

Formulation and Development of Diltiazem Hydrochloride Sustained Release Alginate Beads by Iontropic External Gelation Technique

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Abstract Background of the research: Diltiazem HCL (DTZ), has short biological half life of 3-4 h, requires rather high frequency of administration. Due to repeated administration there may be a chances of patient in compliance and toxicity problems. Objective: The objective of study was to develop sustained release alginate beads of DTZ for reduction in dosing frequency, high bioavailability & better patient compliance. Methodology: Alginate beads were prepared by ionotropic external gelation technique using CaCl_2 as cross linking agent. Prepared beads were evaluated for % yield, encapsulation efficiency, swelling index in 0.1N HCL and 7.4 phosphate buffer, drug release study, FT-IR, FE-SEM analysis. In order to improve %EE and drug release, pectin, methyl cellulose and locust bean gum were used as co-polymers along with sodium alginate. Result: Yield was found to be in the range of 72.41-96.43. % EE was 47.3% (F1), 71.1% (F5). In pH 7.4, beads showed increase in swelling index as compare to in 0.1 N HCL. Among use of different copolymers, locust bean gum sustained the DTZ release up to 55.98% (F6) in 12 hrs. FT-IR analysis revealed no drug excipient interference. Prepared beads were found to be rough, with cracks and pores on the surface. Conclusion: It was concluded that DTZ could be successfully entrapped and sustained in sodium alginate beads with use of locust bean gum.

Keywords Alginate Beads, Diltiazem Hydrochloride, Iontropic Gelation, Swelling Index

1. Introduction

Diltiazem, a benzothiazepine calcium-channel blocker is used alone or with an angiotensin-converting enzyme inhibitor to treat hypertension, chronic stable angina pectoris and Prinzmetal's variant angina [1]. Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste.

It is soluble in water, methanol and chloroform and has a molecular weight of 450.98. Diltiazem hydrochloride extended release capsules contain Diltiazem hydrochloride in extended release beads at doses of 120, 180, 240, 300, 360 and 420 mg [2]. When used as monotherapy, usual starting doses are 120 to 240 mg once daily. DTZ has a relatively short biological half life of 3-4 h [3]. Most common adverse events of DTZ in double-blind placebo-controlled hypertension trials are vasodilatation. Dyspepsia, diarrhea, palpitations etc [2]. Conventional dosage forms like tablets, capsules, syrups etc are made from the number of excipients. These dosage forms are suffered from several drawbacks like repeated drug administrations, overdosing and under dosing, rapid decline in plasma drug concentration below minimum therapeutic drug level and that leads to the unwanted side effects. In order to solve all these issues sustained drug delivery is essential. Sustained drug delivery dosage forms have wide number of advantages like minimization in dosing frequency, maintenance of steady state plasma concentration over extended period of time, minimization in unwanted side effects and better patient compliance.

Alginate is a natural polymer which is obtained from the brown algae and is composed of 1-glucuronic acid and d-mannuronic acid. Alginates have unique property of forming hydrogels when comes in contact with divalent cations like Ca^{+2} [4-5]. Alginate hydrogels has been used extensively in pharmaceutical industry due to its high biodegradability and biocompatibility [6]. Sodium alginate is used as a matrix material in medicine to achieve a sustained release drug delivery due to its hydro gel forming properties [7-8].

The main objective of the present study was to formulate DTZ alginate beads to control the drug release. The effect of some formulation parameters on drug entrapment efficiency, namely concentration of alginate as well as of calcium chloride, the contact time with hardening agent and the addition of pectin, methyl cellulose and locust bean gum to alginate were investigated. The effects of different additives

on the in vitro release characteristics of alginate gel beads were evaluated. Alginate beads designed for sustained oral delivery will definitely bring reduction in dose and better patient compliance.

2. Materials and Methods

2.1. Materials

DTZ was received from Wockhardt research centre, (Aurangabad, India) as a gift sample for research work. Sodium alginate (125 cps for 1 % at 250 C), Locust bean gum (3000 cps for 1%) and Pectin were purchased from Himedia. Methyl cellulose was purchased from Merck Specialties Private Limited (Mumbai, India). Calcium chloride dihydrate was purchased from Sisco research laboratories. Other reagents were commercially available and used as received.

2.2. Methods

Preparation of Alginate beads by ionotropic external gelation technique: In ionotropic external gelation technique CaCl_2 gets cross linked with the alginate due to opposite charges on the both gelatin and CaCl_2 . Other polymers like pectin, methyl cellulose, locust bean gums reinforces the formation of beads.

Table 1. Formula composition

Batch	F1	F2	F3	F4	F5	F6
DTZ	100	100	100	100	100	100
Sodium alginate	200	200	200	200	200	200
Pectin	...	200
Methyl cellulose	200
Locust bean gum	200	250	300
Calcium chloride	3000	3000	3000	3000	3000	3000
Water	100	100	100	100	100	100

Alginate beads were prepared by ionotropic external gelation technique [9]. Formula composition was showed in Table 1. The sodium alginate, alginate-methyl cellulose, alginate-pectin, alginate-locust bean gum were dissolved in distilled water to get aqueous suspension. DTZ was added in aqueous dispersion by simple mixing process using magnetic stirrer (Remi, India). Drug polymer dispersion was sonicated for removal of air bubbles from the suspension using ultra bath Sonicator. This bubble free dispersion was dropped in to gelling solution of CaCl_2 (3%) through 21G syringe needle under mild agitation. The formed spherical beads were cured for 5 h in the gelling solution at room temperature with gentle stirring on

magnetic stirrer. The beads were collected by filtration and washed with distilled water and dried at room temperature.

3. Characterization

3.1. Yield of Calcium Alginate Beads

DTZ loaded beads from each batch were weighed accurately and yield of beads was calculated by using following equation [10].

$$\% \text{ Yield} = \text{Weight of dried beads} / \text{Weight of drug, polymer and Exceptient X 100} \quad (1)$$

3.2. Determination of Encapsulation Efficiency

The DTZ content in the alginate beads was determined by the digestion method [11]. Sample of beads equivalent to 10 mg of the drug were pulverized and stirred in 20 ml of distilled water at room temperature for 24 h. The solution was filtered using whatman filter paper no.41 and made up the volume up to 100 ml by using distilled water. From this solution 1 ml was pippered out into 10ml volumetric flask and made up to the volume with distilled water. The solution was assayed spectrophotometrically for DTZ content at the wavelength of 236 nm.

3.3. Determination of Swelling Index (%S.I.)

The swelling properties of the calcium alginate beads were determined in 0.1N HCL (pH 1.2) and standard phosphate buffer (SBP) pH 7.4. Samples of beads of known weight (10 mg) were placed in glass vial containing 10 ml of swelling solution and allowed swelling at 37°C. The swollen beads were periodically removed and weighed. The weight of the swollen beads were determined by the blotting them with filter paper to remove moisture adhering to surface, immediately followed by weighing on an electronic balance. The percentage of swelling of beads was calculated from the formula (11).

$$\text{Wt} - \text{W}_0 / \text{W}_0 \times 100 \quad (2)$$

Where,

Wt= final weight of beads

W₀= Initial weight of beads

3.4. In Vitro Drug Release Studies

The percentage cumulative release of DTZ from calcium alginate beads were measured by using the dissolution test apparatus (Basket type dissolution tester- Electolab TDT-08L). Amounts of beads equivalents to 20 mg of drug were used and the dissolution media (900 ml distilled water) were maintained at 37±0.5°C throughout the study with stirring speed of 100 rpm. About 5 ml of sample was withdrawn at desired intervals of time and analyzed for drug

content spectrophotometrically at the wavelength of 236 nm.

3.5. FTIR Study

The possible interaction between drug and polymers were assessed using Fourier transform infrared spectroscopy (FTIR), model Shimadzu FTIR 8400. FTIR spectra were obtained at room temperature, about 2mg of pure drug, polymers and formulations were dispersed in KBr powder and the pellets were made by applying 6000kg/cm² pressure. FT-IR spectra were obtained by powder diffuse reflectance on FT-IR spectrometer.

3.6. Morphology Observation (FESEM)

The surface of the beads was examined using field emission scanning electron microscope (FESEM-HITACHI S4800) prior to observation; samples were mounted on metal grids using double sided adhesive tape under vacuum before observation.

4. Result and Discussion

4.1. Yield of Alginate Beads

Sustained release DTZ loaded alginate beads were successfully formulated by ionic external gelation technique. Table 2 represents the summary of the yield of beads. The yield of alginates beads were found to be in the range of 72.41 % - 96.43 % of total solid content employed during the formulation of beads. The yield was found to be satisfactory and good. The maximum amount of yield was due to the insolubility of alginate, pectin, methyl cellulose and locust bean gum in calcium chloride solution and resulted in to the minimum loss of the dispersion. In batch F1, only sodium alginate was used and yield was found to be 75.15%. But when in batches F2 and F3 pectin and methyl cellulose was used respectively, yield was increased up to the 85.44%. This might be due to the formation of more viscous, dense and homogeneous dispersion as compare to the single sodium alginate dispersion. The yield of beads was further increased up to the 96.43% when locust bean gum was used in combination with the sodium alginate. Calcium chloride present in external solution might be cross linked with the polymeric system and helped in increasing the yield of the beads.

4.2. Drug Entrapment Efficiency (%DEE)

The % DEE of alginate beads containing DTZ were within the range of 47.3 (F1) and 71.1(F5) as shown in Table II. The formulation of the calcium alginate beads and higher entrapment efficiency is based on both the concentration of sodium alginate and the ability of the calcium ions to cross link with sodium alginate. The degree of cross linking is depending upon both the concentration of

the calcium chloride solution and the time of contact of beads with this solution. The alginate beads with single sodium alginate without using any supporting polymer showed very low entrapment of DTZ. This was due to the insufficient cross linking and large pore size permitting the hydrophilic drug to diffuse out during and after gelation. The porosity of alginate beads could be responsible for the lower encapsulation efficiencies [12]. Moreover, the encapsulation efficiencies of water soluble drugs are in general lower than that for slightly soluble or insoluble drugs [13]. In order to increase the entrapment efficiency addition of methyl cellulose, pectin and locust bean gum was employed separately in combination with sodium alginate. During our experiments it was found those additions of various polymers to the formulation alter the drug entrapment efficiency. Use of pectin and methyl cellulose increased the DTZ entrapment efficiency. As compare to the pectin and the methyl cellulose, locust bean gum showed the highest drug entrapment efficiency. The rank order of the entrapment efficiency of beads was found to be Alg<Alg-Pect<Alg-MC< Alg-locust bean gum. The highest efficiency of drug loading was obtained for beads containing bean gum.

Table 2. Evaluation of beads

Batch	% Yield	% EE	% S.I. in pH 1.2	% S.I. in pH 7.4
F1	75.15±2.5	47.3±1.2	36±2.5	191± 2.5
F2	83.1±4.5	51.2±3.2	48±4.6	206±3.7
F3	85.44±3.8	55.6±4.5	59±2.5	254±4.6
F4	72.41±5.4	59.2±3.8	62±3.8	250±5.4
F5	90.68±2.2	68.7±4.6	74±4.0	288±4.8
F6	96.43±3.5	71.1±5.8	72±3.5	280±2.8

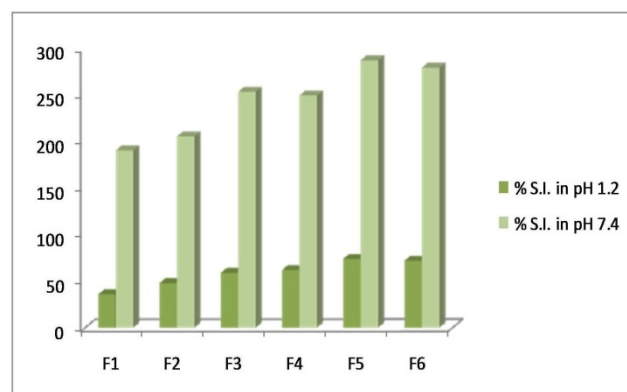


Figure 1. % Swelling Index in 0.1N HCL (pH 1.2) & standard phosphate buffer (pH 7.4)

4.3. Swelling Index (S.I)

The S.I. of various alginate beads containing DTZ was evaluated in 0.1 N HCL (pH 1.2) and SPB pH 7.4 after 4h as shown in Table II and Fig. 1. The S.I. values of beads in

pH 1.2 were within the range between 35-74% and in pH 7.4 were 190-288% (Fig. 1). The S.I. of beads containing DTZ was lower in 0.1 HCL (pH 1.2) in comparison with that of in SPB (pH 7.4). In pH 7.4, beads showed increase in S.I. The higher the pH value, the higher the swelling index [14]. Core is soluble in higher pH. Hence the solvent reaches the core and beads get swelled. The swelling property of the beads is affected by the concentration change of polymer. As the bean gum concentration increases the swelling index also get increased.

4.4. In Vitro Drug Release Study

DTZ loaded beads as described in Table 1 have been investigated for the percent cumulative release of drug in distilled water as shown in Fig. 2. The release of DTZ from beads (F1), within 2-3 hrs 90.45% was found. In batch F1 sodium alginate was used without use of any co-polymer. Due to low level of polymer DTZ becoming a small molecule and very hydrophilic in nature, has the tendency to diffuse out easily. From this it was clear that sodium alginate alone failed to maintain sustain release pattern of DTZ. The rate and extent of drug release from prepared beads significantly decreased with the use of co-polymers like pectin, methyl cellulose and locust bean gum. This could be attributed to the increase of alginate matrix density and in the diffusion path length which the drug molecules have to traverse [15]. In batch F2 equal amount of sodium alginate and pectin was used and drug release was found to be 87.9 % in 12 hrs. In this formulation drug release was decreased as compare to batch F1. In case of batch F3 alginate –methyl cellulose system, drug release was further decreased up to 80.88%. Significant decrease in drug release was found when locust bean gum was used. The effect of locust bean gum was concentration dependent. As concentration of gum increased drug release was retarded. Drug release was found to be 74.2% (F4), 63.78% (F5), and 55.98% (F6). The rank order of the sustain release tendency of beads was found to be Alg<Alg-Pect<Alg-MC<Alg-locust bean gum

The drastic change was observed when locust bean gum employed during formulation of beads. During our experiments we found that as the concentration of locust bean gum was increased, the viscosity of the dispersion was also increased. Sustained release pattern is due to formation of more viscous and denser dispersion of locust bean gum with sodium alginate in water which would have resisted diffusing out the hydrophilic drug molecule from the beads.

4.5. FTIR Study

As shown in fig. 3, FT-IR spectra of DTZ showed characteristic peaks at 3433.13 cm^{-1} (aliphatic C-H stretching), 2931.90 cm^{-1} (O-CH₃, C-H stretching), 2387.93 cm^{-1} (amine HCL, N-H stretching), 1741.78 cm^{-1}

(acetate C=O stretch), 1678.13 cm^{-1} (lactum C=O stretch), 831.33 cm^{-1} (O-substituted aromatic C-H out of plane deformation), 773.48 cm^{-1} (P-substituted aromatic C-H out of plane). All these characteristic peaks were found in alginate-locust bean gum beads. This observation confirmed that there was no drug excipient interaction.

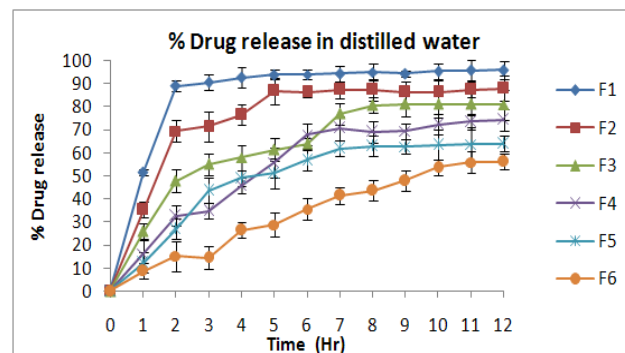


Figure 2. % Drug release

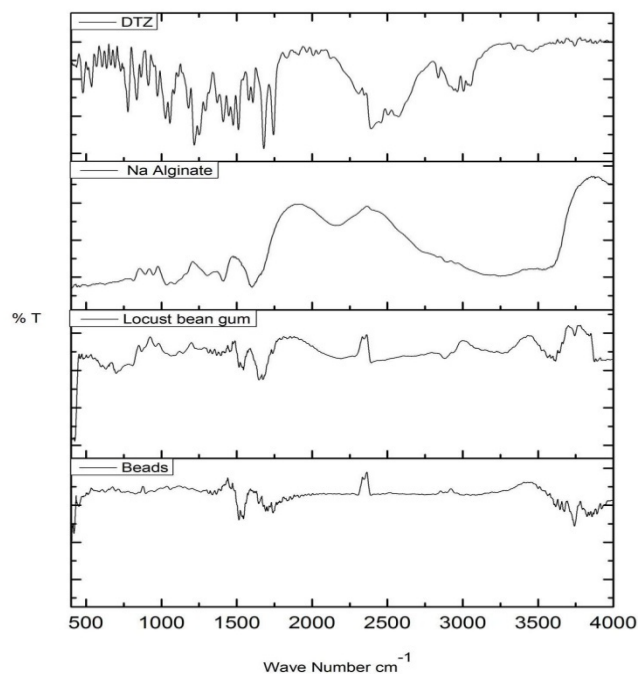


Figure 3. FTIR- IR of DTZ, sodium alginate, Locust bean gum and DTZ loaded beads

4.6. Morphology Observation

FE-SEM photographs of the surface of alginate-locust bean gum beads are shown in fig.4. The surface of dried beads exhibited very rough surface, with cracks and pores. Beads were found to be spherical in shape with curvatures on the surface. The cracks and pores may be caused by partly collapsing the polymeric gel network during the drying. Cracks and pores on the surface of the beads played vital role for the release of the DTZ in external release media.

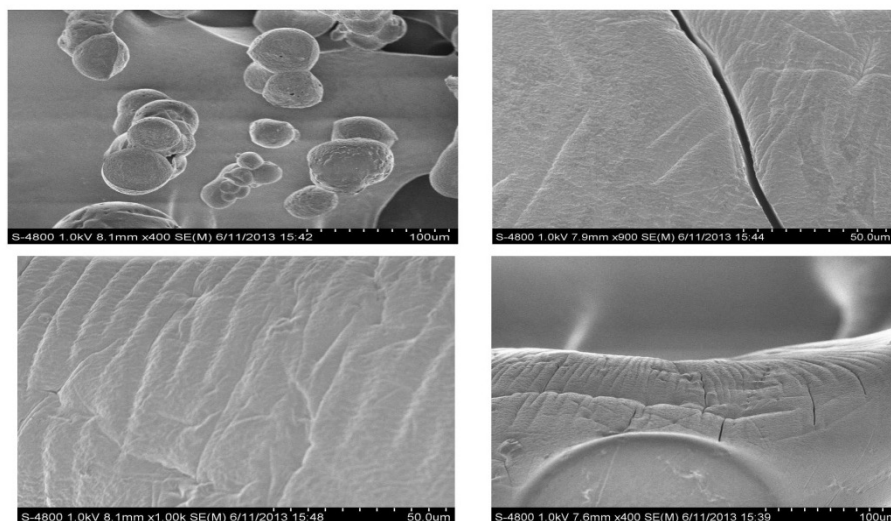


Figure 4. SEM analysis- Images showing sphericity, cracks on surface, rough surface on beads

5. Conclusion

The present study reports the development of sodium alginate sustained release DTZ beads by external gelation technique. Encapsulation efficiency was increased from 47.3 to 71.1% by using copolymers. Highest encapsulation efficiency was observed in case of locust bean gum 71.1% (F6). Swelling study revealed maximum swelling in 7.4 phosphate buffer. Locust bean gum successfully sustained the drug release of the DTZ up to 55.98% (F6) in 12 hrs. FTIR study showed no drug excipient compatibility study. The FESEM images of prepared beads were found to be rough, with cracks and pores on the surface.

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Conflict of Interest

No Conflict of Interest

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