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Sodium alginate microspheres for extending drug release: formulation and *in vitro* evaluation

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Abstract

In the present study, spherical microspheres of theophylline (TP) using sodium alginate as the hydrophilic carrier were prepared to prolong the release. The shape, surface and size characteristics were determined by scanning electron microscopy. The microspheres were found to be discreet and spherical in shape and had a smoother surface. The mean diameter of seven alginate microspheres formulations were between 7.6 ± 0.52 and 22.35 ±0.31 µm. It was observed that mean particle size of the microspheres increased with an increase in the concentration of polymer. The entrapment efficiency was found to be in the range of 70–93%. Optimized alginate microspheres were found to possess good sphericity, size and adequate entrapment efficiency. The in vitro release studies were carried out in pH progression media (pH 1.2, 2.5, 4.5, 7 and 7.4 solutions). Results indicated that percent drug release decreased with an increased alginate concentration. TP-loaded Alginate microspheres showed extended in vitro drug release thus use of microspheres potentially offers sustained release profile along with improved delivery of TP.

Keywords: Extended drug delivery; Sodium alginate; Microspheres; Bronchial asthma

Introduction

Advances over the last decade in site-specific and/or controlled drug delivery systems are contributing to new and/or improved drug therapies. Drug delivery is becoming an increasingly important aspect in new product research and development in the pharmaceutical industry [1]. The main advantages of natural polymers are that they are biocompatible, biodegradable and produce no systemic toxicity on administration [2]. Numerous hydrophilic polymers, and in particular polysaccharides, as well as their derivatives, have been proposed for the formulation of modified-release dosage forms [3]. Alginates, natural hydrophilic polysaccharide derived from seaweed, consist of 1→4, linked D-mannuronic acid and L-glucuronic acid residues arranged as blocks of either type of unit or as a random distribution of each type. Alginates do not gel since they have poly (L-gluronic acids) which are rigid. Alginates are easily gelled in presence of a divalent cation as calcium ion. The gelation or crosslinking is due to the stacking of the glucuronic acid blocks of alginate chains [4].

Microsphere technology is an established technique that has been used to deliver several different types of drugs including antigens, steroids, peptides, proteins,

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and antibiotics by injection or oral administration. Biodegradable polymer microparticles, either microspheres or microcapsules, are often employed as supports to deliver bioactive compounds. An emulsification/internal gelation technique provides a safe method for mass production of microspheres. The method is based on the release of calcium ions from an acid-soluble calcium salt in emulsified sodium alginate solution. Oil-soluble acid partitions to the dispersed aqueous alginate phase to release calcium and thereby initiate alginate gelation [5].

Asthma is considered as the most relevant pulmonary disease which is located at bronchial airways. Oral TP is one of the most prescribed drugs for an effective treatment of bronchial asthma for over 70 years. Increasing evidence shows that TP has anti-inflammatory effects in asthma and improves pulmonary function during the late asthmatic response (LAR). However, the frequency of TP side-effects has recently reduced its usage. Inhaled TP has not been successful either, mostly due to the lack of retention in the airways and irritation [6-7]. The purpose of the present work was to develop TP loaded microspheres and to determine the physicochemical characteristics of the developed microspheres.

Materials and Methods

Materials

Sodium alginate was obtained from Central Drug House, India. TP was obtained as a gift sample from IPCA Laboratories Ltd., Ratlam (M.P) India. All the other chemicals used were of analytical grade.

Methods

Preparation of alginate microspheres

The emulsification method was utilized for the preparation of microspheres followed by cross-linking with calcium chloride Core material, TP (100 mg) was dispersed in 2-8% aqueous solution of sodium alginate (10 ml). The aqueous phase was emulsified in light liquid paraffin in the ratio 1:10 containing 2% (v/v) Span 80 using a mechanical stirrer (Remi Motors, India) at 400–1000 rpm for 60 min to it 5ml of 0.2M calcium chloride dissolved in a mixture of methanol and isopropyl alcohol (2:3) was added slowly to the emulsion and stirred to assure efficient cross-linking. Microspheres were collected by filtration in vacuum, washed with isopropyl alcohol thrice and finally air-dried at room temperature. Various formulations of alginate microspheres were prepared using the variables as shown in table 1.

Table 1. Various formulations of Theophylline-loaded microspheres

Formulation Batch code	TP % (W/V)	Sodium Alginate % (W/V)	Crosslinker $CaCO_3$ % (W/V)	Agitation Speed (rpm)
F1	0	2	5	400
F2	2	4	5	600
F3	2	6	5	800
F4	2	8	5	1000
F5	2	8	6	1000
F6	2	8	8	1000
F7	2	8	10	1000

Morphological and particle size study

The morphological and Particle Size analyses of the microspheres were performed by optical and electron microscopy (SEM). For SEM, samples of microspheres were mounted on metal stubs, gold coated under vacuum and examined in JEOL JSM-840 SEM Japan.

Determination of drug entrapment efficiency

The weighed amount of the microspheres was incubated with PBS, pH 7.4, for 48 h. It was centrifuged at 10,000g for 30min & drug concentration in the supernatant was determined by UV-Visible Spectrophotometer at 271.5 nm (GBC-Cintra-10).

Swelling ratio

Alginate microspheres (100mg) were placed in a wire basket and put in 100ml of different solutions (distilled Water, pH 1.2, 4.5, 7.4 buffer solutions) and allowed to swell at 37oC. Initially the microspheres were weighed, then they were periodically removed, blotted with filter paper; and their changes in weight were measured during the swelling.

Calcium content

Alginate microspheres (100mg) were dissolved in 5ml concentrated nitric acid by boiling. The samples were diluted with deionized water and the calcium content was determined by Flame photometer.

In vitro drug release study

The drug release study from microspheres was performed in the pH progression medium according to

method reported by Rodriguez et al. [8]. The dissolution studies were carried out in 100 ml dissolution medium, which was stirred at 100 rpm at 37 ± 1◦C. The change in the pH of solution was performed with respected to time starting with 0.1M HCl, following this 340mg of KH_2PO_4 and 450mg of $Na_2PO4.2H_2O$ were added, adjusting the pH to the desired value 1.2, 2.5, 4.5, 7 and 7.4 dissolution media for 1, 1, 1.5, 1.5 and 3h, respectively using either 1.2 M NaOH or 1.2 M HCl. Samples were withdrawn at predetermined time intervals and assessed for TP by UV-Visible Spectrophotometer at 271.5 nm (GBC-Cintra-10). At least three dissolution runs were carried out for each batch of microspheres and the results averaged.

Statistical analysis

Data were analyzed for statistically significant differences by one-way analysis of variance (ANOVA). The level of significance was taken as $p < 0.05$.

Results and Discussion

In the present study, spherical microspheres able to prolong the release of TP were successfully prepared by the typical emulsification method using sodium alginate as the hydrophilic carrier. The effect of various formulation variables (Table 1) was analyzed in order to optimize the formulation. Uniform, surface crosslinked, and almost spherical microspheres were obtained as shown in scanning electron photomicrographs (Figure 1).

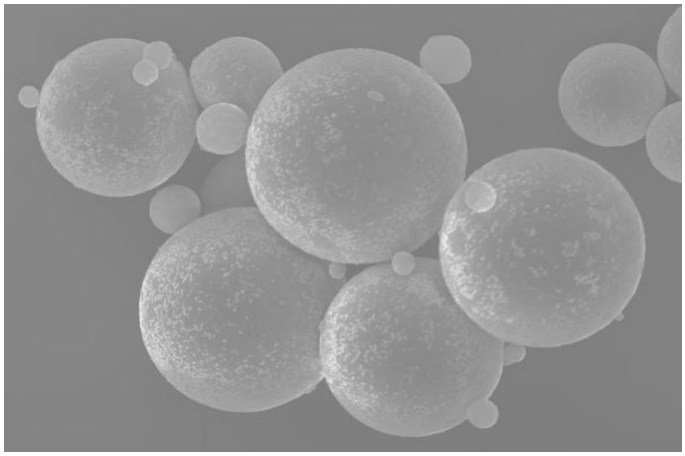

Figure 1. SEM photograph of Theophylline loaded microspheres.

A higher concentration of polymer produced a more viscous dispersion, which formed larger droplets and consequently larger microspheres. Increase in particle size was also observed with increase in the concentration of the cross-linker. However, when formulations F7 were tried with higher concentration of crosslinker above 10%, microspheres with irregular shape were obtained. This could be due to the instant gelling of sodium alginate on addition of calcium chloride. The value of entrapment efficiency was found to be in the range of 72.63 –93.65 %, as shown in Tables 2. The highest Entrapment Efficiency was found in F4 formulation.

Table 2. Physicochemical properties of Theophylline-loaded microspheres

Formulation Batch code	Mean particle size (μm)	Entrapment Efficiency	Ca Content (Per 10 mg)	Morphology
F1	7.6 ± 0.52	-	0.14	Spherical & Smooth
F2	8.2 ± 0.26	72.63 ± 0.35	0.18	Spherical & Smooth
F3	9.65± 0.59	86.00 ± 0.62	0.25	Spherical & Smooth
F4	12.25 ±0.33	93.65 ± 0.48	0.32	Spherical & Smooth
F5	13.22 ±0.47	92.84 ± 0.36	0.26	Spherical & Smooth
F6	16.95 ±0.25	82.67 ± 0.52	0.33	Spherical & Smooth
F7	22.35 ±0.31	79.81 ± 0.75	0.41	Irregular Shape

Swellability of different microspheres formulations were determined. The ionic character of the alginates allows pH-dependent disintegration of the microspheres. This might also affect the release properties of alginate based formulations. Figures 2 show the swelling ratio of the microspheres. When the swelling ratio of the formulations was compared, the lowest swelling ratio was obtained in water and pH 1.2, whereas the highest was obtained in pH 2.5 and 4.5. In pH 7- 7.4, the alginate matrices swelled and they were broken in these pH values after 45-60min. These results suggest that calcium-alginate microspheres do

not disintegrate in the stomach, and thus resulted in delayed release of TP in simulated intestinal fluids.

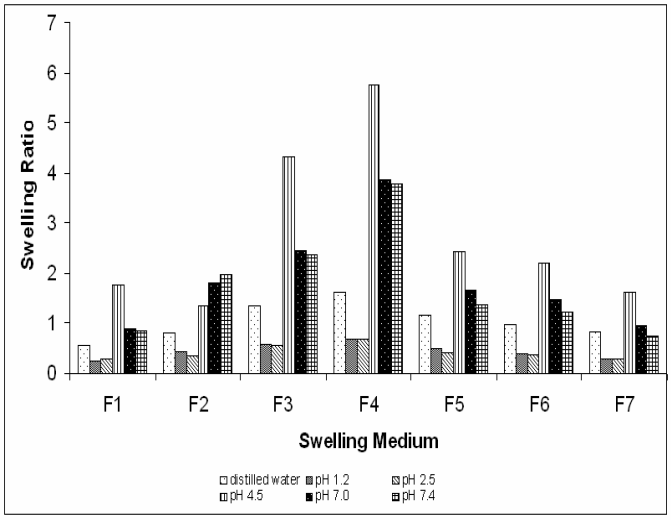

Figure 2. Swelling ratio of formulations of alginate microspheres in different swelling medium.

Calcium content in the microspheres was determined. It was observed that the greater the amount of polymer, the greater the Ca content. It was also noted that concentrations of $CaCl_2$ also affect the amount of Ca in the alginate microspheres. (Table 2). An increase in $CaCl_2$ concentration from 5% to 10% caused an increase in the Ca amount of the microspheres.

The cross-linked microspheres of alginate were subjected to in vitro drug release rate studies. Release rate were determined in pH progression medium of 1.2, 2.5, 4.5, 7 and 7.4 pH for 1, 1, 1.5, 1.5 and 3h, respectively in order to investigate the capability of the formulation to withstand the physiological environment of the stomach and small intestine.

The effect of drug–polymer ratio on TP release from different batches of microspheres is shown in Figure 3. The amount of the drug released from F1 to F4 formulation was found to be between 96.82 ± 3.52% to 75.11 ± 5.29% respectively after 8 hours of study. This decrease in the rate and extent of release with relative increase in the polymer concentration in microspheres can be attributed to the increase in the density of the polymer matrix with increased polymer concentration. In vitro drug release of optimized formulation during 8 hours of study was found to be 2.57± 23.41%, 8.74± 25.55%, 20.73± 9.72%, 38.65 ± 45.76% and 76.55± 34.44% in pH progression medium of 1.2, 2.5, 4.5, 6.8 and 7.4 pH respectively.

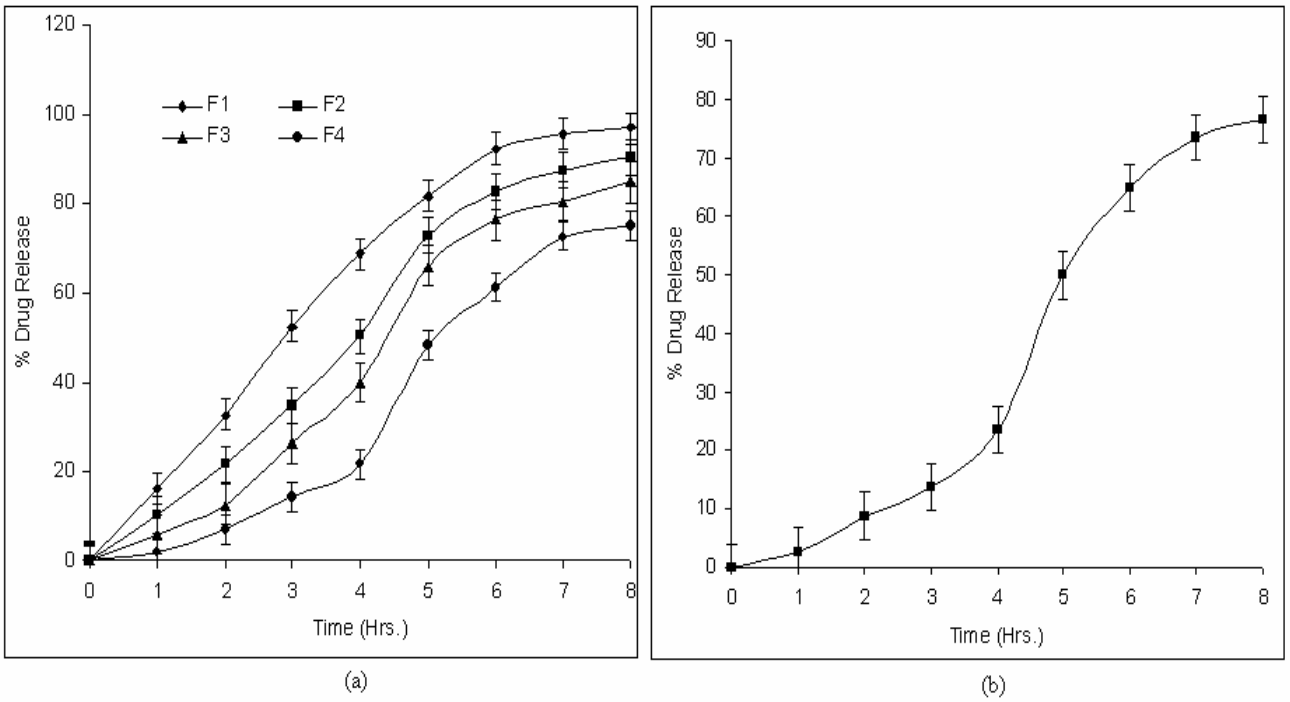

Figure 3. Percentage cumulative in vitro Theophylline release from alginate microspheres in pH progression medium (a) Containing differentdrug :alginate ratios (b) Optimized formulation.

Conclusion

Hydrophilic polymers microspheres swell in water and form gel which retards the drug release this could be attributed due to gel strength of the alginate microspheres in the dissolution media might be too high and prevented the release of drug from formulation. While in acidic environment alginate microspheres shrink due to tightening of the gel meshwork. At basic environment polymer is eroded and the contents are released in a sustained manner by both diffusion and slow erosion of polymer matrix.

We can conclude that sodium alginate microspheres of TP showed extended drug release profile in pH progression medium. Therefore, designed drug delivery system can be effectively used to improve the delivery of TP.

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