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DESIGN AND IN-VITRO CHARACTERIZATION OF GASTRORETENTIVE SYSTEM OF CEFPODOXIME PROXETIL TO IMPROVE BIOAVAILABILITY: EFFECT OF CROSSLINKING AGENT AND POLYMER ON ENTRAPMENT EFFICIENCY AND DRUG RELEASE

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ABSTRACT

Cefpodoxime proxetil,an oral 3rd generation Cephalosporin antibiotic has low bioavailability about 50% also having short biological half life about 2-3 hours. The main objective of this study is to evaluate the potential of floating gellan gum beads as a drug carrier for Cefpodoxime proxetil, to prolong gastric residence time of drug in its absorption window. Floating beads were prepaed from Gellan gum solution containing $CaCO_3$ as gas-forming agent. The beads were prepared by ionotropic gellation technique.In order to overcome the limitation of drug leaching during preparation, and to have improved sustained release characteristics, gellan gum beads were prepared with the addition of polymers like 0.5% Hydroxy propyl methyl cellulose (HPMC). The prepared beads were evaluated for percentage drug loading, entrapment efficiency, and in vitro release characteristics to know the effect of addition of these polymers and the addition of $CaCO_3$ and crosslinking agent . The prepared beads showed improved percentage drug loading, it also exhibited sustained drug release in the pH 1.2. So these floating gellan gum beads may act as a promising carrier for to Cefpodoxime proxetil improve its oral bioavailability.

INTRODUCTION

The increased interest in developing oral controlled release dosage forms can be attributed to their ability to maintain an effective drug concentration in the systemic circulation for a long time and offering improved therapeutic advantages such as ease of dosing administration, patient compliance, flexibility in formulation. However, the short gastric retention time and unpredictable rapid gastric rate can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to decreased therapeutic efficacy of administered dose[1].

The major absorption zone, stomach or upper part of intestine, can result in incomplete drug release from the drug delivery system leading to diminished efficacy of the administered dose. Therefore, localizing the drug delivery in a specific region of the gastrointestinal tract due to its mucoadhesiveness increases the intimacy and duration of contact between the drug containing polymer and the mucous surface. Such a drug delivery system offers numerous advantages, especially for drugs exhibiting an absorption window or for drugs with a stability problem in the stomach. Overall, the intimate and prolonged contact of the drug delivery system with the absorbing membrane has the potential to maximize the rate of drug absorption [2,3]. In this study, calcium carbonate was used as gas-forming agent, dispersed in a gellan matrix. The calcium carbonate present in the formulation, releases carbon dioxide in the gastric environment, thereby making the formulation buoyant, thus prolonging the residence time. The floating gellan beads are multiple-unit systems which may be more advantageous than single-unit systems by avoiding "all or-none" emptying from the stomach during migrating myoelectric complex (MMC) motility of the stomach.[4]. Gellan gum is a bacterial exopolysaccharide commercially prepared by aerobic submerged fermentation of *Sphingomonas elodea*. There are two chemical forms of gellan gum: native or natural form, which has high acyl contents, and low or deacetylated form [5]. The gelling mechanism of gellan can be induced by cations and is temperature dependent. In aqueous solution, the gelation of gellan is accompanied by a two-step process, namely, formation of double helices from random coil chains and an aggregation of pairs of double helices[6]. The coil–helix transition is greatly affected by electrostatic interaction with cations present in the solution. Gellan forms gels in the presence of monovalent (Na^{+}, K^{+}) and divalent cations (Ca^{2+}, Mg^{2+}) but its affinity for the latter is much stronger than for the former.

Cefpodoxime proxetil (CP) is a prodrug of the third generation cephalosporins, which is broad-spectrum antibiotic and is administered orally. In human, the absolute bioavailability of cefpodoxime proxetil administered as a 130mg tablet (equivalent to 100mg of cefpodoxime) is about 50% [7]. Reported studies have pointed possible reasons for low bioavailability as: low solubility, typical gelation behavior of CP particularly in acidic environments [8-10].It has been reported that the absorption of cefpodoxime proxetil is optimum at low pH [11]. Also the drug has only 2 to 3 hours half life.

In the present study it is intended to formulate and evaluate the floating multiparculate drug delivery system for increasing the bioavailability of cefpodoxime proxetil. Formulation of Floating beads containing cefpodoxime proxetil as a drug candidate which would remain in stomach and/or upper part of GIT for prolonged period of time thereby maximizing the drug release at desired site within the time before Gastroretentive floating drug delivery system (GRFDDS) left the stomach and /or upper part of GIT.

Gastroretentive floating drug delivery system (GRFDDS) will also greatly improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at the gastric mucosa, which are sustained over a long period of time.

MATERIALS AND METHODS

Materials

Cefpodoxime proxetil was obtained as a gift sample from Aurobindo Pharma Limited ,Hyedrabad, Gellan gum obtained as a gift sample from CP kelco,UK Ltd.All other reagent were of Analytical grade.

Methods

Preparations of Floating beads of Cefpodoxime proxetil:

The beads, whose composition is shown in Table 1, were prepared by ionotropic gelation technique with some modification. Gellan solution (0.5-1.5 % w/v) was prepared by dissolving gellan in deionized water at 90 °C with stirring.The drug, Cefpodoxime proxetil, and Calcium carbonate were dissolved/dispersed uniformly in the gellan solution at or just below 40 °C with continuous stirring until a uniform dispersion was obtained. The bubble-free slurry (dispersion) was added dropwise into the gelation medium consisting of 100ml crosslinking medium of different concentration (calcium chloride) + 10 % v/v acetic acid with a 25 ml hypodermic

syringe through a 20 G needle into the gelation medium.with continuous stirring. For preparing Gellan gum / HPMC beads ,HPMC (0.5%) was added to drug/gellan gum/$CaCo_3$ solution and dropped in to cross linking solution . The medium was continuously stirred during bead formation to enhance the mechanical strength of the beads and also to prevent their aggregation. The beads were cured for 10 min, separated by filtration, and dried at 40 °C in a hot air oven.

Table 1: Formulation Design

Formulation code	Gellan gum (%W/V)	HPMC (%W/V)	$CaCo_3$ (%W/V)	$Cacl_2$ (%W/V)	Drug (mg)
U1	0.5	--	1.5	3	130
U2	0.75	--	2	4	130
U3	1.0	0.5	1.5	6	130
U4	1.5	0.5	2	6	130

Particle size analysis:

The size was measured using an optical microscope and the mean size was calculated by measuring 30 particles with the help of a calibrated ocular micrometer.

Percentage drug loading and Entrapment efficiency:

To determine the percentage drug loading and entrapment efficiency , accurately weigh 100mg beads were thoroughly triturated and suspended in a minimal amount of alcohol, suitably diluted with 0.1 HCl (pH 1.2) and filtered to separate . Amount of Cefpodoxime proxetil was analysed spectrophotometrically at 263 nm. Calculate Percentage drug loading and Entrapment efficiency using following formula.

%Entrapment efficiency =(Calculated drug conc. / Theoretical drug conc.) x 100.

% Drug loading = Amount of drug in bead / Amount of bead taken * 100

In vitro Drug Release:

In Vitro Drug Release Study was carried out by using USP II (Paddle type) apparatus, 900ml of 0.1N HCl as medium with 100 rpm rotation speed maintained at 37°C. Sampling was done for every one hour till 8 hrs. and analyzed at 263 nm by UV Spectrophotometer after suitable dilutions[12]. Cumulative percentage drug release was calculated.

Floating properties:

Floating properties of dry beads were analysed in the in SGF (pH 1.2). Temperature was maintained at 37^{o}C. The time taken for the beads to start float (floating lag time) and the time up to which the beads floated (floating time) was noted by placing fifty beads in the media.

RESULT AND DISCUSSION

Table 2: Physicochemical Characteristics of Prepared Floating Beads of Cefpodoxime proxetil

Formulation code	Bead size (Micro meter)	%drug loading	%entrapment efficiency	Floating lag time (second)	Duration of floating (hours)
U1	0.87	61.25	55.4	< 90	More than 12 hours
U2	0.93	75.50	70.8	< 90	More than 12 hours
U3	1.06	78.25	85.25	< 90	More than 12 hours
U4	1.10	82.56	89.20	< 90	More than 12 hours

Bead size:

The mean diameter of gellan beads are shown in Table 2. It has been observed that the diameter of beads increased significantly by increasing polymer Concentration. This could be attributed to increase in microviscosity of the polymeric dispersion due to increasing concentration of gellan, which eventually led to formation of bigger beads.

Effect of Gellan gum and HPMC:

The drug loading and entrapment efficiency increase from formulation U1 to U4 as concentration of gellan gum and HPMC increases.The reticular structure was formed which may lead to better entrapment efficiency.The formulation U1 and and U2 showed slight decrease in the drug loading and entrapment efficiency than U3 and U4.

***In Vitro* Drug Release:**

The *in vitro* drug release profiles of gellan floating beads with different polymer concentrations are shown in Figure 1 and 2. As the gellan concentration of the prepared floating beads increased, the rate and extent of drug release was decreased significantly . This could be attributed to increase of gellan matrix density and increase in diffusion path length which the

drug molecules have to traverse (by formation of bigger size of beads). The release of drug from these beads was characterized by an initial phase of high release (burst effect) due to good solubility of Cefpodoxime proxetil at low pH. However, as gelation proceeds (cross linking of gellan with Ca^{+2} ions from calcium carbonate), the remaining drug was released at a slower rate followed by a second phase of moderate release. This bi-phasic pattern of release is a characteristic feature of matrix diffusion kinetics.[13] The release from the formulation U3 and U4 was also in the sustained manner and this may be due to the formation of dense internal structure by HPMC in these beads.

Effect of Crosslinking agent:

The entrapment efficiency was found to be more in high calcium chloride concentration in batch U3 and U4 ,85.25% and 89.20% respectively shown in Table 2 The Effect of Crosslinking agent on Entrapment efficiency shown in figure 3 . This may be attributed to more cross linking, which will entrap high amount of drug. In the present study calcium chloride at three different concentrations (3, 4, 6 %w/v) were used. The results indicate that as the concentration of the cross-linking agent increased there was a significant decrease in the drug release shown in figure 4. The three-dimensional network by complexation with cations, decrease the porosity of gellan matrix thereby slowed down the drug diffusion from matrix.

***In vitro* floating properties:**

The *In vitro* floating properties of the prepared formulations was evaluated in SGF (pH 1.2). The time the formulation took to emerge on the medium surface (floating lag time) and the duration of floating time on medium surface were noted and are shown in Table 2. Upon contact with an acidic medium, gelation and cross linking by Ca^{+2} ions occurred to provide a gel barrier at the surface of the formulation. The calcium carbonate effervesced, releasing carbon dioxide and calcium ions. The released carbon dioxide is entrapped in the gel network, which is invariably a three dimensional network, producing a buoyant formulation. The floating time of the formulation mainly depends on calcium carbonate and gellan concentrations.The beads containing 1.5 and 2.0% of the gas-forming agent (calcium carbonate) demonstrated good floating lag time (<90 seconds) and duration of floating (more than 12 hours hours of floating).

Entrapment efficiency:

The effect of various formulation parameters on the Entrapment efficiency of prepared floating beads are shown in Table 2. Entrapment was found to be consistently higher for all the batches of beads prepared were found to be in the range of 55.4 to 89.20. Similar high Entrapment efficiencies were achieved for various model drugs having low solubility. However, the entrapment efficiency of beads increased progressively with increasing polymer concentration as shown in Table 2. This is because of increase in the gellan concentration resulted in the formation of larger size of beads entrapping more amount of the drug.

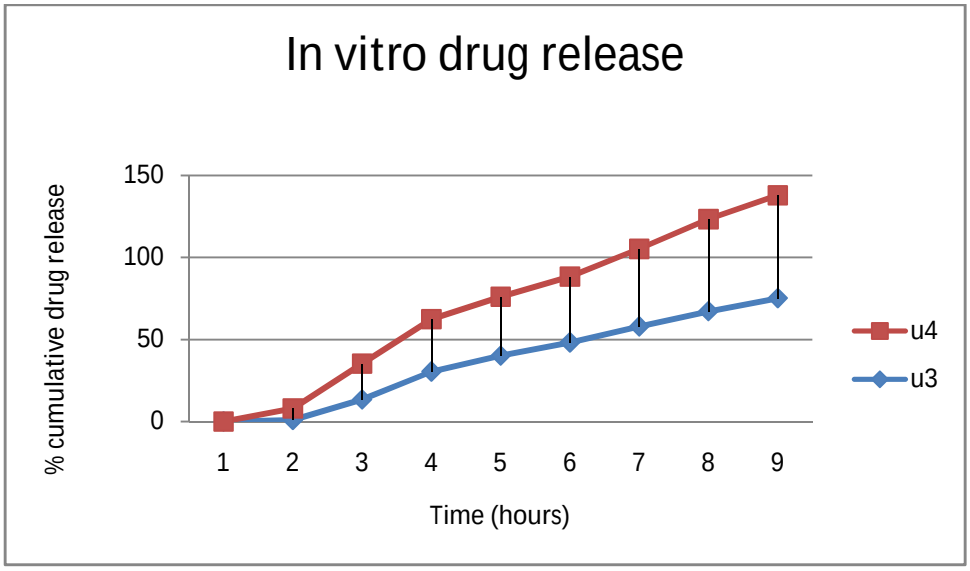

Figure 1: *In Vitro* Drug Release from formulation U3 and U4

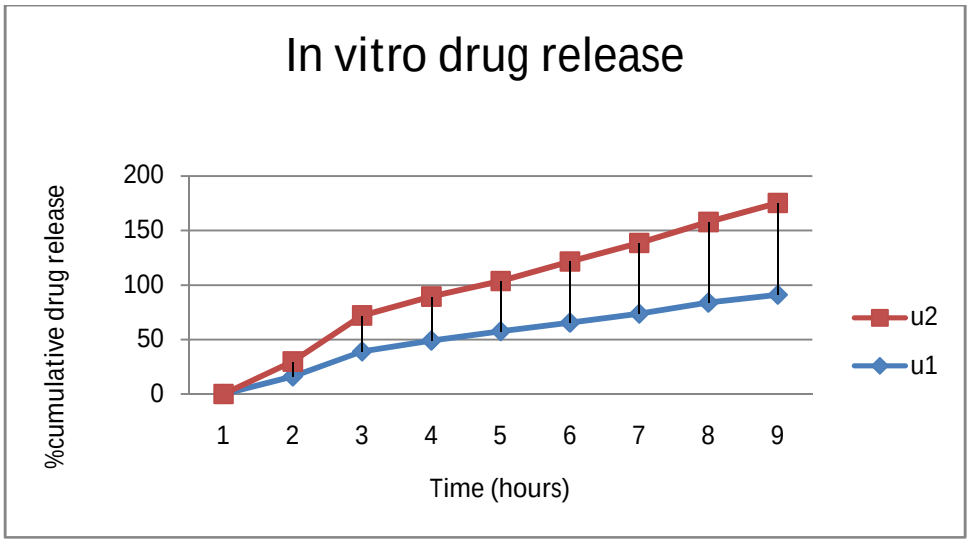

Figure 2: *In Vitro* Drug Release from formulation U1 and U2

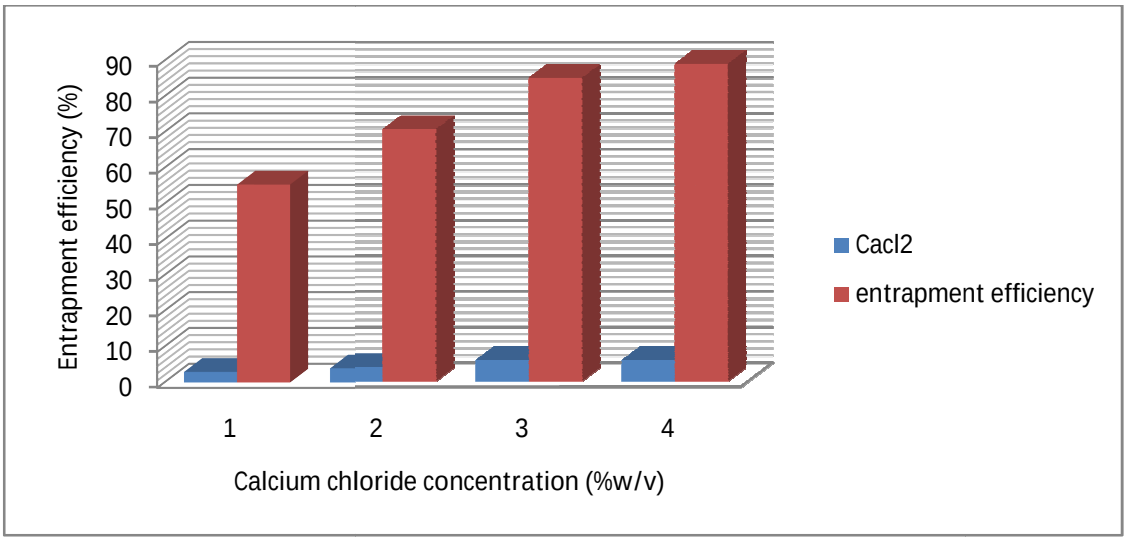

Figure 3: Effect of crosslinking agent on Entrapment efficiency

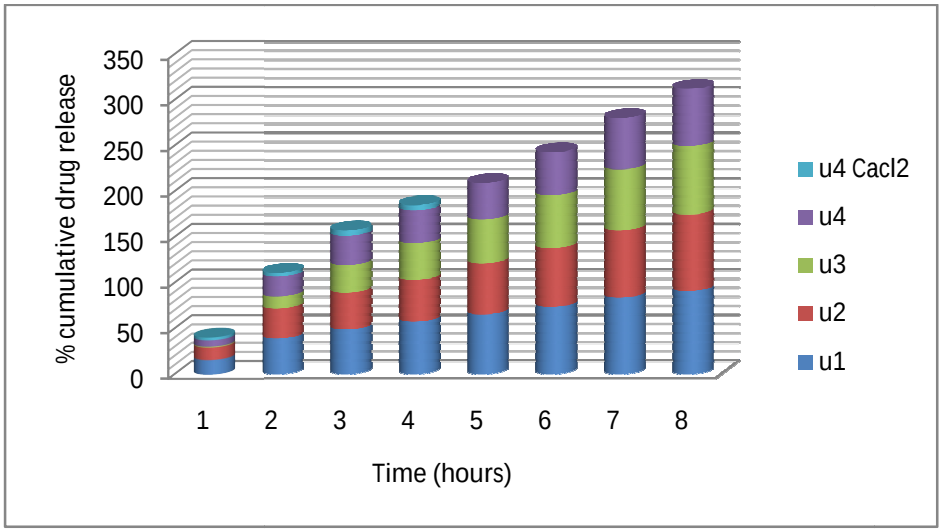

Figure 4: Effect of crosslinking agent on In vitro drug release

CONCLUSION

The effect of polymer and cross linking agent on *in vitro* release of Gellan gum beads was investigated. The results show that as the concentration of polymer and cross linking agent increases, entrapment efficiency increases and release rate decrease. The studies reveal that the beads exhibited sustained release characteristics. So this floating gellan gum beads may act as a promising drug carrier for Cefpodoxime proxetil.

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