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Research Article

Preparation and characterization of Cefadroxil loaded alginate microbeads

Sowjanya Battu*[1], R. Indira Prasanna[1], K. Jyothshna Devi[2], Narayana Swamy[1], C. Madhusudhana Chetty[1], M. Purushothaman[3], K. Gnanaprakash[1]

[1] Department of Pharmaceutics, Annamacharya College of Pharmacy, Rajampeta - 516 126, Kadapa Dist., Andhra Pradesh, India

[2] Department of pharmaceutics, Sri Venkateshwara University, Tirupathi, Chitoor Dist., Andhra Pradesh, India

[3] Department of Pharmaceutics, Vasavi College of Pharmacy, Bakrapeta - 516 126, Kadapa Dist., Andhra Pradesh, India

ABSTRACT

Cefadroxil is a broad spectrum antibiotic that acts against an extensive variety of bacteria, including Gram-positive and Gram-negative bacteria. The major drawback of orally administered drug like cefadroxil is its shorter half life of 1.2 hrs. The goal of the study is to prolong the drug release, producing a desired blood serum level, reduction in drug toxicity and improving the patient compliance by prolonging the dosing intervals. The present research highlights the formulation and evaluation of cefadroxil loaded microbeads using polymers such as carbopol and sodium carboxy methyl cellulose while sodium alginate being the common polymer with a cross linking agent being calcium chloride. The beads were prepared by "Ionotropic gelation technique" and characterized for its particle size shape, micromeritic properties, percentage drug loading, percentage drug entrapment efficiency, swelling ratio and *In vitro* drug release studies. The release studies were obtained up to 12 hrs from 3 batches. The *in vitro* release data were fit to different equations and kinetic models to explain release profiles. The kinetic models used were zero order, Higuchi's and Peppa's. The correlation coefficient value (r) indicates the kinetic of drug release was zero order and the mechanism of drug release was found to be super case II transport.

Keywords: Cefadroxil; Ionotropic gelation technique; Carbopol 934; Sodium alginate; Sodium carboxy methyl cellulose.

INTRODUCTION

Novel drug delivery technology is one of the frontier areas of research in the field of science and technology. Considerable attention is focused on the development of controlled drug delivery systems (Majeti N et al., 2000,) offering the advantages of better therapeutic efficacy and easier to comply with than the conventional regimens requiring more frequent dosing (Sachan NK et al., 2006).

An ideal drug delivery system should release the drug in the right compartment at the rate required for a specific treatment. Most available drug delivery system use biodegradable, biocompatible and natural biopolymers (Bodmeier R et al.,2001) and are capable of rate and (or) time controlled drug release. Considerable research effort is being spent on oral sustained drug delivery system with majority of this system being solid dosage form (Lauwo JAK et al., 1990). Beads loaded with antibiotics would be useful for oral delivery to treat gastric diseases such as peptic ulcers, ulcerative colitis, infections of the intestine etc. Sodium alginate is widely used in various fields of application due to its remarkable mechanical and hydrogel forming properties (Kikuchi A et al., 1997). Sodium carboxy methyl cellulose, a mucoadhesive, semi synthetic polymer and carbopol 934, a mucoadhesive, synthetic polymer were used in combination with sodium alginate (M.A. Altaf et al., 2008) to study the impact of drug release. Cefadroxil, a semi synthetic 1st generation cephalosporin antibiotic Inhibiting cell wall biosynthesis, is used especially in the treatment of respiratory and urinary tract infections with a very short biological half life of about 1.2 hrs (Francesco la rosa et al., 1982).In the present study , an attempt has been made to formulate cefadroxil loaded microbeads by Ionotropic gelation technique. These beads were characterized for its particle size and shape, Drug Content, %Drug loading, %Drug encapsulation efficiency, swelling index, water uptake studies, gel fraction, invitro drug release studies. An attempt was also made to understand the mechanism involved in the release kinetics of these microbeads.

* Corresponding Author
Email: dazlingdude.s@gmail.com
Contact: +91- 9703239351
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MATERIALS AND METHODS

Cefadroxil was purchased from Drugs India, Hyd, Sodium alginate, calcium chloride (2 %) was obtained from ANCP, Rajampet, Sodium carboxy methyl cellulose and Carbopol 934 was purchased from Sri Lakshmi enterprises, Bangalore. All other chemicals used in this present study were of analytical grade.

Formulation of cefadroxil loaded microbeads

Cefadroxil loaded microbeads were prepared by ionotropic gelation technique (Lim LY et al., 1997). An aqueous solution of desired concentration (1% W/V) of sodium alginate was prepared using distilled water with vigorous stirring and heating to form a solution. To this solution a known quantity of the drug (1 g) was added and stirred continuously until a uniform suspension was obtained. Then the suspension was extruded into a beaker containing calcium chloride (2 %) solution using a 5 ml hypodermic syringe with 18 gauze needle and stirred at 100 rpm for 10 mns. After this, the beads were washed with distilled water and allowed to solidify for a period of 30 minutes and dried at room temperature for 24 hrs and then performed the evaluation studies.

Table 1: The composition of microbeads using cefadroxil

Ratio	Formulation Code	Sodium alginate	SCMC	Carbopol 934
1:1	CM I	1%	-	-
1:1	CM II	1%	1%	-
1:1	CM III	1%	-	1%

EVALUATION

Micromeritic properties

Angle of repose (θ^0) by funnel method : Microbeads of known weight were taken and allowed to pass through the funnel in a jet after completely pouring the beads into the funnel by closing the other end and is calculated using the formula,

$$\theta = \tan^{-1} h / r$$

Where, θ = Angle of Repose.
h = Height of the heap.
R = Radius of the base of the heap.

Bulk density, tapped density (g/cc) and Carr's index (%): Determined by taking known weight of the microbeads in a measuring cylinder (bulk volume) and tapped for 100 times (tapped volume) and finally Carr's index (%) is also calculated.

$$BD = \frac{\text{Mass}}{\text{Bulk volume}} \times 100$$

$$TD = \frac{\text{Mass}}{\text{Tapped volume}} \times 100$$

$$\%\ CI = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

Where, BD is bulk density

TD is tapped density

Particle size and shape using SEM analysis

The morphology and surface of the microbeads were observed using scanning electron microscopy. The dry microbeads samples were dispersed over metallic studs and coated with platinum and observed in micrometer range.

Drug content (mg)

100 mg microbeads were powdered and transferred into a 100 ml volumetric flask and the volume was made upto the mark with 7.4 pH phosphate buffer and kept aside for 12 hrs with occasional shaking and filtered. Then the absorbance was analysed spectrophotometrically at 263 nm. Three determinations were carried out for each formulation. The drug content was calculated by using the formula;

Drug content = concentration × dil factor × conversion factor × amt. of stock sol.

Drug loading (%) (DL)

The amount of cefadroxil loaded in microbeads was determined by the following formula.

$$\%\ DL = \frac{\text{Weight of drug in NP's}}{\text{Total weight of NP's taken}} \times 100$$

% Encapsulation efficiency (EE)

The amount of cefadroxil entrapped within microbeads was determined by the following formula

$$\%\ EE = \frac{\text{Practical Drug Loading}}{\text{Theoretical Drug Loading}} \times 100$$

Table 2: Evaluation parameters of prepared microbeads

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	Carr's index	% Drug loading	% Encapsulation efficiency
CM I	0.56 ± 0.005	0.68 ± 0.011	27° 24″± 0.12	14.5 ± 0.057	40.8 ± 0.2	81.2 ± 0.104
CM II	0.58 ± 0.018	0.66 ± 0.01	27° 34″ ± 0.05	15.4 ± 0.152	40.5 ± 0.16	80.5 ± 0.28
CM III	0.58 ± 0.01	0.65 ± 0.005	27° 12″ ± 0.26	14.68 ± 0.12	43.8 ± 0.12	87.2 ± 0.37

Swelling Ratio (Kockish S et al., 2004**)**

A known weight of microbeads were placed in a test tube containing 10 ml of o.1 N HCl buffer and 7.4 pH phosphate buffer at 37 ± 0.5˚ C with occasional shaking. The microbeads were periodically removed, blotted with filter paper and their changes in weights were measured during the swelling unit equilibrium was attained. Finally the weight of the swollen microbeads was recorded after a time period of 4 hrs and the swelling ratio (SR) was then calculated using the formula,

Table 4: The in vitro drug release studies

S.No	Formulation Code	% Cumulative drug release at 12th hour
1	CM I	88.2% ± 1.1%
2	CM II	77% ± 1.2 %
3	CM III	72% ± 0.9 %

Table 3: Results for swelling studies of prepared microbeads

F.Code	Initial weight of microbeads (mg)	Final weight after 4 hrs in 1.2 pH HCl (mg)	Final weight after 4 hrs in 7.4 pH phosphate buffer (mg)
CM I	50	55 ± 0.5	58 ± 0.57
CM II	50	59 ± 0.48	62 ± 0.49
CM III	50	47 ± 0.5	67 ± 0.5

1a **1b**

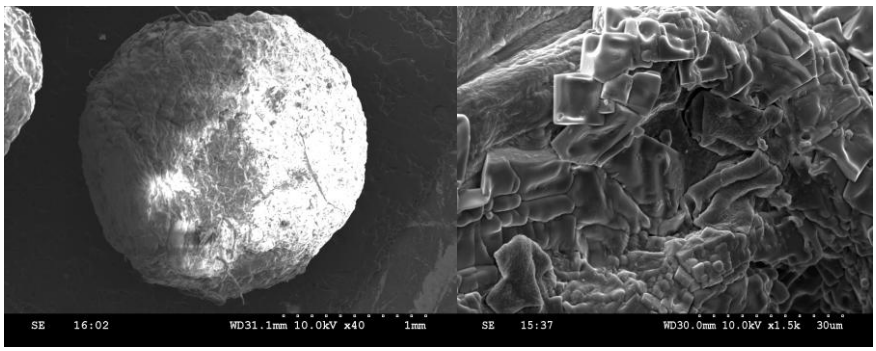

Figure 1: SEM analysis for CM III microbeads

Figure 1a: size and morphology of CM III Microbead; Figure 1b: drug –polymer matrices of CM III Microbead

$$\text{Swelling ratio (SR)} = \frac{W_s - W_o}{W_o}$$

Where, W_o = initial weight of dry microbeads

W_s = swollen weight of microbeads at equilibrium

In vitro drug release studies

The cefadroxil loaded polymeric microbeads, equivalent to 250 mg of cefadroxil were suspended in a modified dialysis membrane (muslin cloth). This membrane was tied to the paddle of USP dissolution apparatus II containing 1.2 pH HCl buffer (gastric pH) for first two hours (to ensure the absence of drug release in gastric pH) and later in 7.4 pH Phosphate buffer (intestinal pH) for 10 hrs (simply the beaker containing gastric medium was replaced with intestinal medium and the paddle holding the same formulation used for first two hrs was dipped) operating under the standards of 37°C Temp., at 50 rpm. The samples were collected at specified time interval and analyzed at 263 nm after suitable dilutions if necessary using UV Spectrophotometer.

Table 5: Diffusion characteristics of cefadroxil microbeads

Formulation code	Correlation coefficient values (r)		Diffusion exponent value (n)
	Zero order	Peppas model	
CM I	0.9973	0.9711	0.9977
CM II	0.9973	0.9983	0.9984
CM III	0.9939	0.8977	0.9942

RESULTS AND DISCUSSION

Cefadroxil microbeads were prepared by ionotropic gelation technique with different combinational polymers such as carbopol 934 and sodium carboxy methyl cellulose using sodium alginate in common. The prepared microbeads were found to be discrete and free flowing.

SEM Analysis

The micrographs of cefadroxil microbeads re as shown in fig 1 and 2 and they indicate that the microbeads were almost spherical , discrete and covered conti-

nuously with the polymers and their size was found to be in the range of 0.75 ± 1.5 to 0.84 ± 1.1 mm diameter.

Drug content and % Encapsulation Efficiency

The drug content of microbeads determines the amount of drug entrapped in the microbeads. The drug loading estimated in 100 mg microbeads was found to be in the range of 40 ± 0.2 to 43 ± 0.12 mg in phosphate buffer. The encapsulation efficiency determines the percentage of encapsulated drug with respect to the total drug introduced into polymer solution. The encapsulation efficiency ranged from 81 % ± 0.104 to 87 % ± 0.37.

Swelling ratio

Swelling studies of the prepared microbeads were carried out in both 1.2 and 7.4 pH buffer solutions and found that the microbeads showed higher swelling ratio value in pH 1.2 after 4 hrs than that in pH 7.4 medium.

***In vitro* dissolution studies**

In vitro drug release studies of various formulations are shown in fig 3. The drug from microbeads showed sustained drug release over a period of 12 hrs. The release rate was increased due to the decrease in the size of the particle as well as due to the increase in the composition of polymer coating i.e., combinational polymers. The percentage drug released from the microbeads CM I, CM II and CM III were found to be 88.2 %, 77 % and 72 % respectively after 12 hrs and the release may be extended further (Rajaonarivoy M et al., 1993) (Takka S et al., 1999).

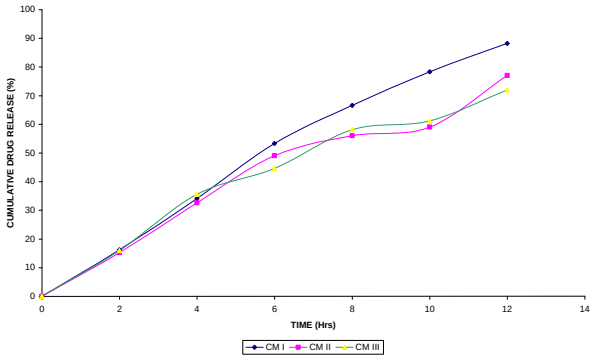

Figure 2: In vitro drug release profile for prepared cefadroxil microbeads

The obtained results in these formulations were plotted in various model treatment are as follows. i.e., Cumulative percentage release of drug Vs Square root of time (Higuchi's) and Log cumulative percentage release Vs Log time (Peppas). The formulations CM I to CM III comparative plotted graphs of Higuchi's and Peppas were shown in the Fig. 2 and 3 respectively. To find out the mechanism of drug release from hydrophilic matrices, the *invitro* dissolution data of each formulation

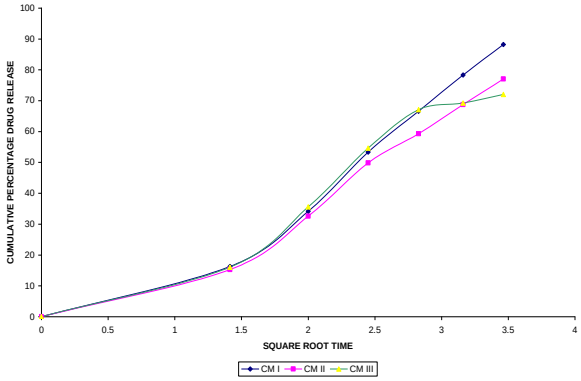

Figure 3: Higuchi's Pot for prepared cefadroxil microbeads

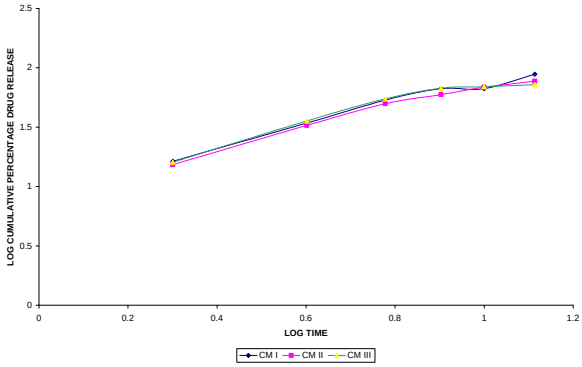

Figure 4: Peppa's Plot for prepared cefadroxil microbeads

with different kinetic drug release equations. Namely Zero order: Q=K0t; Higuchi's square rate at time: Q=KHt1/2 and Peppas: F=Kmtn, where Q is amount of drug release at time t, F is Fraction of drug release at time t, K0 is zero order kinetic drug release constant, KH is Higuchi's square root of time kinetic drug release constant, Km is constant incorporating geometric and structural characteristic of the films and n is the diffusion exponent indicative of the release mechanism. The correlation coefficient values (R) indicate that the kinetics of drug release was zero order and the mechanism of drug release by peppas model indicates the super case II transport evidenced with diffusion exponent values (n).

CONCLUSION

In the present work cefadroxil microbeads were formulated using sodium alginate as a common polymer in combination with other two polymer compositions which allows the drug to be released slowly than a single polymer coated microbeads. Thus this work differs from other works carried out using the same method and different drugs. The drug release from CM III was found to be only 72 % after 12 hrs and shows release further. It showed particle size of 0.75 ± 1.5 mm with spherical shape and drug loading and entrapment efficiency of about 43.8 ± 0.12 % and 87.2 ± 0.37 % respectively. Since the drug release from the third formula-

tion is slow and showed best results for all the other evaluation parameters, we conclude the formulation coded CM III is the best composition which follows Zero order kinetics and super case II transport mechanism.

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