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Formulation And Evaluation Of Sustained Release Sodium Alginate Microbeads Of Carvedilol

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Abstract: The main aim of the study is to formulate Carvedilol loaded microbeads of sodium alginate using gelatine and pectin as release modifiers by ionotropic gelation method. The microbeads were prepared by varying the concentration of sodium alginate, gelatin and pectin. The drug-polymer compatibility was studied by FTIR studies. The prepared microbeads were evaluated for swelling ratio, particle size, drug entrapment, Scanning electron microscopy (SEM), bio adhesion study and *invitro* release study. Particle size distribution of both placebo and drug loaded formulations were measured by an optical microscope and particle size of optimized beads was determined by SEM. No significant drug-polymer interactions were observed in FT-IR studies. *In-vitro* drug release profile of Carvedilol micro beads was examined in pH 1.2 N Hydrochloric acid for first 2 hours followed by phosphate buffer pH 7.4 for remaining time. The in vitro wash-off test indicated that the sodium alginate micro beads had good mucoadhesive properties. The formulated beads had shown higher entrapment efficiency, drug loading, low particle size and moisture content. The formulation F3 released Carvedilol for longer duration (24 hours) and showed better mucoadhesion.

Key-words: Carvedilol, sodium alginate, microbeads, ionotropic gelation, Cross linking.

Introduction

Multiple unit dosage forms such as microspheres or micro beads have gained in popularity as oral drug delivery systems because of more uniform distribution of the drug in the gastrointestinal tract, more uniform drug absorption, reduced local irritation and elimination of unwanted intestinal retention of polymeric material, when compared to non-disintegrating single unit dosage form. Microbeads are small, solid and free flowing particulate carriers containing dispersed drug particles either in solution or crystalline form that allow a sustained release or multiple release profiles of treatment with various active agents without major side effects.

Carvedilol, widely prescribed in the treatment of hypertension, has shorter elimination half-life (6.4 hour), and use in chronic diseases makes it a suitable candidate for prolongation of its release from dosage forms. In this study, an attempt has been made to develop a sustained release dosage form by formulating Carvedilol embedded alginate microbeads by ionotropic gelation technique using gelatin and pectin as release modifiers. These microbeads were characterized by FTIR, particle size, swelling ratio, Scanning electron microscopy (SEM), drug entrapment, mucoadhesion study and invitro release study. The objective of the study is to reduce the number of doses of the conventional dosage form and thus improve patient compliance.

Materials and Methods

Carvedilol was a gift sample from Ranbaxy Laboratories, Delhi, India. Sodium alginate, pectin and calcium chloride were purchased from Nice Chemicals, Bangalore. Gelatin was purchased from SD fine chem Ltd Mumbai. All other reagents and solvents used were of analytical grade.

Preparation of Placebo Microbeads:

The microbeads were prepared by the ionotropic gelation technique. Microbeads were prepared by using sodium alginate alone and combination with coating polymers like gelatin and pectin and calcium chloride used as counter ion., 25 ml of a 2% w/v aqueous solution of sodium alginate was introduced drop wise from a glass syringe with a size-23 needle into 100 ml of an aqueous calcium chloride solution being stirred at 100 rpm. The concentration of CaCl₂ in the solution should be 2% w/v. Allowed the beads to be formed by running the stirrer for 15 min. Check the beads under microscope. Then rigidize the beads by adding 1ml of 25% solution of glutraldehyde. Allow stirring for further 1 hour at 100 rpm. After stirring for one hour filter the solution and collect the beads. Obtained microbeads were washed with water and dried at 50°C in an oven. Total Nine sets of placebo microbeads (S, G1, G2, G3, G4, P1, P2, P3 and P4) were prepared for the selection of best concentration of polymer solution by using sodium alginate alone and combination with coating polymers like pectin, and gelatin and calcium chloride used as counter ion. The detailed composition of the various formulations mentioned in Table 1.

Preparation of Alginate–Gelatin Microbeads:

Four batches of drug loaded microbeads (F1, F2, F3 and F4) were prepared using optimized concentration of sodium alginate and gelatin (sodium alginate 1.75% and gelatin 0.25%) as a coating polymer. To 50ml of deionized water, gelatin was added and stirred with the electric stirrer to form mucilage. Then sodium alginate was added to form uniform dispersion. Weighed quantity of Carvedilol was added and homogenized for 5 min. The resulting dispersion was dropped through syringe with needle into 100ml of 2% w/v aqueous calcium chloride solution and stirred at 100rpm. After stirring for 1 hour, the formed beads were separated by filtration, washed with distilled water, dried at 50° C in an oven.

Preparation of Alginate-Pectin Microbeads:

Four batches of drug loaded microbeads (F5, F6, F7 and F8) were prepared using optimized concentration of sodium alginate and Pectin (sodium alginate 1.75% and Pectin 0.25%) as a coating polymer. To 50ml of deionized water, Pectin was added and stirred with the electric stirrer to form mucilage. Then sodium alginate was added to form uniform dispersion. Weighed quantity of Carvedilol was added and homogenized for 5 min. The resulting dispersion was dropped through syringe with needle into 100ml of 2% w/v aqueous calcium chloride solution and stirred at 100rpm. After stirring for 1 hour, the formed beads were separated by filtration, washed with distilled water, dried at 50° C in an oven.

Evaluation of Placebo Microbeads:

Percentage Practical Yield:

The yield of microbeads was determined by comparing the whole weight of microbeads formed against the combined weight of the copolymer and drug.

Mass of microbeads obtained % Practical yield = ------ X 100

Total weight of drug and polymer used

Particle Size Analysis:

The sample of prepared microbeads was randomly selected and their size was determined using an optical microscope with the help of eye piece and stage micro meter. In all measurements at least 50 beads in five different fields were examined. Each experiment was carried out in triplicate.

Swelling Index Study:

The extent of swelling was measured in terms of % weight gain by the beads. The swelling behaviors of all the formulations were studied. In this test 20 mg of beads from each formulation was kept in petridish containing distilled water. At the end of 1 hour, the beads were withdrawn, soaked with tissue paper and weighed. Then for every 1 hour, weights of beads were noted and the process was continued till the end of 8 hours. The % weight gain by the beads was calculated by the following formula:

Swelling Index (SI) = $[\{W_t - W_0\}/W_0] \ge 100$

Where, W_t = Mass of swollen beads at time t W_0 = Mass of dry beads at t=0

Evaluation of Drug Loaded Microbeads:

Percentage Drug Entrapment Efficacy (%DEE):

Accurately weighed microbeads equivalent to 100mg were suspended in 100ml of simulated intestinal fluid of pH 7.4 \pm 0.1 and kept for 24hrs. Next day it was stirred for 5min and filtered. After suitable dissolution, the drug content in the filtrate was analyzed spectrophotometrically at 241nm using Shimadzu UV spectrophotometer. Finally, drug encapsulation efficiency is calculated by-

Actual drug content
Percentage Drug Entrapment Efficiency = ------ X 100

Theoretical drug content

Loose Surface Crystal Study (LSC):

This study was conducted to estimate the amount of drug present on the surface of the microbeads which showed immediate release in dissolution media. 100mg of microbeads were suspended in 100ml of phosphate buffer (pH 7.4), simulating the dissolution media. The samples were shaken vigorously for 15min in a mechanical shaker. The amount of drug leached out from the surface was analyzed spectrophotometrically at 241 nm. Percentage of drug released with respect to entrapped drug in the sample was recorded.

Fourier Transform Infrared Spectroscopy:

FTIR spectral measurement was performed using Shimadzu FTIR spectrophotometer to confirm the presence of any interaction between the polymer and drug. The polymer and the drug were finely ground with KBr to prepare the pellets under a hydraulic pressure of 600psi and spectra were scanned between 400 and 4000cm⁻¹.

Scanning Electron Microscopy:

The surface morphology of drug-loaded beads obtained from various percentages of polymer, $CaCl_2$ and drug were studied by using a scanning electron microscope (model JEOL JSM-6360, Japan). The beads were mounted on an appropriate stub and then coated with carbon and gold (100 and 50 Å thickness respectively) sputter module in a vacuum evaporator in an argon atmosphere. The coated samples were then observed under a scanning electron microscope operated at 15 KV.

Invitro Dissolution Study:

Dissolution studies of Carvedilol microbeads was performed according to USP XXII type I dissolution apparatus in pH 1.2 for first 2 h and rest of the release study was performed in phosphate buffer of pH 7.4. The

temperature was maintained at $37\pm0.5^{\circ}$ C and the rotation speed was 100 rpm. The 5 ml of sample was withdrawn at various time intervals and replenished with an equal volume of fresh dissolution media. The drug content in the sample was analyzed spectrophotometrically at 241nm.

Mucoadhesive Test:

The mucoadhesive property of microbeads was evaluated by an in vitro adhesion testing method known as wash-off method. Freshly excised pieces of chicken intestinal mucosa were mounted on to glass slides with cotton thread. About 20 microbeads were spread on to each prepared glass slide and immediately thereafter the slides were hung to USP II tablet disintegration test. When the test apparatus was operated, the sample is subjected to slow up and down movement in the test fluid at 37 ^oC contained in a 1-litre vessel of the apparatus. At an interval of 30min up to 8 hours the machine is stopped and number of beads still adhering to mucosal surface was counted. The test was performed at intestinal (phosphate buffer pH 7.4) condition.

Formulation	Sodium	Gelatin	Pectin	Calcium	Crosslinking	Curing Time
Code	Alginate(%)	(%)	(%)	Chloride (%)	Agent (%)	(hour)
S	2	-	-	2	1	1
G1	1	1	-	2	1	1
G2	1.25	0.75	-	2	1	1
G3	1.5	0.5	-	2	1	1
G4	1.75	0.25	-	2	1	1
P1	1	-	1	2	1	1
P2	1.25	-	0.75	2	1	1
P3	1.5	-	0.5	2	1	1
P4	1.75	-	0.25	2	1	1

Table 1: Composition of various formulations of microbeads.

Results and Discussion

Chemical reaction between sodium alginate and calcium chloride to form calcium alginate was utilized for the microencapsulation of Carvedilol core material. For slowing the drug release hydrophilic polymers were added in different concentration so that the drug will release constantly for 24 hours. The yield of all the formulations was within the range of 73.0 ± 0.83 to 85.4 ± 1.27 . The production yields are summarized in table 2. The mean particle sizes of the various formulations of microbeads were obtained in the range between 1103.68 ± 0.017 and $1543.602\pm1.34\mu$ m (Table 2). By increasing the concentration of sodium alginate, the mean particle size of microbeads increased. From results it can be seen that larger microbeads were obtained by increasing the concentration of sodium alginate. On adding gelatin and pectin, the particle size was found to decrease when the concentration of sodium alginate and the polymer are 1.75 and 0.25 respectively. The swelling behavior of the beads was studied by measuring the weight of the beads after exposure to phosphate buffer, pH 7.4 for 8 hours. Degree of swelling is proportional to ratio of drug to polymer, and it affects the property of drug release from polymer, which was shown in table 2.

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Formulation Code	Percentage Yield (%)	Particle Size (µm)	Swelling Index (%)
S	98.01 <u>+</u> 0.89	1543.602 <u>+</u> 1.34	1769 <u>+</u> 0.093
G1	79.11 <u>+</u> 0.38	1243.58 <u>+</u> 0.97	1048 <u>+</u> 0.048
G2	82.04 <u>+</u> 0.73	1230.25 <u>+</u> 0.29	1340 <u>+</u> 0.042
G3	84.91 <u>+</u> 0.26	1196.906 <u>+</u> 0.12	1456 <u>+</u> 0.056
G4	85.4 <u>+</u> 1.27	1103.55 <u>+</u> 0.73	1662 <u>+</u> 0.024
P1	73.0 <u>+</u> 0.83	1351.93 <u>+</u> 1.08	940 <u>+</u> 0.055
P2	73.5 <u>+</u> 1.08	1342 <u>+</u> 0.54	1110 <u>+</u> 0.093
P3	74.61 <u>+</u> 0.93	1316.93 <u>+</u> 1.22	1247 <u>+</u> 0.021
P4	81.09 <u>+</u> 0.39	1190.23 <u>+</u> 0.16	1387 <u>+</u> 0.087

 Table 2:Characteristics of drug loaded microbeads

Based on the characterization of placebo microbeads, 1.75% sodium alginate and 0.5% polymer was found to be the optimized formulation. The drug loading was done in the optimized formulation and the drug entrapment efficiency is summarized in table 3. The encapsulation efficiency determines the percentage of encapsulated drug with respect to the total drug introduced into polymer solution. Loose surface crystal (LSC) study was an important parameter giving an indication of the amount of drug on the surface of the microbeads without proper entrapment. Its results are given in table 3.

Formulation code	Drug in mg	%DEE	%LSC
F1	5	79.47 <u>+</u> 0.13	3.0529 <u>+</u> 0.013
F2	10	80.31 <u>+</u> 0.12	5.793 <u>+</u> 0.072
F3	15	89.77 <u>+</u> 0.31	0.3891 <u>+</u> 0.042
F4	25	82.76 <u>+</u> 0.76	4.243 <u>+</u> 0.023
F5	5	68.46 <u>+</u> 0.43	3.0622 <u>+</u> 0.011
F6	10	72.76 <u>+</u> 1.09	1.4406 <u>+</u> 0.089
F7	15	84.18 <u>+</u> 0.38	4.0988 <u>+</u> 0.008
F8	25	9156 <u>+</u> 1.72	0.457 <u>+</u> 0.063

 Table 3: Composition and characteristics of drug loaded microbeads



Figure1: FTIR spectra of a)Carvedilol pure drug b)Carvedilol+sodium alginate+ Pectin c)Carvedilol+sodium alginate+ Gelatin

The compatibility of Carvedilol with various polymers was investigated by IR-spectroscopy study. The IR spectra of the drug and polymer combination were compared with the spectra of the pure drug. In which no shifting of peaks was significantly found, indicating the stability of the drug during encapsulation process. The spectra are included as figure 1. The morphological evaluation of the optimized micro beads formulation (sodium alginate micro beads coated with gelatin was done by scanning electron microscopy (Figure 2). SEM study revealed that the microbeads were almost spherical in shape with rough outer surface.

Invitro drug release for all formulations were carried out using USP dissolution apparatus Type 1 filled with pH 1.2 hydrochloric acid for first 2 hours followed by pH 7.4 phosphate buffer for the remaining 22 hours.5ml samples were withdrawn at predetermined intervals. The samples were analyzed by UV spectrophotometrically. The formulations F1- F8 containing 1.75% of sodium alginate and 0.25% of coating polymers like pectin and gelatin and four different concentration of drug showed a release range of 90.3829 to 94.3783. This indicates that the release rate is further retarded due to addition of coating polymer. From the dissolution study, F3 and F8 were found to the best among the prepared microbeads. The batches that showed better drug release (F3 and F8) were subjected to mucoadhesive test and batch F3 was found to be the best among the prepared batches with 72% mucoadhesive property.



Figure 2: SEM of Carvedilol microbeads



Figure 3a: In Vitro Drug release studies for Prepared Carvedilol microbeads coated with Gelatin



Figure 3b: In Vitro Drug release studies for Prepared Carvedilol microbeads coated with Pectin

Conclusion

Carvedilol microbeads were successfully prepared by ionotropic gelation method. Polymer-drug ratio influences the particle size, swelling index, cumulative % release and drug entrapment efficiency. Among the batches, F3 and F8 showed better drug release. Batch F3 was found to have better mucoadhesion. Therefore, one can assume that the Carvedilol microbeads are promising pharmaceutical dosage forms by providing sustained release drug delivery systems and improving bioavailability. The entire process is feasible in an industrial scale and demands pilot study.

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