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Development and Characterization of Microcapsule of Flurbiprofen for Colon Specific Drug Delivery System

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Abstract: Colon specific drug delivery has gained increased importance not just for delivery of drug for the treatment of local diseases, associated with the colon but also potential site for systemic delivery of therapeutic drug. Flurbiprofen is non-steroidal anti-inflammatory drug with short half life. Two types of flurbiprofen microcapsules named, alginate microcapsules (AM) and chitosan treated alginate microcapsules (CTAM) were prepared for delivery of drug to colon via oral route by ionic gelation method. The prepared microcapsules were evaluated for various *in vitro* parameters such as flow property, particle size, entrapment efficiency, scanning electron microscopy (SEM) and drug release study. *In vitro* drug release studies were performed in stimulated colonic fluid i.e. pH 6.8-phosphate buffer containing 2% (w/v) rat ceacal material. Formulation $CTAM_3$ shows excellent flow property, entrapment efficiency (78.08±1.01%) and showed sustained release characteristics with constant fashion over extended period of time for 8 h. Hence the prepared Flurbiprofen loaded chitosan treated alginate microcapsules may prove that it be a convenient colon targeted carrier for the controlled release and potential candidate for safe and effective colon drug delivery.

Key words: Colon Targeted Drug Delivery · Chitosan · Microcapsules · Flurbiprofen

INTRODUCTION

The word new or novel in the relation to drug delivery system is a search for something out of necessity. An appropriately designed sustained or controlled release drug delivery system can be major - advance towards solving the problem associated with the existing drug delivery systems [1, 2]. The colon targeted drug delivery of both conventional and labile molecule was developed [3]. It is a drug delivery site for the treatment of local disease, associated with colon like crohn's disease, ulcerative colitis, irritable bowel syndrome; also it is a potential site for systemic delivery of therapeutic drugs [4, 5]. Colon is also found to be a promising site when delay in absorption is desirable from therapeutic point of view for the treatment of disease that have peak symptoms in early morning and that exhibit circadian rhythm, such as rheumatoid arthritis (RA), nocturnal asthma and angina pectoris [6, 7]. In case of rheumatoid arthritis, peak symptoms occur early in the morning due to the imbalance between anti-inflammatory effect by cortisol and proinflammatory effects exerted by melaton [8]. The widely used approaches for colon specific targeting are bacterially triggered, pressure controlled, pH dependent and time dependent control drug delivery system [3]. Microcapsules have received considerable attention among various drug delivery system investigated so far to achieve efficient and selective delivery of therapeutic agents to the target site [9-11]. This efforts have been focused on microcapsules prepared with natural polymers such as alginates and chitosan [10-12]. Chitosan Microcapsules are used for controlled release of various drugs and nutrients. Chitosan has reactive hydroxyl and amino groups which can be modified chemically, for various biomedical applications [12- 14]. Flurbiprofen [1, 1-biphenyl] -4-acetic acid, 2-fluro-alpha-methyl, is a important analgesic and non-steroidal anti-inflammatory drug (NSAID) also with

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anti-pyretic properties whose mechanism of action is the inhibition of prostaglandin synthesis. It is used in the therapy of rheumatoid disorders. Flurbiprofen is rapidly eliminated from the blood, its plasma elimination half-life is 3-6 hours and in order to maintain therapeutic plasma levels, the drug must be administered approximately 150-200 mg daily by oral individual dosage [15]. The aim of this work was to develop alginate microcapsules and chitosan treated alginate microcapsules of Flurbiprofen, whose physicochemical properties and short half life make it suitable candidate for colonic drug delivery system.

MATERIALS AND METHODS

Flurbiprofen was obtained as a gift sample from M/s FDA Pharmaceutical Ltd. (India). Chitosan (purified viscosity grade 50) was obtained from Central Institute of Fisheries Technology, Cochin, India. All other chemicals were purchased from commercial sources and were used of analytical grade.

Preparation of Microcapsules of Flurbiprofen: Alginate microcapsules were prepared by using ionic gelation method [16]. According to this, 100 mg of flurbiprofen 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 2% (w/v) calcium chloride solution with mild agitation for 5 minutes. The chitosan was added to the calcium chloride solution (2%, w/v) for the preparation of chitosan treated alginate microcapsules. Microcapsules were separated after 10 min. of reaction time. These were washed with distilled water and air dried for 24 hours.

Optimization of Formulation Variables: Various formulation variables were tried to prepare microcapsules such as: sodium alginate of different concentrations (1.5%, 2%, 3% w/v) for the preparation of alginate microcapsules and different concentrations of chitosan (1.5%, 2%, 3%) for the preparation of chitosan treated alginate microcapsules were optimized (Table 1). The effects of above formulation variables on the particle size, flow properties, drug loading and *in vitro* drug release study was determined.

Characterization of Microcapsules of Flurbiprofen

Morphology of Microcapsules: Morphological study of the microcapsules was performed by Scanning Electron Microscopy (SEM). The microcapsules were coated with 20 nm gold palladium under an argon atmosphere using a gold sputter module in a high vacuum evaporator. The coated samples were then observed with a scanning electron microscope.

Micromeritic Properties of Microcapsules: Average particle size of beads was determined by sieving method using automatic sieve shaker (HICON, India) [17]. Flowability of microcapsules was determined by angle of repose. The determination of angle of repose of Flurbiprofen microcapsules were carried out by employing fixed funnel method [18, 19].

Angle of repose $\theta = \tan^{-1}(H/R)$

H = Height of the pile
R = Radius of the pile

Determination of Entrapment Efficiency: 100 mg of microcapsules were digested in 100 ml phosphate buffer of pH 6.8 containing 2% (w/v) rat ceacal material. The solution was filtered through whatman filter paper and from the filtrate appropriate dilutions were made and absorbance was measured at 247 nm by using UV-spectrophotometer 1700 (Shimadzu, Japan). Percentage entrapment efficiency was also calculated according to the following relationship [20].

Table 1: Formulation Composition, Micromeritic properties and Percentage Entrapment Efficiency of Alginate Microcapsule (AM) and Chitosan Treated Alginate Microcapsule (CTAM)

Process Variable	Code	Composition (% w/v)	Average Particle Size (mm±S.D.)	Angle of repose (degree)	Entrapment Efficiency (%)
Sodium Alginate	AM_1	1.5	0.88±0.011	21	69.26±0.96
Concentration	AM_2	2.0	1.040±0.001	18	76.86±1.12
	AM_3	3.0	1.088±0.009	22	84.51±1.23
Chitosan	$CTAM_1$	1.5	0.98±0.061	17	75.10±1.15
Concentration	$CTAM_2$	2.0	1.082±0.010	23	77.11±1.12
	$CTAM_3$	3.0	1.115±0.081	16	78.08±1.01

$$\% \text{ Entrapment efficiency} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

***In vitro* Drug Release Study in the Presence of Colonic Fluid Containing 2% Rat Ceacal Material:** The drug release studies of each formulation was carried out in stimulated colonic fluid i.e. 900 ml of pH 6.8-phosphate buffer containing 2% (w/v) rat ceacal material by employing USP XXIII rotating basket method (100 rpm, 37±0.5°c). Microcapsules equivalent to 150 mg of Flurbiprofen was loaded into the basket of the dissolution apparatus. Five milliliters of the sample was withdrawn from the dissolution media at suitable time intervals and the same amount was replaced with fresh buffer. The absorbance of the filtrate was determined at wavelength of 247 nm by using UV–vis spectrophotometer.

RESULTS AND DISCUSSION

The Flurbiprofen loaded alginate and chitosan treated alginate microcapsules were successfully prepared by using ionic gelation method. The microcapsules were formed by ionic interaction between the negatively charged carboxyl groups of sodium alginate and the positively charged counter ion such as Ca++ [21]. The scanning electron microscopy (SEM) studies was shown that the Microcapsules were spherical and smooth surfaced in nature as given in figure 1. The surface is more porous in the alginate microcapsules whereas chitosan treated alginate microcapsules had some cracks on their surfaces. The value of angle of repose of all microcapsules formulations was found within the range of 16°to 23°(Table 1) which indicating that all formulations exhibited excellent flow properties. The average particle size of alginate microcapsule formulations were ranged between 0.88±0.011 mm (AM_1) to 1.088±0.009 mm (AM_3) as shown in table (1), whereas chitosan treated alginate microcapsules shown the value of average particle size in the range of between 0.98±0.061 mm ($CTAM_1$) to 1.115±0.081 mm ($CTAM_3$). These results indicate that the particle size of the microcapsules increased with increasing the polymer concentration due to subsequent increase in the frequency of collision, resulting in the fusion of semi formed particles and production of an overall increase in the size of the microcapsules. Other researchers have reported a similar relationship between the polymer concentration and the particle size [22].

The percentage entrapment efficiency of drug loaded alginate microcapsule and chitosan treated alginate microcapsules was also estimated and results are shown in table (1). AM_3 alginate microcapsules exhibited highest% entrapment efficiency value (84.51±1.23). As seen in table (1), the% entrapment efficiency was also influenced by the concentration of sodium alginate i.e. an increase in the concentration of polymer from 1.5% to 3.0% (w/v) led to an increase in the% entrapment efficiency of the alginate microcapsules but in case of chitosan treated alginate microcapsules, no significant change in entrapment efficiency were observed by increasing the concentration of chitosan. Increase in the Na-alginate concentration resulted in the formation of lager size of microcapsules entrapping greater amount of the drug. This effect might have occurred due to the greater availability of active calcium-binding site in polymeric chains and consequently, the greater degree of cross-linking as the quantity of sodium alginate increased [23].

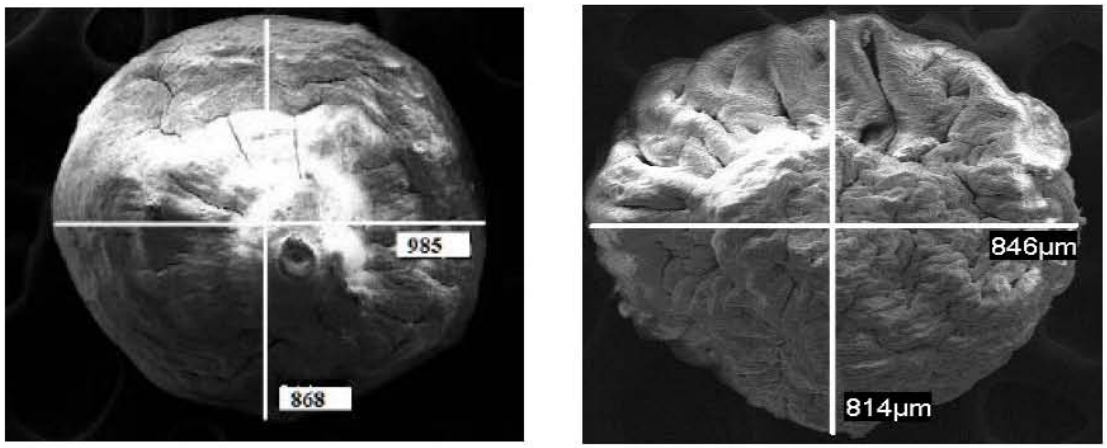

Fig. 1: SEM photographs of Flurbiprofen Loaded Microcapsules: (a): Alginate Microcapsules (b): Chitosan Treated Alginate Microcapsules

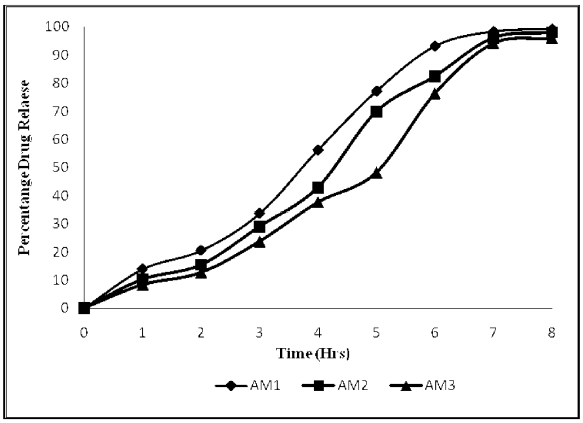

Fig. 2: Effect of Sodium Alginate Concentration on Drug Release from Alginate Microcapsules

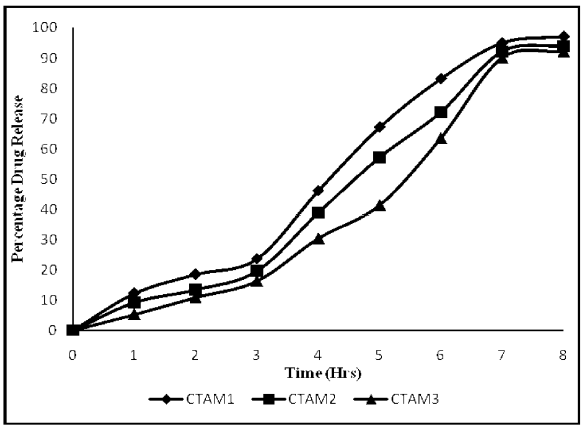

Fig. 3: Effect of Chitosan Concentration on Drug Release from Chitosan Treated Alginate Microcapsules

In vitro drug release studies for prepared microcapsules formulations which carried out in stimulated colonic fluid i.e. 900 ml of pH 6.8-phosphate buffer containing 2% (w/v) rat ceacal material. The maximum drug release from alginate microcapsules (AM_3) was about 99.19% within 8 h (Fig. 2), whereas, the drug release from chitosan treated alginate microcapsules was reached to 97.19% ($CTAM_1$) within 8 h (Fig. 3). Site specific drug delivery can be achieved by microcapsules, coated with chitosan and sodium alginate; which release the drug only in the colon. Controlled release of blue dextrans from alginate beads has been reported earlier [24, 25]. 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.

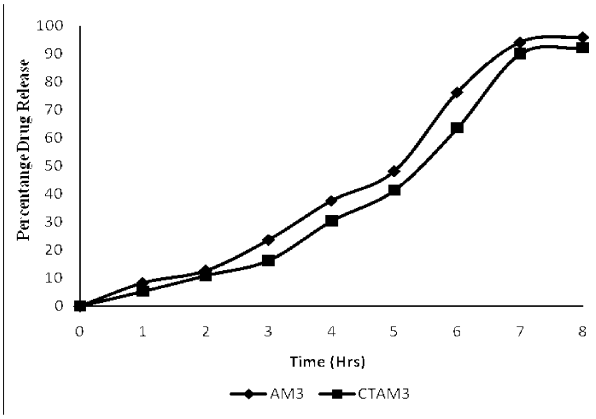

Fig. 4: Comparative percentage drug release profile of Alginate Microcapsules (AM_3) and Chitosan Treated Alginate Microcapsules ($CTAM_3$)

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 [26, 27].

In general, drug release was affected by alginate and chitosan concentration. Fig.(2) indicates the effect of alginate concentration on the release profile of the flurbiprofen. The drug release from the microcapsules was reduced with increase in alginate concentration from 1.5% to 3%. Fig.(3) cleared that chitosan concentration also has an effect on flurbiprofen release. Increase in its concentration caused retardation in the drug release properties from chitosan treated alginate microcapsules. When a comparison is done between the release behavior from alginate microcapsules (AM_3) and chitosan treated alginate microcapsules ($CTAM_3$) it was found noticeably that there was a significant reduction in drug release from chitosan treated alginate microcapsules (Fig.4). Release was slower from the chitosan treated microcapsules as compared to the alginate microcapsules. Thus it proves that the addition of chitosan to the gel structure reduced the drug 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 flurbiprofen. The release can be varied by changing a number of parameters.

CONCLUSION

From the results it seems that formulation ($CTAM_3$) was found to be satisfactory in terms of excellent flow properties, entrapment efficiency (78.08±1.01%) and showed sustained release characteristics with constant

fashion over extended period of time for 8 h. it was observed that concentration of polymers affect all the evaluation parameter significantly. Thus it proves that the addition of chitosan to the gel structure reduced the drug release from microcapsules. Hence the prepared Flurbiprofen loaded chitosan treated alginate microcapsules may prove that it be a convenient colon targeted carrier for the controlled release and potential candidate for safe and effective colon drug delivery.

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