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Research Article

Development and Evaluation of Gellan Gum Based Hydrogel Microbeads for Controlled Release of Ketoprofen

BS MANGOND, V SREEDHAR, VV BARASKAR, RV KULKARNI*

Department of Pharmaceutics, BLDEA's College of Pharmacy, BLDE University Campus, Bijapur 586 103, India

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ABSTRACT

Compared to single unit-dosage forms, multi-unit controlled release dosage forms like microbeads and microparticles are advantageous as they prevent the exposure of absorbing site to high drug concentration on chronic dosing. Gellan gum based hydrogel microbeads loaded with ketoprofen were prepared by ionotropic gelation method and evaluated for size analysis, surface morphology, dynamic swelling and drug release behavior. The scanning electron microscopy (SEM) revealed that the prepared beads were spherical in nature. The effects of crosslinking agent and polymer concentrations on the release of drug were studied. With increase in concentrations of crosslinking agent and polymers, a decreased drug release was observed. The release data were fitted to an empirical equation to calculate the release mechanism. Drug release followed non-Fickian mechanism. Thus the prepared microbeads are useful carriers for controlled release of ketoprofen

INTRODUCTION

Ketoprofen is a widely used non-steroidal anti-inflammatory drug (NSAID) in the treatment of musculoskeletal and joint disorders. It is readily absorbed from the gastro-intestinal tract and exhibits a short biological half life of 2 h. When administered orally, it causes certain gastric side effects like gastric irritation, ulceration, hemorrhage etc. The shorter biological half life and associated side effects make the ketoprofen a suitable candidate for controlled release formulations [1]. However, when compared to single unit-dosage forms, multi-unit controlled release dosage forms like microbeads and microparticles pass through the gut as if a solution avoiding the vagaries of gastric emptying and different transit rates, release drugs more uniformly in a predictable manner and spread over a large surface area preventing exposure of the absorbing site to high drug concentration on chronic dosing [2-5]. Multiple units can be filled into hard gelatin capsules or they can be compressed into tablets [6].

Polymeric hydrogels are three-dimensional cross-linked networks that have the ability to absorb water and swell without losing their shape [7]. 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) [8, 9]. Hydrogels have been widely used in medicine and pharmacy as controlled delivery devices of various active materials [10-12].

Author for Correspondence:
Email: pharma_75raghu@yahoo.com

Recently, much research has been focused on the development of multi-unit controlled release systems using natural hydrophilic polymers as they are easily available. However, there is no report on the gellan gum (GG) based hydrogel microbeads for prolonged release of ketoprofen.

The present work is aimed at the development and evaluation of gellan gum based hydrogel microbeads for the prolonged release of ketoprofen by ionotropic gelation method.

MATERIALS AND METHODS

Ketoprofen (KP) was obtained as gift sample from Rhone-Poulenc, (Mumbai, India) Gellan gum (GG), calcium chloride dihydrate 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 microbeads

An accurately weighed quantity of ketoprofen was dispersed in an aqueous solution of GG and mixed homogeneously using magnetic stirrer. Twenty milliliters of dispersion was extruded in the form of droplets into 100 ml aqueous solution of $CaCl_2$ solution using 25 ml hypodermic syringe through a needle (number 23). The beads were removed after the gelation period of 30 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^{O}C for 10 h [13]. The composition of beads is given in Table 1.

Table 1: Composition of microbeads

Code	GG (% w/v)	Ketoprofen (% w/w of dry polymer)	$CaCl_2$ (% w/v)
G1	1.0	20	3
G2	1.5	20	3
G3	2.0	20	3
G4	2.0	20	6
G5	2.0	20	9
G6	2.0	40	9

Scanning electron microscopic studies (SEM)

The microbeads 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 X70 and X200 magnifications at room temperature.

Measurement of bead size

The microbead size was measured using a digimatic micrometer (MDC-25S Mitutoyo, Japan) having an accuracy of 0.001 mm. The average diameter of the 100 beads per batch was measured [13].

Estimation of drug entrapment efficiency (DEE)

Known amount of microbeads 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 supernant solution was analyzed for the drug content using UV-visible spectrophotometer (Model Pharmaspec UV-1700, Shimadzu, Japan) at 260 nm. The entrapment efficiency was calculated using the following equation [14]:

$$DEE = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100 \quad \ldots\ldots (1)$$

Dynamic swelling study

The dynamic swelling behavior of the microbeads 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 [15].

***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 microbeads 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 analyzed using UV-visible spectrophotometer at a λ_{max} of 260 nm with suitable dilutions [13].

RESULTS AND DISCUSSION

The obtained microbeads were spherical in shape having rough and dense surface with microscopic cracks on the surface as evidenced by SEM (Fig.1) and they fell in the size range of 812 to 1452 µm (Table 2). As the concentration of $CaCl_2$ was increased, smaller beads were produced and on the other hand, by increasing the concentrations of GG and drug in the microbeads, an increase in size of the beads was observed. Table 2 shows that drug entrapment efficiency (DEE) of the beads prepared with lower concentration of $CaCl_2$ was lowest as compared to those prepared with higher concentration of $CaCl_2$.

The Fig. 2 depicts dynamic swelling behavior of microbeads 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 GG and extent of crosslinking in the beads. It was observed that swelling of the beads increased with an increasing amount of GG in the beads and swelling decreased with an increasing amount of $CaCl_2$. 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.

The release profile of ketoprofen from microbeads is shown in Fig.3. The beads which were prepared with higher concentration of $CaCl_2$ released the drug more slowly because increase in concentration of the gel forming ions provided increased rigidity of the network due to increased cross-link density. On the other hand, increase in concentration of GG the in formulations resulted in decreased drug release, which may be due to increased diffusional path length for drug penetration.

Table 2: Average bead size, drug entrapment efficiency (DEE), diffusion coefficients (D) and release parameters (n) of the microbeads

Beads	Average size (µm)	DEE (%)	*D* (cm^2/s)	*n*	*r**
G1	812 ± 2.15	52.71 ± 0.46	5.12×10^{-4}	0.56	0.981
G2	1276 ± 2.87	54.85 ± 0.85	4.98×10^{-4}	0.59	0.987
G3	1452 ± 4.46	56.45 ± 0.62	4.01×10^{-4}	0.62	0.994
G4	1342 ± 6.70	62.89 ± 0.75	3.15×10^{-4}	0.66	0.989
G5	1198 ± 5.52	70.46 ± 0.35	2.42×10^{-4}	0.73	0.986
G6	1264 ± 1.78	75.56 ± 0.95	2.95×10^{-4}	0.64	0.991

*r** values indicate correlation coefficients

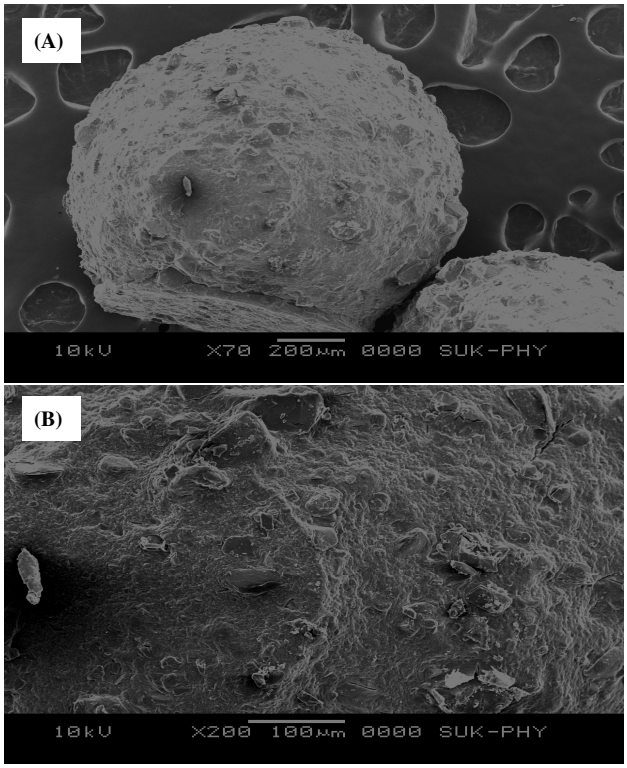

Figure1. SEM photographs of single microbead (A) and its surface morphology (B).

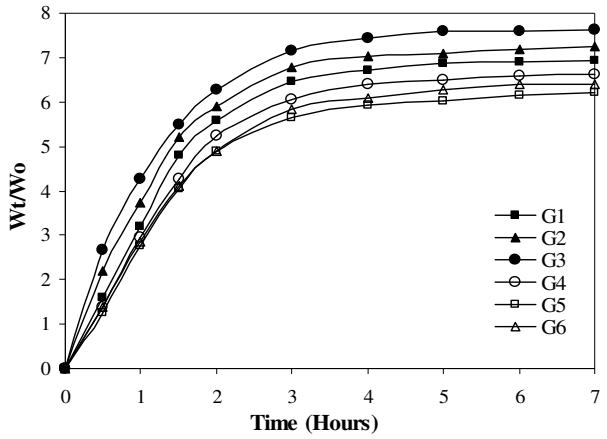

Figure 2: Effect of polymer concentration and crosslinking agent on swelling behavior of microbeads

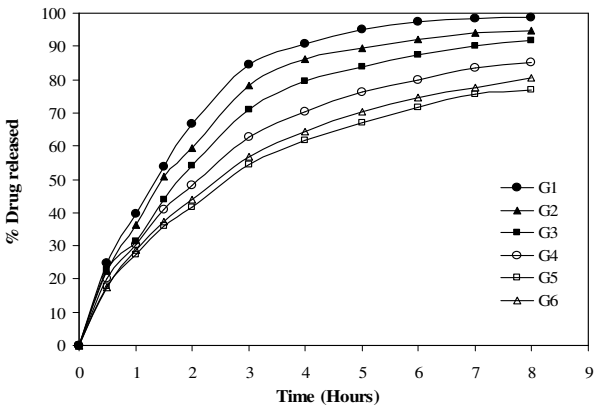

Figure 3: *In-vitro* release profiles of ketoprofen from microbeads

An increase in initial drug loading also increased the drug release. To understand the drug release mechanism in the hydrogel network, release data was fitted to an empirical equation [16]:

$$\frac{Mt}{M\infty} = Kt^{n} \qquad \ldots\ldots\ldots (2)$$

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 GG concentration; the *n* values increase with increase in cross-link density and GG concentration. Calculated *n* values suggested that the mechanism of drug release followed non-Fickian transport.

CONCLUSION

The gellan gum based hydrogels microbeads were prepared by ionotropic gelation method for the controlled release of ketoprofen. The swelling of beads and drug release depends upon the polymer concentration and extent of crosslinking in the hydrogel matrix. Drug release followed non-Fickian mechanism. This work demonstrates the feasibility of preparing multiparticulate drug delivery system for controlled release of ketoprofen.

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REFERENCES

[1] Palmieri GF, Bonacucina G, Di Martino P, Martelli S. Gastro-resistant microspheres containing ketoprofen. J Microencapsul. 2002 Jan-Feb;19(1):111-9

[2] Setty CM, Sahoo SS, Sa B. Alginate-coated alginate-polyethyleneimine beads for prolonged release of furosemide in simulated intestinal fluid. Drug Dev Ind Pharm. 2005 May;31(4-5):435-46.

[3] Tamilvanan S, Sa B. Studies on in vitro release behaviour of indomethacin-loaded polystyrene microparticles. Int J Pharm. 2000 May 25;201(2):187-97.

[4] Halder A, Sa B. Preparation and in vitro evaluation of polystyrene-coated diltiazem-resin complex by oil-in-water emulsion solvent evaporation method. AAPS PharmSciTech. 2006 May 26;7(2):E46.

[5] Halder A, Mukherjee S, Sa B. Development and evaluation of polyethyleneimine-treated calcium alginate beads for sustained release of diltiazem. J Microencapsul. 2005 Feb;22(1):67-80.

[6] Galeone M, Nizzola L, Cacioli D, Mosie G. In vitro demonstration of delivery mechanism from sustained release pellets. Curr Ther Res. 1981; 29: 217-234.

[7] Kulkarni RV, Sa B. Electrically responsive smart hydrogels in drug delivery: A review. J Appl Biomater Biomech. 2007; 5: 125-139.

[8] Siegel RA. Hydrophobic weak polyelectrolyte gels: Studies of swelling equilibria and kinetics. Adv Polym Sci. 1993; 109: 233-239.

[9] Yao KD, Peng T, He YY. Swelling kinetics and release characteristics of crosslinked chitosan:polyether polymer

network (semi-IPN) hydrogels. J Polym Sci. Part A. 1994; 32: 1213-1223.

[10] Kulkarni RV, Sa B. Novel pH-sensitive interpenetrating network hydrogel beads of carboxymethylcellulose-(polyacrylamide-grafted-alginate) for controlled release of ketoprofen: preparation and characterization. Curr Drug Deliv. 2008 Oct;5(4):256-64.

[11] Kulkarni RV, Sa B. Enteric delivery of ketoprofen through functionally modified poly(acrylamide-grafted-xanthan)-based pH-sensitive hydrogel beads: preparation, in vitro and in vivo evaluation. J Drug Target. 2008 Feb;16(2):167-77.

[12] Kulkarni RV, Sa B. Evaluation of pH-sensitivity and drug release characteristics of (polyacrylamide-grafted-xanthan)-carboxymethyl cellulose-based pH-sensitive interpenetrating network hydrogel beads. Drug Dev Ind Pharm. 2008 Dec;34(12):1406-14.

[13] Kulkarni RV, Sa B. Polyacrylamide-grafted-alginate based pH-sensitive hydrogel beads for delivery of ketoprofen to the intestine: *In vitro* and *in vivo* evaluation. J Biomater Sci. 2009; 20: 235-253.

[14] Boppana R, Kulkarni RV, Mutalik SS, Setty CM, Sa B. Interpenetrating network hydrogel beads of carboxymethylcellulose and egg albumin for controlled release of lipid lowering drug. J. Microencaps. 2009; In press.

[15] Boppana R, Kulkarni RV, Setty CM, Kalyene NV. Carboxymethylcellulose-aluminum hydrogel microbeads for prolonged release of simvastatin. Acta Pharm Sci. 2009; In press.

[16] Ritger PL, Peppas NA. . A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. J Control Release, Vol. 5, No. 1. (June 1987), pp. 37-42.