EFFECT OF SURFACTANT AND METHODS OF DRYING ON METHOTREXATE HYDROCHLORIDE LOADED CHITOSAN BEADS

ABSTRACT

To get chitosan beads, an ionotropic gelation technique was used in which drug containing chitosan solution added into tripolyphosphate solution. Obtained beads were evaluated to study the effect of Span 80 and methods of drying on their properties. Air drying method resulted in shrunken beads, the oven drying method resulted in dark, brittle and cracked beads, and freeze-drying method showed adverse effect on sphericity and surface topography of the beads. Higher proportion of Span 80 in the beads showed faster release. Oven-dried beads gave delayed release compared to air- and freeze-dried beads. *In vitro* drug release data depicted $t_{70\%}$ at 365 min with 88.17 % drug release for 12 h. Thus, formation of controlled release beads can be inferred.

Keywords: Chitosan, Methotrexate, Span 80, oven drying, air drying and freeze-drying

INTRODUCTION

Different particle drug delivery systems have been researched to achieve selective and effective medication targeting the site of action. Beads among such systems have drawn a lot of attention[1-2]. Beads made with natural polymers like alginates and chitosan have received a great deal of attention. Since the 1980s, numerous processing methods have been created to produce chitosan beads[3-4]. Chitosan, a polycationic (pK_a 6.5), biodegradable and biocompatible polymer, has been extensively explored in preparing particulate dosage forms to achieve desirable drug release. In acidic media, chitosan can react with oppositely charged species like tripolyphosphate (TPP), sodium sulfate etc[5-7]. This characteristic employed here to formulate controlled release chitosan beads with methotrexate HCl (MTX), as a model drug using ionotropic gelation method.

MATERIALS AND METHODS

Materials

MTX was a gratis sample from Sun Pharmaceuticals Ltd., Mumbai. Chitosan was a gratis sample from Central Institute of Fisheries Technology, Cochin. All other chemicals were AR grade and used as received.

Preparation of beads

MTX (10 mg) was disseminated in 1% V/V aqueous glacial acetic acid with 1% w/V chitosan solution (Disperse phase). Using an 18-gauge disposable syringe, the bubble-free dispersion phase was dropped into a mildly stirred 1% w/V TPP solution containing 0.5% V/V span 80 to create the beads (10 mL). Resultant beads were separated after 10 min of stirring by filtration and dried.

% yield of beads

% Yield = [weight of beads÷(weight of drug+weight of polymer)]× 100

Drug content of beads

To extract the drug, beads were treated with 0.1N HCl solution for 36 h. The acidic extract was filtered through membrane filter (0.45 µm) and analyzed at 303 nm, using 0.1N HCl as the blank by spectrophotometer. Drug content was calculated.

In vitro release studies of beads

Dissolution investigations were conducted using USP dissolution apparatus type I (Scientific USP standards, Model DA). With the basket's stirring speed set to 100 rpm, a dissolving medium (phosphate buffer saline, 500 mL, pH 7.4, 37 0.5 ^{0}C) was added. A basket of beads (50 mg) was added. At regular intervals, 1 mL samples were taken, and each sample's concentration was assessed using a blank in a UV spectrophotometer at 303 nm.

RESULTS AND DISCUSSION

During ionotropic gelation $–NH^+_3$ sites of polycationic chitosan had interacted with hydroxyl and phosphoric ion of sodium tripolyphosphate to get the chitosan beads. Chitosan beads were subjected to tests to see how the concentration of Span 80 and drying techniques would affect them (Table I). With increasing Span 80 concentration, the % yield and drug contents were found decreasing. This might be attributed to the presence of Span 80 which could not partition entirely into beads but remained partly in the continuous phase. A delayed drug release was observed for the formulation containing 0.5% V/V Span 80 with $t_{70\%}$ of 370 min. When it was increased

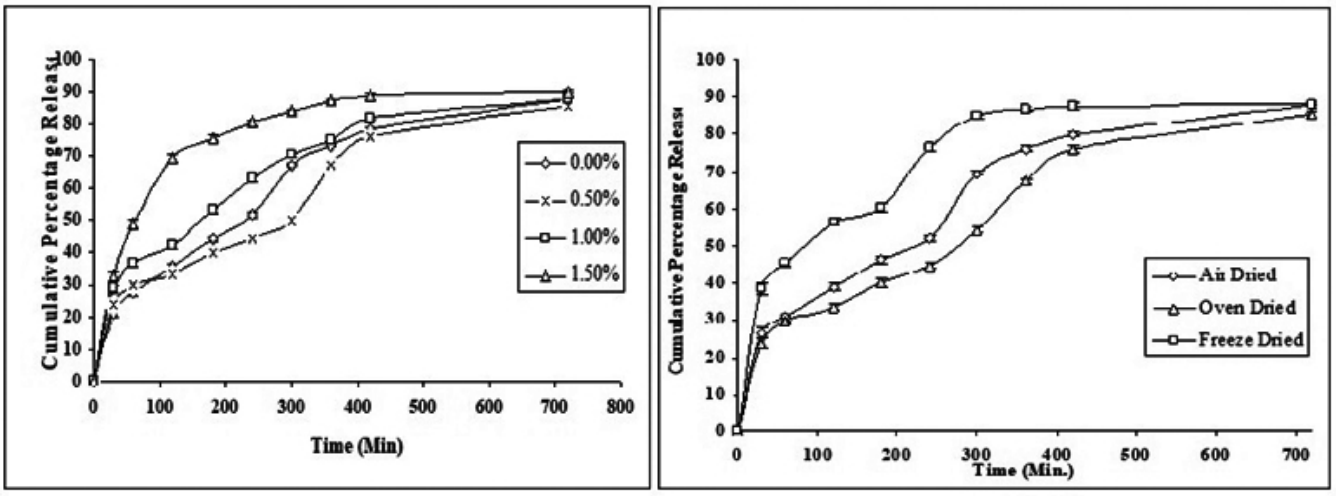

Fig. 1: Cumulative drugs release profiles

Table I: Effect of Span 80 and methods of drying on chitosan beads

Batch Code	Method of drying	Span 80 (%)	Yield (% ± SD)	Drug content (% ± SD)	t_{70} (min)
CHI01	Air drying for 24 h	0.0	80.18 ± 0.44	56.56 ± 0.59	316
CHI02	Air drying for 24 h	0.5	81.00 ± 0.13	58.56 ± 0.52	370
CHI03	Air drying for 24 h	1.0	76.70 ± 0.25	49.70 ± 0.76	300
CHI04	Air drying for 24 h	1.5	69.20 ± 0.33	39.48 ± 0.77	125
CHI05	Air drying for 24 h	0.5	81.00 ± 0.13	58.56 ± 0.52	300
CHI06	Oven drying for 6 h	0.5	80.66 ± 0.22	59.04 ± 0.57	375
CHI07	Freeze drying for 6h	0.5	86.66 ± 0.77	65.12 ± 0.87	220

to 1.0 % V/V and 1.5 % V/V, a faster drug release was observed. The excess of Span 80 in the formulation might have prevented the aggregation of beads and could have increased the surface that has contact with dissolution medium, which had resulted in faster drug release. The effect of methods of drying on % yield was insignificant. However, % drug content of freeze-dried beads was higher than air-dried and oven-dried beads. During air drying, the beads contracted significantly. During oven drying, dissolved MTX might have drifted with the outer surface of beads and observed as dried crystals that might be responsible for high drug content. The beads quickly hardened during the freeze-drying process, and water transfer was not possible. Therefore, under these circumstances, MTX could not diffuse outside of the beads. Oven drying resulted in dark beads with a brittle and cracked appearance. These beads had smooth surface relatively with some residual drug crystals on to it. Such drug crystals might be attributed to the rapid emulsion droplet formation before the drug got entrapped. The oven-dried beads showed ($t_{70\%}$=375 min) extended drug release profile than air-dried ($t_{70\%}$=300 min) and freeze-dried beads ($t_{70\%}$=220 min). Slow release of drug in oven-dried beads was attributed to the temperature employed in oven drying that might have affected the glass transition temperature of the chitosan (Fig. 1).

CONCLUSION

In present work, an attempt was made to prepare chitosan beads containing MTX using ionotropic gelation technique. Further, effect of Span 80 concentration and methods of drying were chosen as variables to check their effects on properties of prepared beads. It was concluded that 0.5% V/V of Span 80 and oven drying method could be suitable for chitosan beads physico-chemical properties of beads.

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