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Formulation of Gastroretentive floating microparticles for Ofloxacin

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ABSTRACT

In the present study an attempt was made to prepare alginate floating microparticles by ionotropic gelation method with calcium carbonate (CaCO3) 1% w/v in gelation medium used as gas-forming agent for oral delivery of Ofloxacin. Chitosan was used to enhance the drug encapsulation efficiency. Various physiochemical properties such as particle size, shape, in vitro buoyancy and drug release was compared with with non-floating microparticles. Data indicate that gas bubbles form cavities in tha particles which may attributed to enhanced in vitro buoyancy and fast release of Ofloxacin from floating microparticles.

INTRODUCTION

Ofloxacin is fluoroquinolone chemotherapeutic agent having potent bactericidal activity against a broad range of clinically relevant Gram-negative and Gram-positive pathogens, as well as Mycoplasma, Chlamydia, and Legionella [1]. It has been widely used to treat a variety of bacterial infections, including those of the respiratory tract, skin structure, bone, gastrointestinal tract, urinary tract, and bacterial prostatitis, sexually transmitted diseases wound and surgical infections [2]. Ofloxacin is normally given orally and require twice daily administration for consecutive days or weeks. The repeated oral doses of ofloxacin over long time could result in nervous system and gastrointestinal system disorders [3].

Several dosage forms are being developed to improve therapeutic efficacy and reduce frequency of administration The gastroretentive tablet and sustained-release pellet have been developed for once-daily administration [4,5]. In this study, ofloxacin-loaded Chitosan/Alginate microparticles were prepared and their physicochemical properties were evaluated *in vitro.*

MATERIALS AND METHODS

1.1. Materials

Ofloxacin hydrochloride was procured from Ranbaxy (P) Ltd New Delhi, India as a gift sample. Chitosan (Acylation 87%) and Sodium alginate was procured from Sigma Aldrich, Bangalore, India. Calcium chloride and sodium carbonate was purchased from Hi Media, Mumbai. All other chemicals were analytical grade and purchased from local supplier.

1.2. Methods

1.2.1. Preparation of floating microparticles

The floating microparticles were prepared by emulsion solvent diffusion technique [6]. Alginate was dissolved in distilled water at a concentration of 3% (w/v), the solution was stirred thoroughly after Ofloxacin (0.75 % w/v) and calcium carbonate 1.5 %(w/v) were added. The gelation medium was prepared by dissolving calcium chloride ($CaCl_2$) at 2% w/v and chitosan in 1% (w/v) concentrations in 2% (v/v) glacial acetic acid. The homogenous alginate solution was extruded using a 21G syringe needle into the gelation medium stirred at 1500 rpm with double blade propeller. The distance between the edge of the needle and the surface of the gelation medium was about 10 cm. The

gel microparticles formed were left in the solution with gentle stirring for different time (10, 20, 30 min) at room temperature to be cured. After microparticles were collected, washed with distilled water twice and oven-dried subsequently (40°C). The microparticles of ofloxacin without gas forming agent were also prepared using same method for comparative study.

2. Characterization of Microparticles

2.1. Size and shape of Microparticles

The size of microparticles was determined using microscope (Olympus, India) fitted with an ocular micrometer and stage micrometer. Scanning electron microscopy (SEM) (Jeol JSM-1600, Tokyo, Japan) was performed to characterize the surface of the formed microparticles. Microparticles were mounted directly onto sample stub and coated with gold film (~200 nm) under reduced pressure (0.133 Pa).

2.2. *In vitro* buoyancy

The drug content and floating nature of prepared microparticles was determined by previous referred method [7]. Briefly, Microparticles (300 mg) were spread over the surface of a USP XXIV dissolution apparatus filled with 900 mL of 0.1 N hydrochloric acid containing 0.02% Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microparticles were recovered separately. The microparticles were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microparticles that remained floating and the total mass of the microparticles [8].

2.3. Encapsulation efficiency (EE)

To determine incorporation efficiency floating microparticles were dissolved in a minimal amount of dichloromethane and the drug was extracted into a suitable aqueous media (0.1 N hydrochloric acid) by evaporating dichloromethane. The solution was filtered through 0.45 m membrane, diluted suitably and analyzed for drug content spectrophotometrically at 287.8 nm using 0.1 N hydrochloric acid as blank.

2.4. *In vitro* drug release studies

The drug release was studied using a USP XXIV dissolution apparatus at 100 rpm in 0.1N hydrochloric acid as dissolution medium (900 ml) maintained at 37±1°C. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 µ membrane filter and diluted to a suitable concentration with 0.1 N hydrochloric acid. Absorbance of these solutions was measured at 287.8 nm using a UV/Vis double-beam spectrophotometer (UV-1800, Shimadzu). Cumulative percentage drug release was calculated using an equation obtained from a standard curve

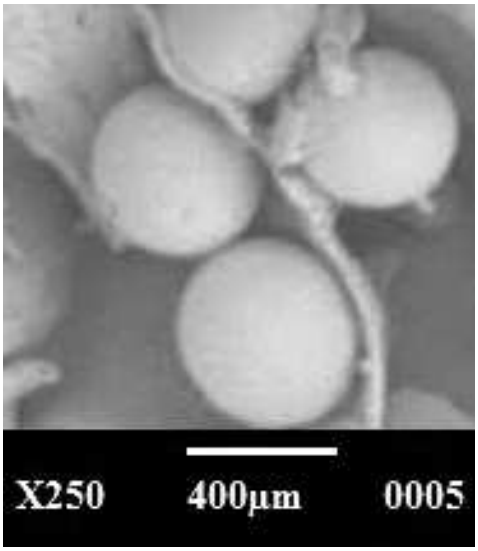
To analyze the mechanism of drug release from the microparticles the *in vitro* dissolution data were fitted to zero order, first order, Higuchi release model, Hixson and Crowell powder dissolution method and Korsmeyer and Peppas model [9].

RESULTS AND DISCUSSION

To improve the Oflaxacin loading in alginate microparticles, chitosan was dissolved in gelation medium to to prevent the diffusion of the Ofloxacin. When alginate solution is allowed to be dropped into the gelation medium which is composed of $CaCl_2$ and chitosan in acetic acid glacial solution, the Ca^{+2} ions diffuse into the interior of the drop of alginate and form the gel matrix through ionotropic gelation. At the same time, cationic polymer chitosan present in the gelation media also crosslinks alginate molecules through electrostatic interactions between negatively charged –COO− groups of alginate and positively charged $–NH_3$ + groups of chitosan. Alginate–chitosan complex block up the large pore of Ca–Alg gel matrix and form a polyelectrolyte complex membrane on the surface of the microparticles and thereby reduce the permeability of the microparticles. Thus, the diffusion of Ofloxacin is effectively prevented during the gelation [10].

The mean particle size of microsphere formulations containing sodium carbonate was measured at 560±90 µm. The particle size of microparticles formulation without $NaCO_3$ was found to be 378 ± 19 µm.

Figure 1: Scanning electron microphotograph of floating microparticles



This significant difference in the size may be caused by the presence of gas forming agent in the microparticles (Table 1). The porous nature and spherical shape of the microparticles are evident from their SEM photomicrographs, shown in figure-1. As can be seen in the photomicrograph, there are many pores and cavities in the microparticles.

Table 1: Characterization of Ofloxacin hydrochloride microparticles

Batch	Mean particle size (µm)	PDI	% In vitro Buoyancy	%Entrapment Efficiency (EE)
NFM	378 ± 19	0.54±0.20	46.19 ± 1.62	84.62 ± 4.05
FM	560±90	0.48±0.19	69.92 ± 1.27	64.31 ± 3.61

The drug entrapment was found to be 84.62 ± 4.05% The extent of loading influenced the particle size distribution of microparticles. When the loading was high, the proportion of larger particles formed was also high. Chitosan in gelation medium enhances the drug entrapment and drug loading in similar studies carried out by [11].

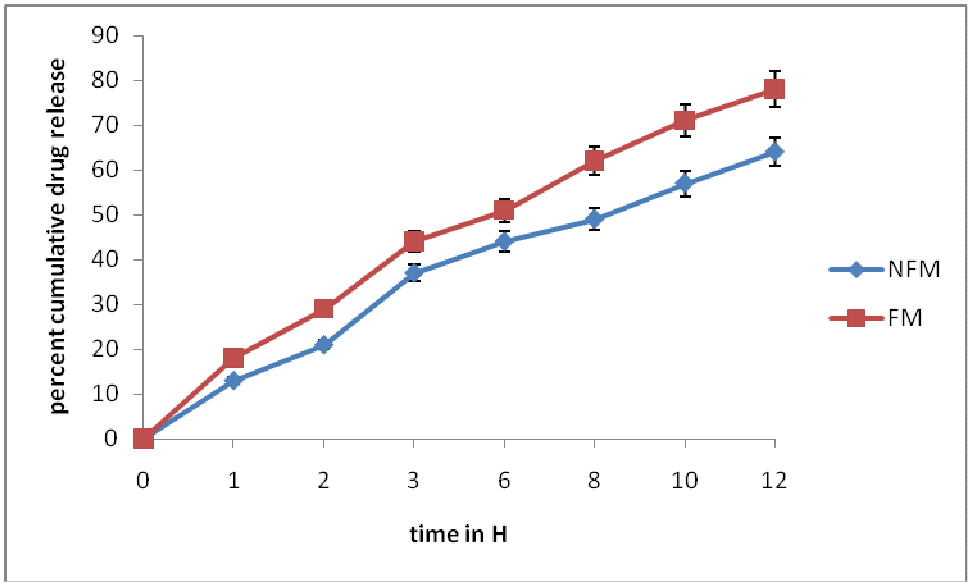
All the gas-forming agent free microparticles sank in the SGF. In contrast, about 90% of the floating microparticles still floating after 24 h. The good buoyancy behavior of the microparticles may be attributed to the hollow nature of the microparticles which result from the production of air bubbles during preparation. Presence of hollow cavities in microparticles increase the drug release. Gas bubbles in the microparticles are suspected to accelerate the ofloxacin release. Present observation is in agreement with other studies reported using chitosan and alginate floating microparticles [11]. This phenomenon may be explained on basis of studies reported by [12]. They have found that $CaCO_3$ is present as an insoluble dispersion in neutral pH aqueous alginate solution; however, in acidic media, the $CaCO_3$ becomes water-soluble. $CaCO_3$ reacts with the acid to produce CO_2, at the same time, the ionized Ca^2+ ions promote internal gelation by cross-linking with the alginate carboxyl group. Therefore, the addition of $CaCO_3$ did not significantly quicken the drug release even though it increased bead porosity and pore size, shown in Figure-2.

Release pattern of Ofloxacin in SGF (pH 2.0) from floating microparticles followed Higuchi matrix model and Peppas-Korsmeyer model. Regression analysis and Slope values suggest that the release of Ofloxacin hydrochloride from floating microparticles followed non-Fickian diffusion mechanism (Table 2).

Table 2. The Regression Coefficients and Rate Constants for Release of Ofloxacin from Floating microparticles in SGF (pH 2.0)

Formulation	Zero-order Model		First-order Model		H-M Model		P-K Model		H-C Model	
	R	k_1	r	k_1	r	k_1	r	k_1	r	k_1
NFM	0.8661	10.6734	0.9799	-0.1611	0.9902	23.2461	0.9523	22.4563	0.9534	-0.0340
FM	0.8642	8.4272	0.9567	-0.1132	0.9931	18.6745	0.9826	20.2456	0.9245	-0.0324

Figure 2: Cumulative release of Ofloxacin from microparticles



CONCLUSION

From the present study it is concluded that the floating microparticles could be used for release of Ofloxacin in stomach-jejunum transit which may enhance bioavailability and eventually lead to better patient compliance. Studies are underway to incorporate release modifiers such as eudragit which could be used to sustain the release of Oflaxacin from Alginate/Chitosan microparticles.

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