



DEVELOPMENT AND CHARACTERIZATION OF TINIDAZOLE MICROCAPSULES FOR COLON DELIVERY

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ABSTRACT

Alginate and chitosan treated microcapsules of tinidazole were prepared for delivery of drug to colon via oral route. A colon specific drug delivery system, containing drug and a saccharide, which generates an organic acid by the action of enterobacteria in the lower part of gastro intestinal tract, is developed by coating it with an organic acid soluble polymer. Further coating with an enteric coating polymer material provides a drug release system that utilizes enterobacteria, which do not form harmful substances due to the release starting mechanism, show rapid degradation and have higher colon specificity. The present work is an effort to develop a delivery system based on polysaccharide polymers for selective delivery of tinidazole to the colon.

Key words: Tinidazole, Microcapsules, Colon delivery.

INTRODUCTION

Traditionally solid oral dosage forms have been designed to release their drug load in the upper regions of the gastrointestinal tract but recently greater emphasis has been placed on controlling the rate and/or site of drug release from oral formulation for the purpose of improving patient compliance and treatment efficacy.

The colonic region of the gastrointestinal tract is one area that would benefit from the development and use of such modified release technologies. Even, colon is vulnerable to a number of disorders including ulcerative colitis and Crohn's disease¹. In recent years, microcapsules have gained increasing importance as oral controlled drug delivery systems and presents several advantages like more predictable gastric emptying, less local irritation and intestinal retention of undigested polymer material in chronic dosing over unit dosage forms². But the design and development of microcapsules pose a challenge to the pharmaceutical scientists due to lack of manufacturing reproducibility, low drug efficiency

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and difficulty in obtaining steady state release kinetics.

Nowadays, complex technologies have emerged using natural and synthetic polymers for construction of appropriate matrices. In many cases, these polymers have already been traditionally employed in standard pharmaceutical processes³. Namely Chitosan, which has reactive hydroxyl and amino groups that can be modified chemically, for various biomedical applications^{4,5}. Chitosan forms a gel at low pH and has antacid and anti-ulcer activities that may prevent or reduce the drug irritation in the stomach.

Tinidazole is a drug of choice in the treatment of intestinal amoebiasis. The pharmacokinetic profile of tinidazole indicates that the drug is rapidly absorbed from the stomach and small intestine. Hence, the administration of tinidazole, in conventional tablet dosage form leads to the entry of most of the drug into the systemic circulation resulting unwanted side effects. The colon-targeted delivery of tinidazole may provide an effective treatment of intestinal amoebiasis with minimal or no systemic side effects⁶.

As a part of our research program, to investigate the controlled and targeted delivery of drug to the colon, microcapsules of chitosan and alginates containing tinidazole were prepared. With this system, our aim was to target the drug to the terminal ileum and colonic region.

EXPERIMENTAL

Materials and methods

Chitosan (purified viscosity grade 50) was obtained from Central Institute of Fisheries Technology, Cochin, India. Tinidazole was supplied generously as a gift sample from M/s Reantis Pharmaceuticals Pvt. Ltd., Ahmedabad, Gujarat. Sodium alginate (Extra pure, LF 20/60) was procured from Central Drug House, Mumbai.

Preparation of microcapsules

Alginate microcapsules were prepared by a method similar to that developed by Yotsuyangi et al⁵. According to this, tinidazole (100 mg) was added and dissolved completely into 10 mL of 1.5% (w/v) sodium alginate solution. This solution was poured drop by drop into 100 mL of 1% (w/v) calcium chloride solution with mild agitation in a period of 5 minutes (30 mL/h). Chitosan was added to the calcium chloride solution of 1% (w/v) for the preparation of chitosan treated alginate beads. Microcapsules were separated after 10 min. of reaction time. These were washed with distilled water and air dried for 24

h after treating with acetone for 2 minutes. All the microcapsules were evaluated to determine the morphological features, drug loading efficiency, *in vitro* release studies in presence or absence of rat ceacal contents.

Characterization of microcapsules

Morphology and particle size

Morphological study of the microcapsules was performed by scanning electron microscopy (SEM). Microcapsules were super coated with 20 nm gold and investigated using (JSM-4700) Scanning Electron Microscope (Joel l.t.d. Japan).

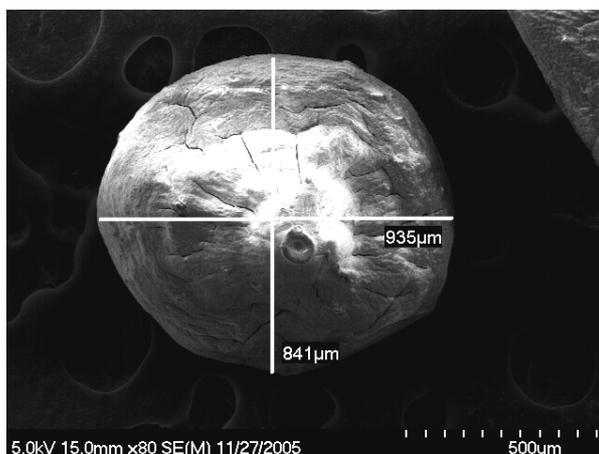


Fig. 1: SEM Photograph of alginate microcapsules

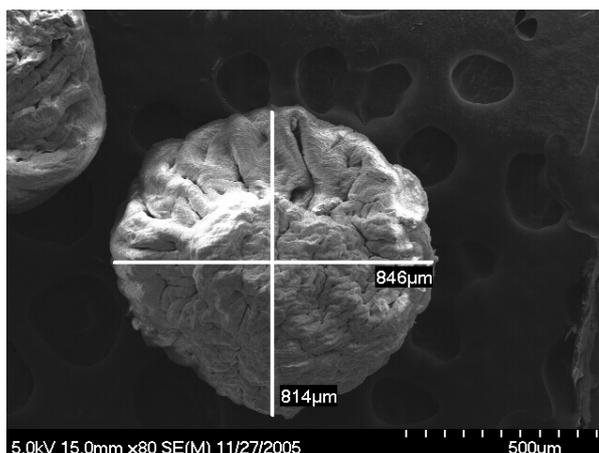


Fig. 2: SEM Photograph of chitosan treated alginate microcapsules

According to the SEM studies, it is clear that the microcapsules were spherical and smooth surfaced in nature (Figures 1 and 2). The size of microcapsules ranged from 0.745 μ m to 1.555 μ m. The surface is more porous in the alginate microcapsules whereas chitosan treated alginate microcapsules had some cracks on their surfaces.

Assessment of drug incorporation into microcapsules

100 mg of microcapsules were digested in 100 mL buffer of pH 6.8. The solution was filtered and the absorbance was measured using U. V. – visible spectrophotometer (U.V. 2100 S, Shimadzu, Japan) at 317 nm.

Table 1. Size and cumulative % release of alginate and chitosan treated microcapsules

Process variable	Code	Percentage composition	Mean particle size (mm \pm S.D.)	<i>in vitro</i> % release after 4 hours	<i>in vitro</i> % release after 7 hours
Sodium alginate concentration	A ₁ TA	1.5	1.0380 \pm 0.011	56.24 \pm 3.45	98.36 \pm 3.11
	A ₂ TA	2.0	1.0400 \pm 0.001	42.88 \pm 2.15	96.11 \pm 3.01
	A ₃ TA	3.0	0.883 \pm 0.009	37.63 \pm 3.11	94.17 \pm 3.11
Chitosan concentration	B ₁ TCA	1.5	1.1136 \pm 0.061	46.13 \pm 5.10	95.10 \pm 4.15
	B ₂ TCA	2.0	0.823 \pm 0.010	38.82 \pm 3.45	92.11 \pm 3.12
	B ₃ TCA	3.0	1.415 \pm 0.081	30.39 \pm 4.55	90.08 \pm 1.01

In vitro drug release study in the presence of colonic fluid containing 2% rat ceecal material

The drug release studies were carried out in stimulated colonic fluid using a USP dissolution rate test apparatus (100 rpm, 37 \pm 1° C). A pre-weighed amount of microcapsules was placed in the 200 mL of dissolution media (PBS pH 6.8) containing 2% W/V rat ceecal material. At different time intervals, the samples were withdrawn and replaced with fresh PBS. The samples were subjected to UV spectrophotometric analysis.

Table 2. Effect of ceecal content on percent tinidazole release from microcapsules without ceecal material and with 2% ceecal material.

Time (Hours)	Cumulative % drug release	
	With 2 % ceecal material	Without ceecal material
1	6	10
2	7	12
3	8	18
4	8	22
5	40	32
6	65	38
7	94	40

RESULTS AND DISCUSSION

Site-specific drug delivery can be achieved by microcapsules, coated with chitosan and sodium alginate; which release the drug only in the colon. These dosage forms exploit the enteric polymers, maintain their integrity and do not allow the release of the drug in the acidic environment of the stomach. As they arrive into small intestine, where pH is alkaline, they start to dissolve and release the drug. Colon specific release of the entrapped drug is achieved by dissolution of the enteric coating at the distal part of the small intestine. When exposed chitosan microcapsules reach to the colon; the drug release is affected by swelling of the polymer as well as by biodegradable effects of polysaccharides.

Drug release profiles of formulation A3TA and B3TCA are given in Fig. 5. Release was slower from the chitosan treated microcapsules as compared to the alginate microcapsules. In general, drug release was affected by alginate and chitosan concentration. Fig. 3 indicates the effect of alginate concentration on the release properties of the tinidazole. The presence of ceecal material in the dissolution medium increased the rate of drug release from microcapsules compared with the control. *in vitro* drug release in simulated colonic fluid without rat ceecal material was 40% but drug release in stimulated colonic fluid with 2% rat ceecal material after 7 hours was 94 %. From this, it can be concluded that the rat ceecal material in the dissolution medium had increased the drug release from microcapsules. Tinidazole release from the microcapsules was reduced with

increase in alginate concentration from 1.5% to 3%. Fig. 4 cleared that chitosan concentration has an effect on tinidazole release. Increase in its concentration caused retardation in the release properties of microcapsules.

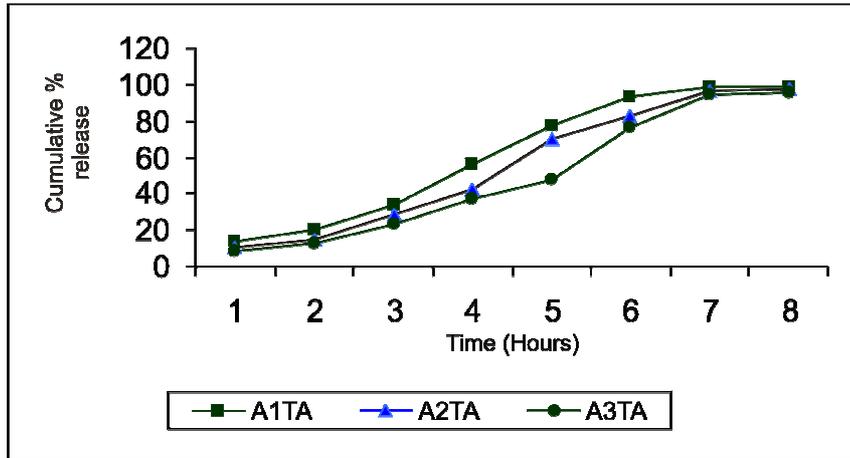


Fig. 3: Effect of alginate concentration on release characteristics of microcapsules

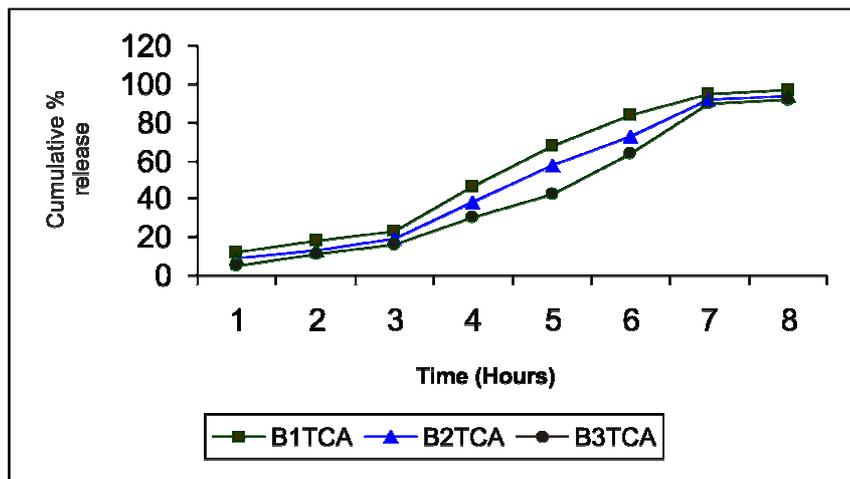


Fig. 4: Effect of chitosan concentration on release characteristics of microcapsules

When a comparison is done between the release properties of alginate and chitosan treated alginate microcapsules, it was found noticeably that there was a significant reduction in drug release from chitosan – alginate microcapsules (Fig. 5). Thus, it proves that the addition of chitosan to the gel structure reduced the drug release from microcapsules.

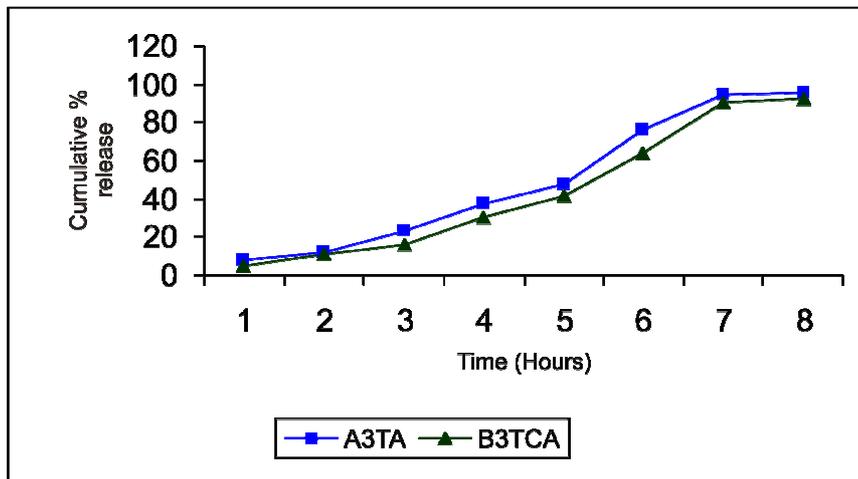


Fig. 5: Release profile of tinidazole from alginate and chitosan treated alginate microcapsules

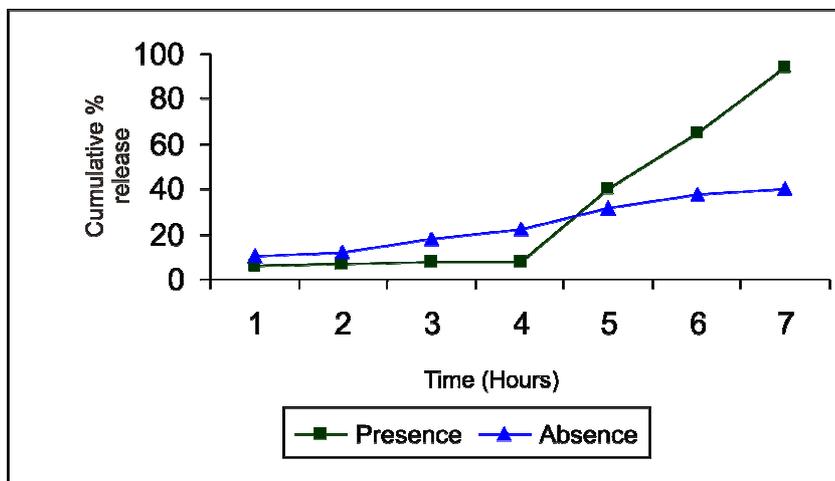


Fig. 6. Effect of presence and absence of 2 % ceacal content on percent Tinidazole release from microcapsules

Hence, our study proved that chitosan treated alginate microcapsules can serve better as a convenient colon targeted carrier for the controlled release of tinidazole. Changing a number of parameters can vary the release.

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