

$$\text{Initial: } t = 0 \int \int 0 \leq r < R \int \int C = C_{in} \quad \text{Inner part of the beads} \quad (4)$$

$$\text{Boundary: } t > 0 \int \int r = R \int \int C = C_{eq} \quad \text{At surface of the beads} \quad (5)$$

Where, r is initial radius of the beads, R is radius of the swollen beads, and C_{in} and C_{eq} are the concentrations at beginning and at the end of diffusion process, respectively. Then the diffusion coefficients were calculated by using the following Eq.

$$D = \left(\frac{r\theta}{6M_\infty} \right)^2 \pi \quad (6)$$

Where θ is slope of linear portion of the plot of M_t/M_∞ versus $t^{1/2}$, r is radius of the beads and M_∞ is the total amount of drug loaded. The diffusion coefficients have been estimated based on the Fickian diffusion model and D values are given in the Table 2. The results indicate that the diffusion coefficient of drug was higher from the beads which were prepared with lower concentration of polymer and AlCl_3 ; as the concentrations of polymer and AlCl_3 was increased, diffusion coefficient of the drug decreased appreciably. This result confirms that as the concentration of AlCl_3 is increased, more rigid gel structure is formed and this hinders the drug diffusion.

To understand the drug release mechanism in the hydrogel network, release data was fitted to an empirical equation (Ritger and Peppas 1987):

$$\frac{Mt}{M_\infty} = Kt^n \quad (7)$$

In which M_t is the amount of drug released at time t , and M_∞ is the total amount of drug loaded, n values are the indication of the type of release mechanism. The calculated n values along with the correlation coefficients have been shown in Table 2. The values of n depend upon the cross-link density and polymer concentration; the n values increase with increase in cross-link density and polymer concentration. Calculated n values suggested that the mechanism of drug release followed non-Fickian transport.

Conclusions

The carboxymethylcellulose-aluminum based hydrogels beads were prepared by ionotropic gelation method for the controlled release of simvastatin. Differential scanning calorimetric studies confirmed the amorphous dispersion of the drug in the hydrogel matrix. The swelling of beads and drug release depends upon the polymer concentration and extent of crosslinking in the hydrogel matrix. Drug release followed anomalous/non-Fickian transport mechanism. This work demonstrates the feasibility preparing multiparticulate drug delivery system for prolonged release of simvastatin.

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