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Formulation and Evaluation of Pseudoephedrine Hydrochloride Loaded Alginate Microbeads

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ABSTRACT

Multiple unit dosage forms such as microbeads have increased acceptance because of added even spreading of the drug in the gastrointestinal tract, unvarying drug absorption, abridged local irritation and removal of undesirable intestinal retaining of polymeric material, when compared to non-disintegrating single unit dosage form. The purpose of the presented research is to develop microbeads of pseudoephedrine hydrochloride utilizing sodium alginate as the hydrophilic carrier in combination with HPMC as drug release modifier to lessen the dosing frequency and thereby advance the patient compliance. The microbeads were formulated by varying concentrations of HPMC and calcium chloride. The optimum formulation was chosen based upon *in vitro* drug release studies and further evaluated. The compatibility of drug-polymer was studied using FTIR analysis. The prepared formulation underwent evaluation for various parameters like drug entrapment, microbeads size, swelling index, mucoadhesive property and stability. No significant drug-polymer interactions were observed in compatibility studies and the formulation was found to be stable on 45 days storage. The formulations exhibited an extended drug release pattern which was the ultimate aim of the study. The microbeads represented good yield, high drug entrapment, low microbeads size and appropriate swelling property. The *in vitro* wash-off test indicated that the sodium alginate microbeads represent decent mucoadhesive properties. Henceforth, the formulated HPMC coated sodium alginate beads can be utilized as a substitute and cost-effective carrier for the oral controlled delivery of pseudoephedrine hydrochloride.

Keywords: microbeads, pseudoephedrine hydrochloride, sodium alginate, drug release

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INTRODUCTION

Oral drug delivery is the furthermost required and ideal way of administering therapeutic candidates for their systemic effects. Furthermore, the oral medication is largely measured as the initial path explored in the discovery and advancement of novel therapeutic entities and pharmaceutical preparations, chiefly owing to patient reception, ease and cost-effective manufacturing procedure [1]. For ample drug candidates, controlled drug delivery system delivers clinically active cure while preserving the essential balance of pharmacokinetic and pharmacodynamic outlines with satisfactory level of safety to the patient [2]. A controlled release system comprises any conveyance arrangement that attains deliberate release of the drug over a prolonged period of time, guarantees safety, efficiency of the drugs and patient compliance. Effective commercialization of a controlled release formulation is often challenging and comprises attention to many issues such as physiochemical properties of the drug, physiological factors and manufacturing variables [3].

Controlled drug delivery system holds promising results in site-specific targeting. One of such approach is the formulation of microbeads as drug carriers. Multiple unit dosage forms such as microspheres or microbeads have increased acceptance because of added even spreading of the drug in the gastrointestinal tract, more unvarying drug absorption, abridged local irritation and removal of undesirable intestinal retaining of polymeric material, when compared to non-disintegrating single unit dosage form [4]. Microbeads are small, solid and free flowing particulate carriers encompassing dispersed drug particles either in solution or crystalline form that permits a sustained release or multiple release profiles of treatment with various active agents without major side effects [5].

Inotropic gelation method for the preparation of microbeads is grounded on the electrostatic interaction amongst polymer's amino cluster and negatively charged assembly of

polyanion. Natural polysaccharides are used as biopolymers in novel drug delivery system, thus ensuring eco-friendly pharmaceutical development. Amongst the natural polymers, sodium alginate has been considered typically and generates reticulated assembly when cross-linked with polyvalent or divalent ions [6]. Pseudoephedrine hydrochloride is a sympathomimetic drug efficacious for treating nasal congestion and vasoconstriction. Biological half-life ($t_{1/2}$) of pseudoephedrine hydrochloride is less, furthermore it is sparingly water-soluble drug and exhibits a low dissolution rate. Pseudoephedrine hydrochloride when formulated in a dosage from such as tablets reveals duration of action of 3 to 4 h, whereas when formulated as extended release form exhibit duration of action of 8 to 12 h [7]; hence, it was thought worth to fabricate one such sustained release form of pseudoephedrine hydrochloride as microbeads.

The aim of the presented research is to develop sustained release oral product namely microbeads of pseudoephedrine hydrochloride using sodium alginate as the hydrophilic carrier in combination with HPMC as drug release modifier to reduce the dosing frequency and thereby improve the patient compliance. Also, to improve its bioavailability by bypassing the first pass metabolism because alginate beads shrink and unable to swell at acidic environment and the encapsulated drugs are not released whereas they easily swell in an alkaline environment and release the drug.

MATERIALS AND METHODS

Preparation of alginate microbeads

Pseudoephedrine hydrochloride microbeads were prepared by dissolving sodium alginate in distilled water at 800 rpm for 30 min to get a bubble free clear solution (2% w/v). Drug and polymer (HPMC) were taken (Table 1) and dispersed in sodium alginate solution and mixed thoroughly to form a smooth viscous dispersion. Resulted dispersion was dropwise added to calcium chloride solution (5% w/v in distilled water), through a needle of 20-gauge size with continuous stirring at the speed of 500 rpm. The cations diffuse into the drug loaded polymeric drops, forming a three-dimensional lattice of ionically cross-linked moiety. The resulting microbeads were collected by filtration and washed repeatedly with purified water to remove excess calcium deposited on the surface of microbeads. The resultant microbeads were dried under vacuum.

Product yield

The yield of the prepared formulations was calculated as the percentage of the weight of the dried product at room temperature compared to the theoretical amount. Production yield is calculated using the following equation:

Percentage yield = [weight of product/(weight of drug + polymer)] × 100

Drug entrapment efficiency

Pseudoephedrine hydrochloride content in microbeads was estimated by UV-spectrophotometric method. Accurately weighed (50 mg) microbeads samples were added in 100 ml of phosphate buffer (pH 7.4) and kept for stirring for 24 h. The solution was filtered and the free drug concentration was determined spectrophotometrically at 257 nm using UV-visible spectrophotometer. The entrapment efficiency for all the formulations was calculated by using following formula:

Percent entrapment efficiency = (estimated drug content/theoretical drug content) × 100

Optimization

Various formulation variables *e.g.* drug concentration, polymer concentration, emulsifier concentration, concentration of cross-linking agent and process variables *viz.* stirring speed were identified and studied (Table 1). In order to get optimized product dissolution studies were carried out.

Table 1: Variables applied for optimization of microbeads formulation.

S. No.	Parameter	Formulation				
		A1	A2	A3	A4	A5
1	Drug	1.0	1.0	1.0	1.0	1.0
2	HPMC	0.5	1.0	1.5	1.0	1.0
3	Sodium alginate	2.0	2.0	2.0	2.0	2.0
4	Calcium chloride	5.0	5.0	5.0	3.0	7.0

In vitro drug release studies

The *in vitro* drug release studies of drug loaded microbeads were carried out using USP dissolution apparatus type I in different mediums. Microbeads were weighed (100 mg) and gently spread over the surface of 900 ml of dissolution medium. The content was rotated at 50 rpm at 37 ± 0.5 °C. Perfect sink condition was maintained during drug dissolution study period. The simulation of gastrointestinal transit condition was achieved by altering the pH of dissolution medium at different time intervals. The pH of dissolution medium was maintained at 1.2 for 2 h using 0.01 N HCl. The medium was filtered through membrane filter (0.45 µm), after few hours when the sample were withdrawn the residue on filter paper was added to the next medium immediately, that is phosphate buffer pH 7.4 and the samples (10 ml) were withdrawn at particular time intervals of 15 min from another medium as well. The samples were analysed using UV-visible spectrophotometer at 257 nm for drug release. The receptor volume was maintained constant by replacing with equivalent volume of medium after each withdrawal. The drug concentration was calculated using regression equation of the calibration curve.

Drug-polymer compatibility study in microbeads

Compatibility studies in optimized formulation were performed using Fourier Transform infrared (FTIR) spectroscopic analysis. To check the compatibility of the pseudoephedrine hydrochloride with polymer, IR spectra of drug, polymer and combination of the drug and polymer were taken on an FTIR spectrophotometer in the wave number region of 400 and 4000 cm^{-1}.

Measurement of microbeads size by optical microscopy

Size of the prepared microbeads in optimized formulation was determined using an optical microscope fitted with a stage and an ocular micrometre. Mean diameter was calculated by measuring diameter of 50 mg dried microbeads of formulation.

Swelling index study

The extent of swelling was measured in terms of percent weight gain by the beads. In this test 20 mg of beads was kept in petri dish containing phosphate buffer (pH 7.4). At the end of 1 h, the beads were withdrawn, soaked with tissue paper and weighed. Then for every 1 h, weights of beads were noted and the process was continued till the end of 8 h. The percent weight gain by the beads was calculated by the following formula:

Swelling index (SI) = $[(W_t - W_0)/W_0] \times 100$

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

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 apparatus. When the test apparatus was operated, the sample is subjected to slow up and down movement in the test fluid at 37 °C contained in a one litre vessel of the apparatus. At an interval of 30 min up to 8 h, the machine was stopped and number of beads still adhering to mucosal surface was counted. The test was performed at intestinal (phosphate buffer pH 7.4) condition.

Stability studies

To assess the long-term physical stability, microbeads from were filled into a hard gelatin capsules manually and wrapped the filled capsule with aluminium foil and entire packet was kept in to self-sealing polyethylene cover. The stability studies were performed at room temperature for period of 45 days. Particle size studies (with optical microscope) and drug content analysis (spectrophotometrically at 257 nm) were conducted every 7 days for the entire period of stability study.

RESULTS AND DISCUSSION

Chemical reaction between sodium alginate and calcium chloride to form calcium alginate was utilized for the microencapsulation of pseudoephedrine hydrochloride core material. For slowing the drug release hydrophilic polymers were added in different concentration so that the drug will release constantly for 24 h. The yield of all the formulations was found to be in the range of 77.23 ± 0.35 to 89.87 ± 0.46%. The drug entrapment efficiency determines the percentage of encapsulated drug with respect to the total drug introduced into polymer solution. Our study indicated that the drug entrapment efficiency for various formulations of pseudoephedrine hydrochloride in microbeads was found to be in range of 76.30 ± 0.38 to 92.14 ± 0.54% (Table 2).

Table 2: Percentage yield and drug entrapment efficiency of various microbeads formulation of pseudoephedrine hydrochloride (n=3).

Formulation	Percentage Yield (Mean ± S.E.M.)	Drug Entrapment Efficiency (Mean ± S.E.M.)
A1	77.23 ± 0.35	86.23 ± 0.51
A2	86.90 ± 0.50	92.14 ± 0.54
A3	89.87 ± 0.46	88.75 ± 0.46
A4	79.34 ± 0.41	80.86 ± 0.48
A5	83.45 ± 0.46	76.30 ± 0.38

It is obvious that increasing calcium chloride concentration produces beads with higher levels of Ca^{2+} ions. Consequently, the cross-linking of the polymer and compactness of the formed insoluble dense matrices also increases, resulting in more drug entrapment in the microbeads. On other hand further increase in the concentration of calcium chloride above (5% w/v) do not enhance the drug loading. This could be due to possible saturation of calcium binding sites in the guluronic acid chain, preventing further Ca^{2+} ions entrapment and, hence, cross-linking was not altered with higher concentration of calcium chloride solution [8]. Therefore, the percentage of calcium chloride in our study was chosen in such a manner to get maximum drug loading efficiency.

Dissolution studies were carried out for formulation optimization. Firstly, we observed the dissolution profile of prepared microbeads in 0.01N HCl and phosphate buffer (pH 7.4) by varying the concentration of polymer (HPMC) and keeping rest of the excipients unchanged. Dissolution rate was found out to be increased with an increase in time. Amongst formulations with various drug polymer ratio *viz.* 1:0.5, 1:1 and 1:1.5, the formulation with 1:1 ratio exhibited best drug release, hence optimized for other preparations (Figure 1).

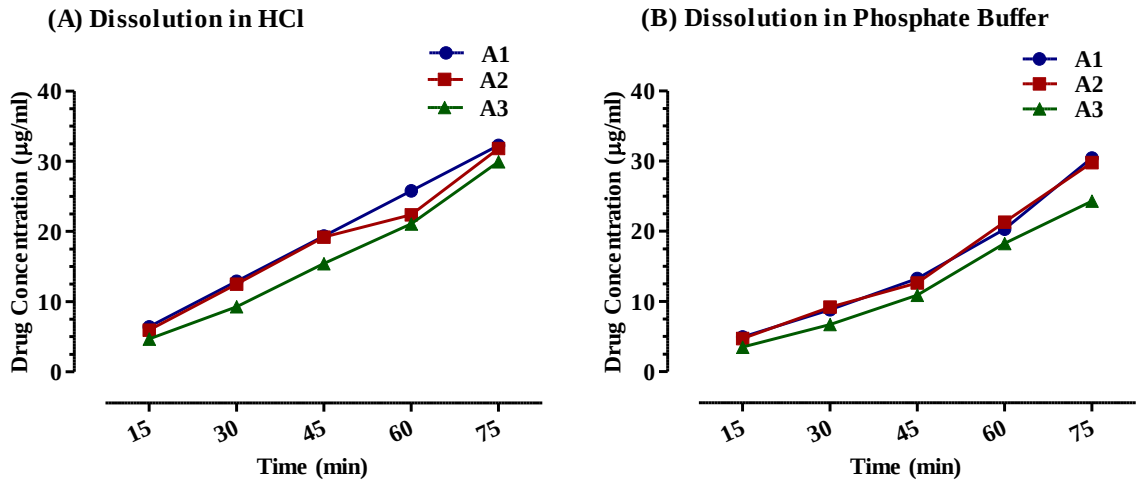

Figure 1: *In vitro* drug release studies for pseudoephedrine hydrochloride loaded alginate microbeads prepared using varying concentration of HPMC.

Calcium chloride is mainly used for crosslinking. We used varying concentrations (3%, 5% and 7% w/v) of calcium chloride in our previously optimized formulation. It was found that, at lower concentration (3%) dissolution increased whereas at higher concentration (7%), dissolution decreased. Hence, the best results were obtained with 5% calcium chloride (Figure 2). Hence, the formulation A2 with drug:polymer:sodium alginate:calcium chloride as 1:1:2:5, has been optimized and utilized for further studies.

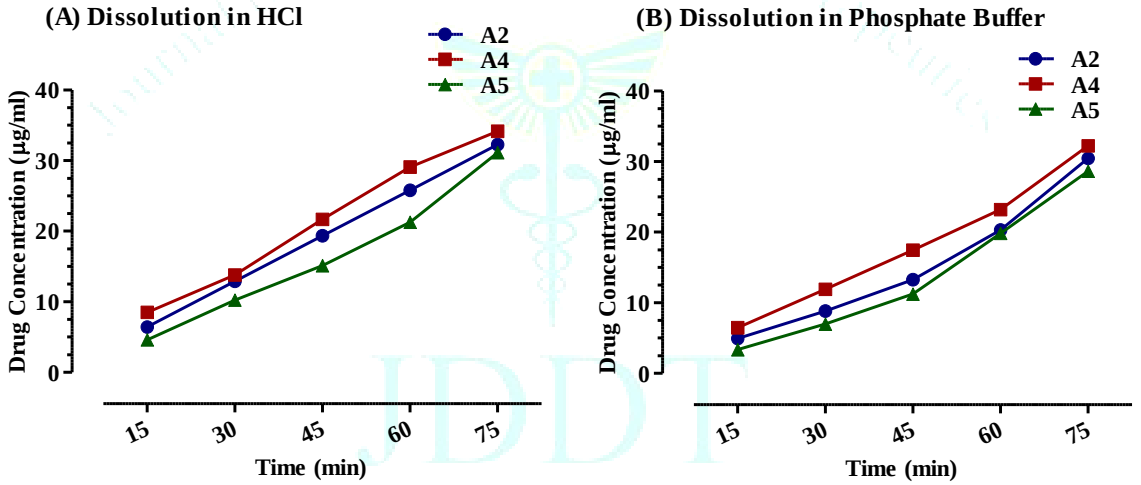

Figure 2: *In vitro* drug release studies for pseudoephedrine hydrochloride loaded alginate microbeads prepared using varying concentration of calcium chloride.

The compatibility of pseudoephedrine hydrochloride with various polymers was investigated by FTIR-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 mean particle size of optimized formulation of pseudoephedrine hydrochloride microbeads was found to be 867.45 ± 3.08 µm. It has been specified that when a drop of alginate solution comes in contact with calcium ions, gelation occurs instantaneously. As Ca^{+2} ions, penetrates into interior of droplets, water is squeezed out of the interior of droplets resulting in contraction of beads [9]. The size of the spherical matrix could easily be controlled by varying the stirring speed and cross-linking time of the system. The swelling behaviour of the beads was studied by measuring the weight of the beads after exposure to phosphate buffer, pH 7.4 for 8 h. Degree of swelling is proportional to ratio of drug to polymer and it affects the property of drug release from polymer. The mean swelling index of optimized formulation of pseudoephedrine hydrochloride microbeads was found to be 62.35 ± 0.14% (Table 3). Under neutral conditions the beads swell and the drug release depends on the swelling and erosion process. Being a polyelectrolyte, alginate can exhibit swelling properties that are sensitive to the pH, ionic strength and ionic composition of the medium [10]. The optimized batch was subjected to mucoadhesive test and formulation A2 exhibited 80.71 ± 0.55% mucoadhesive property. The optimized formulation was subjected to stability studies at room temperature 45 days. Thereafter, the beads size and drug content were determined. Results from the stability studies indicated that beads were physically and chemically stable for more than 45 days, exhibiting no significant change in bead size and drug content.

Table 3: Evaluation parameters of alginate microbeads formulation of pseudoephedrine hydrochloride

Optimized Batch	Microbeads size (µm)	Swelling index (%)	Mucoadhesion (%)
	Mean ± S.E.M. (n=3)		
A2	867.45 ± 3.08	62.35 ± 0.14	80.71 ± 0.55

CONCLUSION

Pseudoephedrine hydrochloride microbeads were successfully prepared by ionotropic gelation method. Among the batches, A2 exhibited better drug release and further used to determine the microbead size, swelling index, mucoadhesive property and stability. All the evaluated parameters found to be in promising range. Therefore, it can be assumed that the pseudoephedrine hydrochloride microbeads are promising pharmaceutical dosage forms, which provide sustained release drug delivery system and improve bioavailability. The entire process is feasible in an industrial scale and can be applied for further pilot study.

CONFLICT OF INTEREST

The author does not have any conflict of interest.

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