Original article

Design and *in vitro* evaluation of controlled release alginate beads of diltiazem hydrochloride

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Abstract

Objective: Oral slow and sustained release drug delivery system can release their drug content with a controlled manner, producing a desirable blood serum level, reduction in drug toxicity and improving the patient compliance by prolonging dosing intervals. The major drawback of orally administered drug like diltiazem as a calcium channel blocker for the treatment of angina pectoris, arrhythmia and hypertension. Its has higher aqueous solubility and shorter elimination half-life. **Methods**: To overcome these drawbacks associated with diltiazem, an attempt has been made to develop a sustained release dosage form of diltiazem embedded alginate microbeads by ionotropic gelation technique employing various concentrations of polymer and keeping the drug concentration constant. **Results**: The beads were characterized for its particle size, drug content and *in vitro* release studies. The results revealed that the surface adhering drug was found to release immediately and a steady state of release was obtained up to 12 h from all the batches. The results indicated there was an inverse relationship between the concentration of alginate and drug release. The drug release was found to follow non-fickian diffusion obeying first order kinetics. **Conclusion**: The developed alginate microbeads offered a sustained release of diltiazem. Hence, the formulated microbeads were found to be potential, cost effective, possess satisfactory *in vitro* release studies.

Keywords: Sodium alginate; Diltiazem; Microbeads; Ionotropic gelation technique ; Peppa's model

INTRODUCTION

Ideally, a drug delivery system release the drug in the right body compartment at the rate required for a specific treatment. Most available drug delivery system use biodegradable, biocompatible and natural biopolymers 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[1,2]. 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 infections of the intestine. In addition, sustained systemic absorption specifically in the intestinal region offers interesting possibilities for the treatment of diseases such as asthma, arthritis or inflammation. Sodium alginate is widely used in various files of application due its remarkable mechanical and hydrogel forming properties[3,4]. Dilti-

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azem, a calcium channel blocker and widely prescribed for the treatment of angina pectoris, arrhythmia and hypertension. Its high aqueous solubility and shorter elimination half-life (3-5 hr)[4,5], and use in chronic diseases makes it suitable candidate for prolongation of its release from dosage forms. Once or twice daily administration of controlled release preparations is recommended and improves patient compliance. In this study an attempt has been made to develop a sustained release dosage form by formulating diltiazem embedded alginate microbeads by ionotropic gelation technique. These microbeads were characterized for its particle size, drug content and *in vitro* drug release studies. An attempt was also made to understand the mechanism involved in the release kinetics of alginate microbeads.

MATERIALS AND METHODS

Diltiazem was obtained as the gift sample from Torrent Pharma, Ahmedabad. Sodium alginate (AR grade) was purchased from S. D. Fine Chemicals, Mumbai. Calcium chloride was obtained from Ranbaxy Laboratories, Delhi. All other chemicals used in the present study were of AR grade.

Preparation of diltiazem embedded alginate microbeads

Diltiazem embedded alginate microbeads (DMB) were prepared by ionotropic gelation technique[6]. An aqueous solution of various concentrations of sodium alginate (0.5, 1, 1.5, 2, and 2.5% w/v) was prepared using distilled water with vigorous stirring and heating to form a clear solution. To this solution, the drug diltiazem (2 % w/v) was added and stirred continuously until a uniform suspension was obtained. The suspension was extruded into a beaker containing calcium chloride (2 %) using a 5 mL of hypodermic syringe with 18 gauze needle and stirred at 100 rpm for 15 min. After extrusion the beads were washed with water allowed to solidify for a period of 30 min and dried at room temperature for 24 h and coded as DMB-I (0.5 %), DMB-II (1.0 %), DMB-III (1.5 %), DMB-IV (2. 0%), and DMB-V (2.5 %).

Estimation of drug content and particle size of microbeads

Four portions each containing 50 mg were randomly picked from the prepared samples and placed in phosphate buffer (pH 7.4). The resulting mixture was agitated using a mechanical stirrer for a period of 24 h to determine the amount of diltiazem. After 24 h the samples were filtered, suitably diluted and spectrophotometrically measured at 237 nm (Shimadzu, Japan). The estimation was done in triplicate to determine the uniformity of drug in microbeads[7]. About 50 microbeads were randomly picked up thrice and their size was measured by using digital vernier caliper[8].

Surface morphology of the microbeads by scanning electron microscopy

An aqueous dispersion of the microbeads was finely spread over a stab and was dried by keeping in a desiccator. The dried film of the microbeads was given a 25 nm thick gold layer and was observed by SEM (JEOL, JSM-6360) for the topography of the alginate beads after gold coating[9].

In vitro release studies of diltiazem from microbeads

In vitro release studies of prepared microbeads were carried out using USP XXIV dissolution (paddle method) apparatus at 100 rpm. Dissolution was carried out for a total period of 12 h using 0.1 N HCl (pH 1.2) for initial 2 h and in stimulated intestinal conditions (pH 7.4) for the rest of the period up to 12 h maintained at a temperature of (37 ± 1)℃. At periodic time intervals, 5 mL of sample withdrawn suitably diluted and absorbance was measured at 237nm[10]. Five milliliters of fresh dissolution media was added each time to sink conditions.

RESULTS

The diltiazem embedded microbeads were prepared by ionotropic gelation method. Table 1 shows the uniformity of drug content with low coefficient of variation. A random sample of 50 microbeads was taken and sizes were determined by using vernier caliper in triplicate. The sizes of the alginate microbeads were

found to be in the range of (0.71 ± 0.90) to (1.27 ± 1.20) mm in diameter. The surface of the alginate beads was found to be spherical and smooth in nature (Figure 1). The drug content in the microbeads was found to be in the range of (82.27 ± 1.30) % to (96.28 ± 1.80) %. Diltiazem release from the microbeads was studied employing stimulated gastric condition (0.1 N HCl for initial 2 hours and at later hours in stimulated intestinal conditions (pH 7.4) for 10 h (Figure 2). The cumulative percentage of drug release from the microbeads was found to be (85.61 ± 1.30) % to (95.27 ± 1.40) %. From the release profiles, it was observed that the drug present at the surface was found to be released immediately. It was observed that the release was found to be uniform and constant during the study period. These findings suggested that the gel strength of the alginate played a vital role in controlling the drug release. Also, the release of drug from the prepared microbeads was found to be decrease as the concentration of alginate was increased[11]. This could be due to the gel strength of alginate in microbeads, which retards drug release from the microbeads. Further, it can be supported by the fact that the release of drug from microbeads controlled by the increasing the concentration of alginate. In order to predict and correlate the release behavior of dissolution data were fitted according to well-known exponential equation, which is often used to describe the drug release behavior from polymeric system[12].

$$m_t/m_\infty = kt^n$$

Where, m_t/m_∞ is the fractional release of the drug, t´is the time, '*k*' is a constant which indicates the properties of a macromolecular polymeric and '*n*' is the release exponent indicative of the mechanism of release. The '*n*' values used for analysis of drug release mechanism from the diltiazem microbeads were determined from log (m_t/m_∞) vs log (t) plots. To calculate the release constant k´the logarithm of remaining diltiazemin microbeads is plotted versus time. Table 1 shows the values of'*k*', '*n*' and '*r*' for four batches are reported, and the '*n*' values were in the range of 0.5035 to 0.6222. The results of the kinetic analysis revealed that the release of diltiazem from alginate microbeads followed non-fickian diffusion obeying first order kinetics.

Table 1 Characteristics of diltiazem microbeads.

Formulation code	Drug content (mg)	Particle Size (mm)	In vitro release kinetics			
			First order plot		Peppa's	
			k	r^2	*n*	*r*
DMB-I	82.27 ± 1.30	0.71 ± 0.90	1.2443×10^{-3}	0.9969	0.5035	0.9947
DMB-II	85.10 ± 1.20	0.82 ± 1.30	1.3331×10^{-3}	0.9799	0.5603	0.9945
DMB-III	88.76 ± 0.90	0.87 ± 1.10	1.3284×10^{-3}	0.9789	0.5766	0.9955
DMB-IV	92.34 ± 0.70	0.95 ± 1.30	1.3443×10^{-3}	0.9976	0.6078	0.9968
DMB-V	96.28 ± 1.80	1.27 ± 1.20	1.3568×10^{-3}	0.9969	0.6222	0.9978

n = 3 ± SD

DISCUSSION

Formulation and evaluation of sustained release microbeads containing diltiazem was found to be potential, cost effective and satisfactory *in vitro* 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 done, frequency of administration, dose related side effects and better patient compliance. However, the in vivo studies are essential to find out its potential effect.

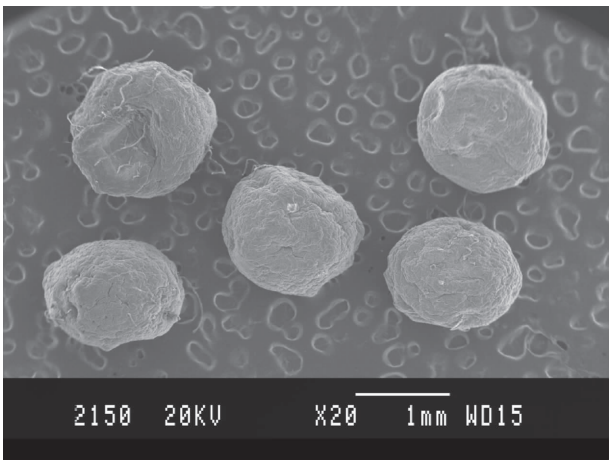

Figure 1 Scanning electron micrograph of diltiazem microbeads.

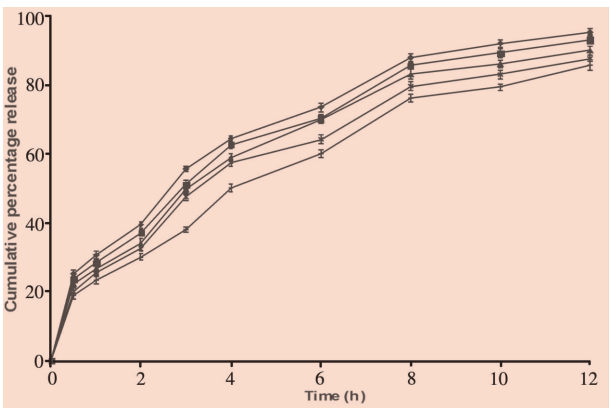

Figure 2 Comparative in vitro release profiles of diltiazem from microbeads DMB -I (◆), DMB-II (■), DMB-III (▲), DMB-IV(×) and DMB-V(+).

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