European Journal of Applied Sciences 5 (2): 47-52, 2013
ISSN 2079-2077

DOI: 10.5829/idosi.ejas.2013.5.2.71224

Formulation and Development of Acrycoat-Coated Chitosan Beads of Ornidazole for Colon Targeting

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Abstract: The goal of the current investigation is to develop a pH-dependent colon targeted drug delivery system containing ornidazole loaded chitosan beads for the management of amoebiasis. The beads were prepared using different ornidazole and chitosan ratios (1:2 to 1:3.5) by ionic gelation technique. Acrycoat S100 was used as pH dependent polymer for coating of chitosan beads exploiting oil- in-oil solvent evaporation method. Prepared beads were characterized for their possible drug interaction by FTIR, particle size with SEM, swelling behavior, drug entrapment and percentage yield. The particle size of beads obtained by SEM analysis showed average particle size of 1.32 ± 0.10 mm in 8 % STPP & 1.61 ± 0.12 mm in 12 % STPP solution. The release profile of ornidazole was found to be pH dependent. In acidic medium, the release rate was much slower; however, the drug was released quickly at pH 7. It is concluded from the present research work that Acrycoat-coated chitosan beads are promising controlled release carriers for colon-targeted delivery of ornidazole.

Key words: Acrycoat · Ornidazole · Chitosan and ion-gelation technique

INTRODUCTION

Colon is being extensively investigated as a drug delivery Site. Protozoal infections are common among people in the under developed tropical and subtropical countries. From the last few decades, a great deal of research work has been devoted to the development of the site specific drug delivery systems which offer several benefits over the traditional drug therapies. The colon, as a site for drug delivery, offers distinct advantages on account of a near neutral pH, a much longer transit time, relatively low proteolytic enzyme activity and a much greater responsiveness to absorption enhancers [1]. In the present study, an attempt was made to design colon targeted chitosan beads of ornidazole for treatment of amoebiasis. The main interest in such dosage form was to target the drug to the colon by ensuring minimal amount of drug release in the physiological environment of the upper GI tract by targeting it to the colon so as to obtain slower release rates or longer release periods by the application of thicker layers of conventional enteric coatings [2]

Chitosan is a cationic polymer, which is the second most abundant polymer in nature after cellulose. Chitin is the primary structural component of the outer skeletons of crustaceans and is, also found in many other species such as molluscs, insects and fungi. The most commonly obtained form of chitosan is the α-chitosan crustacean chitin obtained from crab and shrimp shell wastes [3].

Chitosan is a polysaccharide consisting mainly of unbranched chains of β-(1,4)-2- acetoamido-2-deoxy-D-glucose. The amino group in chitosan has a pKa value of ~ 6.5. It is an amorphous solid which is practically insoluble in water, dilute acids, dilute and concentrated alkalies, alcohol and other organic solvents [4].

Acrycoat S-100 is recommended for sustained release, delayed release formulation. It is an anionic acrylic co-polymer which conforms to USP/NF specifications of "Methacrylic Co-Polymer" Type B. Acrycoat S100 film is resistant to gastric fluid and natural juices but is freely soluble in intestinal tract in pH 7.0 and above by formation of salt with alkalis [5].

MATERIALS AND METHODS

Ornidazole drug was obtained as gift sample from Unidrug Pharma Technologies Ltd, Indore and Acrycoat S100 -was obtained by Coral Pharma Chem, Ahmedabad, Chitosan purchased from Fisher scientific, New Jersey

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Table 1: Different variable used in the preparation of Ornidazole chitosan beads

	8% Sodium tripolyphosphate				12% sodium tripolyphosphate			
Chemicals & reagents	F1 (1:2)	F2 (1: 2.5)	F3 (1:3)	F4 (1:3.5)	F5 (1:2)	F6 (1.2.5)	F7 (1:3)	F8 (1:3.5)
Ornidazole(mg)	250	250	250	250	250	250	250	250
Chitosan(mg)	500	625	750	875	500	625	750	875
Acetic acid (2%) (ml)	20	26	30	34	20	26	30	34
Acrycoat S100 (gm)								
{core : coat} 1 : 5	5	5	5	5	5	5 5	5	

USA. Sodium tripolyphosphate was purchased from Qualikems Fine Pvt. Ltd, Vadodara. All other solvents and reagents were of analytical grade.

Preparation of Chitosan-ornidazole Beads: Chitosan beads containing Ornidazole were prepared by a dispersion technique. Briefly, required quantity of chitosan was dissolved in 2% (v/v) acetic acid with gentle stirring. Required quantity of drug (Ornidazole) was then added to the polymer solution and mix properly. The solution was kept aside for the removal of air bubbles. Then the curing solution i.e. sodium TPP (8&12%) in distilled water was prepared. The beads were formed by injecting 5ml of bubble free chitosan solution drop wise using a disposable plastic syringe with a 22-gauge needle and a push pull syringe pump into the TPP solution under gentle agitation on a magnetic bead stirrer with 100 rpm. The dropping rate was 30 drops/min. The falling distance was 5 cm. The beads formed instantaneously and were kept for 1.5 hr to cure. The solidified beads were extensively rinsed with distilled water [6]. The product was then added in the flask containing 20mL 1% glutaraldehyde solution for the hardening of beads [7] and then dried at room temperature for 24 hrs.

Coating of Chitosan Beads: Chitosan beads were coated with Acrycoat S100 using oil-in-oil solvent evaporation method. Chitosan beads (50 mg) were dispersed in 10 ml of coating solution prepared by dissolution of 500 mg of Acrycoat S100 in ethanol: acetone (2:1) to give 5:1 (coat: core ratio). This organic phase was then poured in 70 mL of light liquid paraffin containing 1% w/v Span 85. The system was maintained under agitation speed of 1000 rpm at room temperature for 3 hours to allow for the evaporation of solvent. Finally, the coated beads were filtered, washed with n-hexane and freeze-dried overnight [8].

Drug-Excipients Interaction Study: The drug and excipients were analyzed by Fourier-Transform I.R spectrophotometer. The interaction of drug with the excipients was identified through interpretation of I.R spectrums.

Particle Size: The particle size of ornidazole hydrogel microbeads were viewed and photographed using Scanning electron microscopy. Ornidazole hydrogel microbeads were coated with gold to make the sample conductive. Coated samples were viewed and photographed in LESMARK opra S1855 SEM machine.

Equilibrium Swelling Studies: The dynamic swelling behavior of the beads was studied by mass measurement. The beads were incubated with 25 ml phosphate buffer pH 7.4 in a Petridish at 37°C. The beads were taken out at different time intervals using stainless steel grid and blotted carefully without pressing hard to remove the excess surface liquid. The swollen beads were weighed using the digital balance. The studies were performed in triplicate and average values were taken in data analysis. The degree of swelling (α) was then calculated from the formula:

$$\alpha = (W_g - W_o) / W_o$$

Where, Wo is the initial weight of beads and Wg is the weight of beads at equilibrium swelling in the medium [9].

Percentage Yield of Chitosan Hydrogel Bead: The yield of chitosan beads was determined by comparing the whole weight of microspheres formed against the combined weight of the copolymer and drug [10].

% yield= weight of microspheres /
(weight of drug + polymer) X 100

Drug Entrapment Efficiency: An accurately weighed amount of the prepared beads (50 mg) was crushed in a glass mortar and digested in phosphate buffer saline (pH 1.2) for 24 hrs in a graduated flask. The solution was filtered through a Whatman filter paper and an aliquot was used to assay for drug content spectrophotometrically (Shimadzu UV 1800) at λmax 277 nm. The encapsulation efficiency was calculated by expressing the actual entrapment level divided by the theoretical entrapment level, as a percentage [6].

Entrapment efficiency = Actual content/ theoretical content ×100

***In-vitro* Drug Release Study:** Chitosan beads were evaluated for the *in vitro* drug release in SGF. The drug dissolution test was performed using rotating basket apparatus (model DS-8000, LAB INDIA) USP dissolution apparatus-1.

Chitosan beads (100 mg) were weighed accurately and gently spread over the surface of 500 ml of dissolution medium (SGF). The content was rotated at 100 rpm at 37°C ± 0.5°C. Perfect sink conditions prevailed during the drug dissolution study period. The simulation of GI transit condition was achieved by altering the pH of dissolution medium at different time intervals.

Simulated gastric fluid (SGF) consisted of NaCl (2gm), HCl (7ml) and pepsin (3.2gm). The pH of the dissolution medium was kept 1.2 for 2 hours using 0.1 N HCl. Then KH_2PO_4 (1.7 g) and $Na_2HPO_4 2H_2O$ (2.2 g) were added to the dissolution medium, adjusting the pH to 4.5 with 1.0M NaOH and the release rate study was continued for an additional 2 hrs. After 4 hours, the pH of the dissolution medium was adjusted to 7.4 with 0.1 N NaOH and maintained up to 8 hrs. The samples were withdrawn from the dissolution medium at various time intervals using a pipette fitted with a microfilter. The rate of ornidazole release was analyzed using UV spectrophotometer. The receptor volume was maintained constant by replacing equivalent amount of SGF [8, 9]. The concentration of ornidazole in the samples was calculated.

Statistical Analysis: To investigate the drug release, the data obtained from *in - vitro* drug release were fitted to models representing Zero order, First order, Higuchi's equation & Korsmeyer -peppas model.

RESULTS AND DISCUSSION

FTIR of drug and polymers used in studies shows that all the peaks of drug and polymer as it is and drug is present in free form. This indicates that there is no Chemical interaction in between Ornidazole and the polymers employed in formulations. The results are depicted in Figs 1, 2, 3 and 4.

The average size of the beads were found to be 1.32 ± 0.10 mm in 8 % STPP and 1.61±0.12 mm in 12 % STPP solution. The average particle size of chitosan beads increased with increase in concentration of sodium TPP from 8% to 12% w/v. This may be due to the reason that multifunctional STPP acts here to facilitate inter-microparticles binding of the chitosan.

The degree of swelling calculated ranges from 0.18 ± 0.02 to 1.31 ± 0.02 for 8% of STPP and 0.10 ±0.02 to 1.28 ± 0.16 for 12 % of STPP. It can be concluded that the swelling nature of the chitosan beads increases with increase in polymer concentration.

The percentage yield for various drug polymer ratios (1:2, 1:2.5, 1:3 and 1:3.5) was found to be 81.00 ± 0.90 % to 84.00 ± 2.2 % with 8 % of sodium tri polyphosphate and 80.0 ± 1.19 % to 83.0 ± 1.9 % with 12 % of sodium tri polyphosphate.

The percentage yield increases with increase in polymer concentration but it gets decreased due to increase in STPP concentration. This can be due to the reason that increases in viscosity with an increase in hitosan concentration retards penetration of phosphate ions into the interior of chitosan beads, resulting in decreased cross linking ions decreased % yield.

The drug entrapment efficiency for various drug polymer ratios (1:2, 1:2.5, 1:3 and 1:3.5) was found to be 51.68 ± 0.53 % to 83.88 ± 0.10 with 8 % of sodium tri polyphosphate and 49.80 ± 0.90 % to 77.94 ± 0.02 % with 12 % of sodium tri polyphosphate. With increase in polymer concentration the entrapment efficiency was found to be increased, may be due to the fact that, with increase in chitosan concentration drug holding capacity increases which leads to decrease in drug leaking from chitosan beads. The entrapment efficiency decreases with increase in strength of STPP concentration; this could be due to the increased binding of the main groups of the drug to the added STPP that might compete with the incorporation of the drug in the polymer matrix [11].

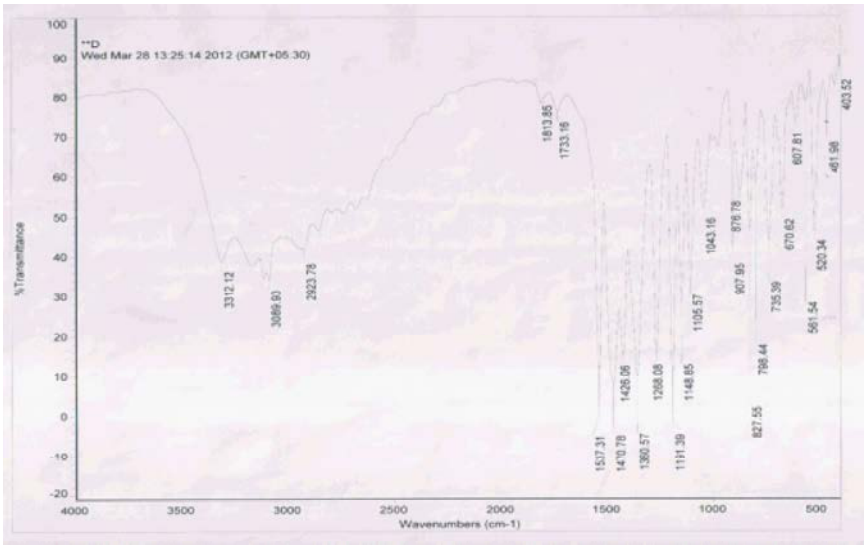

Fig 1: FTIR spectrum for ornidazole

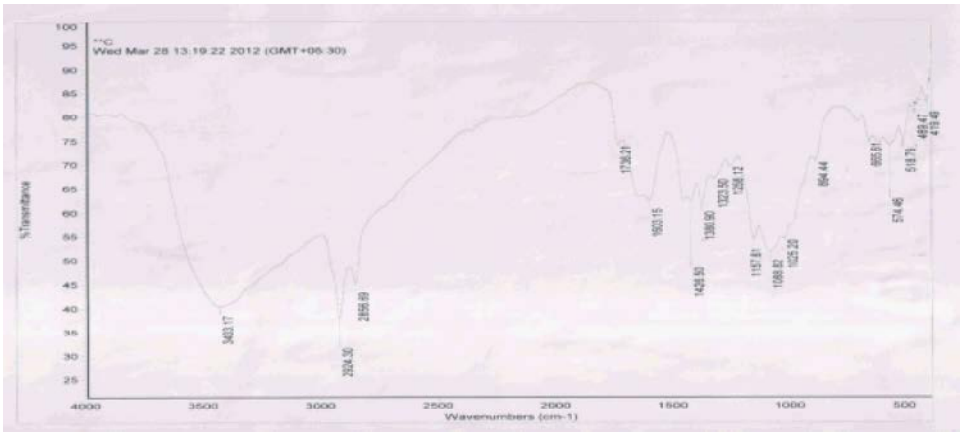

Fig 2: FTIR spectrum for chitosan

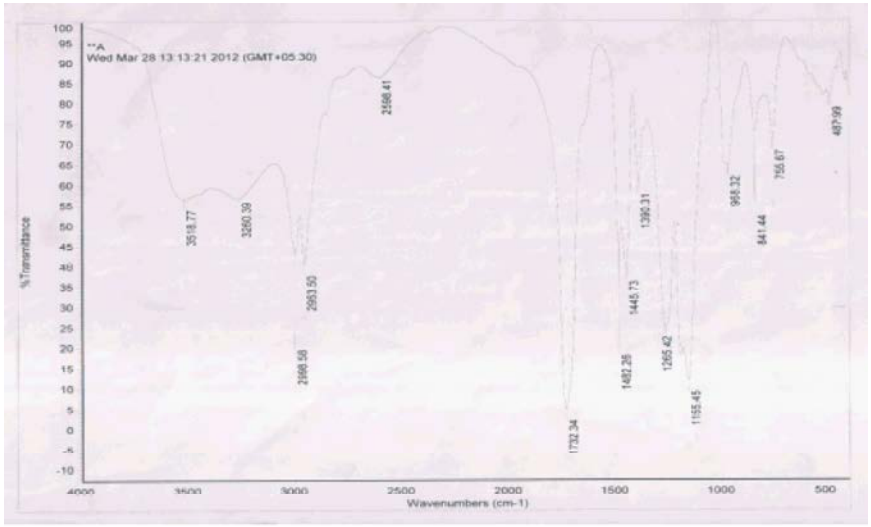

Fig 3: FTIR spectrum of Acrycoat S100

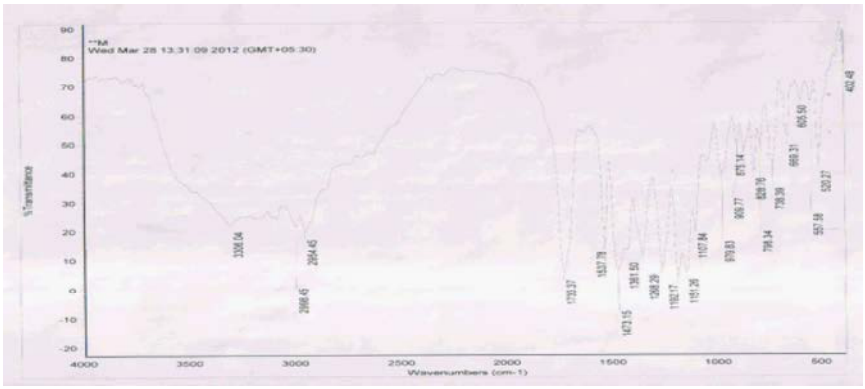

Fig 4: Physical mixture of Ornidazole, Chitosan & Acrycoat (1:1:1)

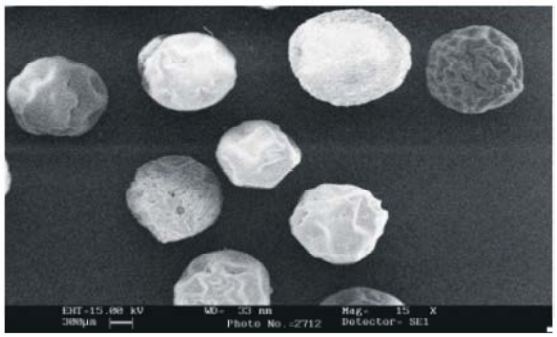

Fig 5: SEM image of Ornidazole chitosan beads for 8 % of STPP

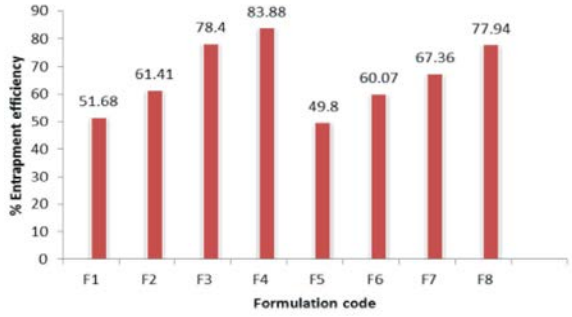

Fig 7: Entrapment efficiency for Ornidazole formulation batches

Fig 6: SEM of Ornidazole chitosan beads for 12 % of STPP

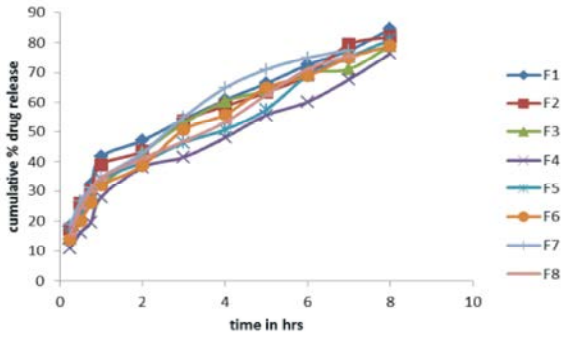

Fig 8: *In-vitro* drug release profile of ornidazole-chitosan formulations

Table 2: Data of Entrapment efficiency, equilibrium swelling studies and percentage yield for of ornidazole-chitosan formulations

Formulation code	Drug: polymer ratio	Percentage of STPP (%)	Entrapment efficiency (%) ± SD	Swelling studies (α)± SD	Percentage yield (%) ± SD
F1	1:2	8	51.68 ± 0.53	0.18 ± 0.02	81.0 ± 0.90
F2	1:2.5	8	61.41 ± 0.59	1.21 ± 0.09	81.5 ± 1.2
F3	1: 3	8	78.40 ± 0.70	1.29 ± 0.15	82.0 ± 2.0
F4	1:3.5	8	83.88 ± 0.10	1.31 ± 0.02	84.0 ± 2.2
F5	1:2	12	49.80 ± 0.90	0.10 ± 0.02	80.0 ± 1.19
F6	1:2.5	12	60.07 ± 0.30	0.19 ± 0.04	81.37 ± 1.0
F7	1:3	12	67.36 ± 0.04	1.20 ± 0.10	81.80 ± 2.5
F8	1:3.5	12	77.94 ± 0.02	1.28 ± 0.16	83.00 ± 1.9

The *in vitro* drug release was found to be decreased from 84.50 % to 76.37% in 8% of STPP and 81.0% to 75.60% in 12 % of STPP solution. The rate of drug release from the beads was found to be reduced with increase in polymer concentration due to decrease in drug leaking from chitosan beads on increasing polymer concentration [12].

The release profile of ornidazole from Acrycoat-coated chitosan beads was found to be pH dependent. The release rate was much slower in acidic pH with maximum drug release of 41.76% in 8% STPP and 34.37 %of drug release in 12 % of STPP solution at 1hr; however the drug was released quickly at pH 7 showed maximum drug release of 84.5 % in 8 % of STPP and 81.0 % drug release in 12 % of STPP solution at 8 hrs.

Best linearity was found in Higuchi equation plot with maximum R^2 value corresponding near to 1 indicating the release of drug from matrix as a square root of the dependent process based on the Fickian model.

So, it can be concluded from the present research work that Acrycoat-coated chitosan hydrogel beads are promising controlled release carriers for colon targeted delivery of ornidazole.

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