International Journal of Pharmacy and Pharmaceutical Sciences
ISSN- 0975-1491 Vol 2, Suppl 3, 2010

Research Article

DESIGN AND EVALUATION OF GASTRORETENTIVE BEADS OF THEOPHYLLINE BY IONOTROPIC GELATION

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Received: 09 April 2010, Revised and Accepted: 27 April 2010

ABSTRACT

A Gastroretentive bead of theophylline by ionotropic gelation was formulated in two different combinations such as sodium alginate along with guar gum and sodium alginate with hydroxy ethyl cellulose. The gas forming agent's calcium carbonate was also added in four different concentrations. The formulated beads were then evaluated for particle size, drug content, floating properties and *invitro* dissolution. The *invitro* release study showed about 98-99% of drug release at the end of 8 hrs with good buyoncy effect for the batch formulated with the combination of sodium alginate and guar gum. The *invitro* release mechanism was found to be analomous diffusion with first order kinetics.

Keyword: Gastroretentive, Theophylline, Ionotropic Gelation, Sodium Alginate, Guar Gum**,** Buoyancy, Hydroxy Ethyl Cellulose, Calcium Carbonate.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to a proper site in the body in order to promptly achieve and thereby to maintain the desired drug concentration[1]. A number of techniques have been used to produce sustained or controlled drug delivery systems. They include the use of barrier coating, embedding in slowly erodible matrix, skeleton type matrix, ion exchange resin, hydrophilic matrix, polymer resin beads, passage sponge formulation and chemical complexation[2, 3]. Also researchers developed various sustained release dosage forms by embedding the drug in agar and forming a gel. Beads loaded with antibiotics would be useful for oral delivery to treat gastric disease such as peptic ulcer and for the ulcerative colitis, carcinomas and infection of the intestine. In addition, sustained systemic absorption specifically in the intestinal region offers interesting possibility for the treatment of disease such as asthma, arthritis and inflammation[4].

Theophylline and its derivatives have been used for their bronchodilator properties in the management of asthma and Chronic Obstructive Pulmonary Disease (COPD). This drug has the elimination half-life of 3 to 4h and a narrow therapeutic range of 7-5µg to 20µg/ml. Once or twice daily administration of controlled release preparations in patients with COPD is recommended and improves patient's compliance[5, 6]. And also theophylline has pH dependent absorption i.e., an enhanced absorption on the acidic pH. As to improve the absorption of theophylline as well as sustain the release of theophylline in acidic pH a gastric retention dosage form could be ideal.

There are various approaches which have been worked out to improve the retention of an oral dosage form in the stomach, e.g. floating systems, swelling and expanding systems, modified- shape systems, bioadhesive systems, high density systems and other delayed gastric emptying device. Floating drug delivery systems (FDDS) or hydrodynamically balanced systems (HBS) have a bulk density lower than gastric fluids and therefore remains floating in the stomach unflattering the gastric emptying rate for a prolonged period. This leads to an increase in the gastric retention time and a better control over fluctuations in plasma drug concentration[7, 8].

Sodium alginate and guar gum (hydrocolloids) were used to prepare beads as sodium alginate and guar gum is naturally occurring polymer widely used in various formulations and HEC a synthetic polymer[9, 10]. Hence based on all the discussion we have planned to investigate the feasibility of the formulations such as to prepare gastro retentive beads by ionotropic gelation with the help of sodium alginate with HEC and also sodium alginate with guar gum as two different formulations. To find out whether varying the concentrations of calcium carbonate express any substantial effect on the *invitro* release and floating ability for the formulated beads.

MATERIALS

Theophylline was obtained as the gift sample from Tablets India Ltd., Chennai. Sodium alginate, guar gum, hydroxy ethyl cellulose was purchased from S.D. fine chemicals, Mumbai. Calcium chloride, calcium carbonate, acetic acid and ethanol used in the present study were of AR grade.

METHODS

Formulation of floating alginate micro beads

To the aqueous solution of sodium alginate (30%W/V) the drug theophylline (5%W/V) and guar gum (1%W/V) were added with continuous stirring. Then the gas forming agent such as calcium carbonate were added to the above solution in different concentration (0.25, 0.5, 0.75, 1%W/V). A batch without calcium carbonate was also prepared. These batches were named as FTAB-1, FTAB-2, FTAB-3, FTAB-4 and FTAB-5.

Table 1: Formulation chart

Formulation code	Sodium alginate (mg)	Hydroxy ethyl cellulose (mg)	Theophylline (mg)	Guar Gum (mg)	Calcium carbonate: sodium alginate
FTAB-1	900	100	200	-	0.25:1
FTAB-2	900	100	200	-	0.5:1
FTAB-3	900	100	200	-	0.75:1
FTAB-4	900	100	200	-	1:1
FTHB-5	900	100	200	-	-
FTHB-1	900	-	200	100	0.25:1
FTHB-2	900	-	200	100	0.5:1
FTHB-3	900	-	200	100	0.75:1
FTAB-4	900	-	200	100	1:1
FTAB-5	900	-	200	100	-

Similarly other formulation with the same method except the change which is the guar gum is replaced with 1%W/V hydroxyl ethyl cellulose (HEC). And these five different batches were named as FTHB-1, FTHN-2, FTHB-3, FTHB-4 and FTHB-5 [11, 12]. Table 1 shows the composition of different trials, which were undertaken for formulation. Then the prepared batches were extruded with help of 26G syringe needle to a beaker containing mixture of calcium chloride (1%W/V) and acetic acid (10%W/V) on continuous stirring with the help of a magnetic stirrer. The stirring was continued for further 10min and then beads were collected washed with distilled water and dried at room temperature 36 ± 2ºC [13]

Evaluation of theophylline microbeads

Particle size

About 50 micro beads were randomly picked up thrice and their size was measured by using vernier caliper.

Drug content

Four portions each containing 200 mg were randomly picked from the prepared samples and were crushed with help of mortar and pestle. Then it was stirred continuously for 3h with simulated gastric fluid (pH 1.2). After 3 h, the samples were filtered suitably diluted and estimated spectrophotometrically at 271nm. The estimation was done in 5 replicates to determine the uniformity of drug in micro beads [14].

Floating ability

The formulated sodium alginate micro beads containing guar gum and HEC were evaluated for its floating properties for 8h. The type II dissolution apparatus was used for the study and the medium was simulated gastric fluid pH1.2 with 100 rpm maintained at 37ºC. Fifty beads were placed in the media and the percentage of floating samples was measured by visual observation [15].

***Invitro* release studies**

The *invitro* release studies of prepared micro beads were carried out in simulated gastric fluid (pH 1.2) using USP XXII apparatus at 100 rpm maintained at a temperature of 37±1ºC for a period of 8h. At periodic time intervals 5ml of sample was withdrawn suitably diluted and absorbance was measured at 271nm [16].

RESULTS AND DISCUSSION:

The theophylline embedded sodium alginate with agar and HEC were prepared by extrusion method. Table 2 shows the uniformity of drug content with low coefficient of variation. The drug content in the micro beads was found to be in the range of 78 ± 0.7 to 84 ± 0.5mg. A random sample of 50 micro beads from each was taken and sizes were determination by using vernier caliper in triplicate. The size of the prepared micro beads was found to be in the range of 1.34 ± 0.7 to 2.70 ± 1.7 mm in diameter. The surface of the beads was found to be spherical and smooth in nature. On determination of the floating ability of the prepared beads, it was observed that about 80-90% of the guar gum sodium alginate beads were floating even at the end of 8hrs when compared with HEC sodium alginate beads. Here the matrixes were prepared in such a manner that when they come in contact with stomach fluid, carbon dioxide is generated and retain entrapment in the hydrocolloid gel. This leads to an upward drift of the dosage form and maintains it in a floating condition. And the batches prepared without calcium chloride did not show any floating ability. The *invitro* release of theophylline was studied in simulated gastric fluid pH 1.2 maintained at 37ºC for a period of 8hrs. About 95 to 99 % of drug release was observed with HEC sodium alginate beads at the end of 6 hrs. And in guar gum sodium alginate beads about 98 to 99% of drug was released at the end of 8 hrs. Theophylline release was faster from HEC beads with sodium alginate when compared with guar gum sodium alginate. On increasing the concentration of calcium carbonate the rate of release was also increased. In order to predict and correlate the release behavior of drug from the hydrophilic matrix it is necessary to fit in to a suitable model. Hence the dissolution data's were fitted according to the well know exponential equation (Peppas1983,) which is often used to describe the drug release behavior from polymeric system

$$M_t / m_\infty = k\, t^n$$

Where m_t/ m_∞ is the fractional release of the drug't' is the release time. Where m_t/m_∞, is the fractional release of the drug, 't' is the release time, 'k' is a constant which indicate the properties of the macromolecular polymeric system and 'n' is the release exponent indicative of the mechanism of release. The 'n' value used for analysis of the drug release mechanism from the theophylline sodium alginate beads was determined from log (m_t/m_∞) Vs log (t) plots[14]. To calculate release constant 'k', the logarithm of the remaining theophylline in beads is plotted versus time. The release of drug from the beads followed the first order kinetics for the period of 8hrs. The values of 'k', 'n' and 'r' for the 8 different batches are reported and the 'n' values was greater than 0.5 (Table: 3). The results of kinetics analysis revealed that the release of theophylline from sodium alginate beads along with HEC and guar gum followed analomous diffusion.

Table 2: properties of the prepared microbeads

S. No	Polymer	Formulation Code	Drug Content	Particle Size	Buoyancy Time (Hrs)
1.	HEC	FTAB-1	78±0.1	1.34±0.5	4
		FTAB-2	79±0.3	1.37±0.2	5
		FTAB-3	79±0.5	1.49±0.8	5
		FTAB-4	79±0.9	1.57±0.2	6
2.	GUAR GUM	FTHB-1	80±2.4	2.65±0.3	6
		FTHB-2	81±0.2	2.70±0.2	8
		FTHB-3	83±0.7	2.73±0.9	8
		FTHB-4	84±0.3	2.75±0.6	>8

*N= 3 ± Standard deviation

Table 3: *In vitro* release kinetics of the formulated theophylline microbeads

Formulation Code	*Invitro* Release Kinetics			
	First Order Plot		Peppa's	
	k	r^2	n	r
FTHB- I	0.1279	0.9938	0.6812	0.9944
FTHB- II	0.1012	0.9965	0.66445	0.9989
FTHB- III	0.1043	0.9962	0.6296	0.9921
FTHB- IV	0.0986	0.9954	0.6242	0.9977

*N= 4 ± Standard deviation

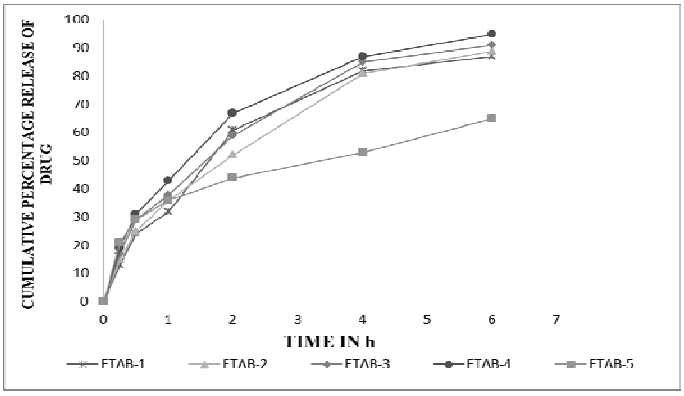

Fig. 1: *Invitro* drug release profile of sodium alginate and HEC containing theophylline in different ratios

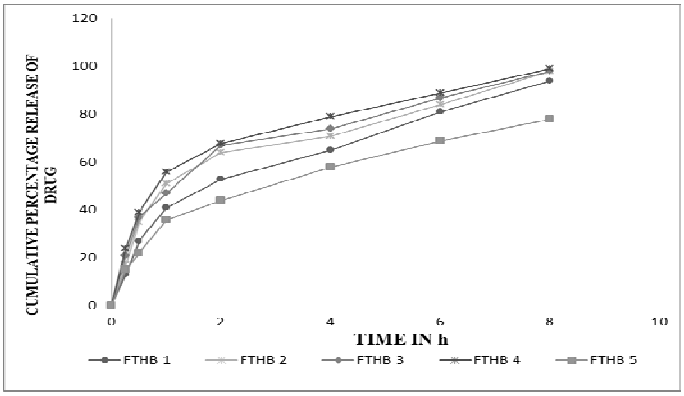

Fig. 2: *Invitro* drug release profile of sodium alginate and Guar gum containing theophylline in different ratios

CONCLUSION

Formulation and evaluation of sustained release guar gum sodium alginate microbeads containing theophylline was found to be potential, cost effective and satisfactory *invitro* release studies. In turn, it may enable to release the drug in a sustained manner for prolonged period of time and thereby accompanying some of the benefits like reduction in total dose frequency of administration, dose related side effects and better patient compliance.

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