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Preparation and Evaluation of Ciprofloxacin Hydrochloride Floating Oral Delivery System

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Abstract . A sustained release system for ciprofloxacin hydrochloride designed to increase its residence time in the stomach was achieved through the preparation of floating microparticles by the solvent diffusion technique, using Eudragit S 100 and Eudragit RL 100 polymers. Eight different ratios of Eudragit mixture were used for the formulation, all of which showed good flow properties and packability. The drug retained in the microparticles decreased with increase in Eudragit RL 100 content, whereas, the floating ability increased with increase in weight ratio of Eudragit RL 100. There were differences between the formulations as to their appearance and size distribution. Fourier transform infrared (FTIR) spectrophotometeric study confirmed intactness of drug in formulations. The formulation containing ES: ERL in a ratio1.5:1 exhibited high percentage of floating particles with a controlled release of drug in 0.1N HCl.

Keywords: ciprofloxacin hydrochloride; floating drug delivery, eudragit

Introduction

The oral route is the most important means of delivery of drugs to the systemic circulation in a controlled manner. Generally after oral administration the bioavailability of these controlled release drug delivery system depends on the transit time of the dosage form through the absorbing area of the gastrointestinal tract (Groning *et al.,* 2007). So this factor reduces the efficacy of drugs having an absorption window in the stomach and upper part of small intestine (Rouge *et al.,* 1996) as dosage form escapes to lower regions of the gastrointestinal tract before the drug is completely released. A modified release drug delivery system with prolonged residence time in stomach is of particular interest for drugs, which are locally active in stomach or with an absorption window in the stomach and upper part of small intestine (Deshpande *et al.,* 1996). Various attempts have been made to prolong the retention time of dosage forms in the stomach that include bioadhesive system, swelling type or plug type system, modified shape systems and hydrodynamical balanced systems. (Baumgartner *et al.,* 2000, Hwang *et al.,* 1998; Moes, 1993). Floating drug delivery systems are expected to remain buoyant and swim in gastric contents due to their lower density than gastric fluids (~ 1.004 g/cm^3) for several hrs and release the drug in a controlled manner (Sato *et al.,* 2003; Hilton and Deasy, 1992, Kawashima *et al.,* 1991).

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Ciprofloxacin HCl is a fluoroquinolone antibacterial agent with wide spectrum of activity. It has a short half life of 3-4 h.The absorption window of the drug lies in the stomach and upper part of small intestine. About 70% of drug is absorbed from the above mentioned region (Tripathy *et al.,* 2001). It possesses all the suitable characteristics for development of a floating drug delivery system and hence it was chosen as the drug of choice in the above study. Eudragit S 100 and Eudragit RL 100 which are generally biocompatible and extensively used in the controlled release formulation were used for designing of floating drug delivery system.

In the present investigation, attempts were made by using eight different ratios of Eudragit mixture in order to develop a suitable delivery system which will not only control the release of drug but also remain buoyant for several hrs in the gastric fluid so that the basic objectives behind the study could be achieved.

Materials and Methods

Materials. Ciprofloxacin HCl (courtesy of Get-Rid Pharm. Pune, India), Eudragit S100 (ES) and RL100 (ERL) (Alkem, Mumbai), Ethanol and dichloromethane (Emerck Ltd., India) were used. All other chemicals were of analytical grade.

Methods. Floating microparticles containing ciprofloxacin HCl were prepared using the solvent-diffusion technique

(El-Kamel *et al.*, 2001). The drug: polymer ratio used to prepare different formulations was 1:2. The polymer content was a mixture of ES: ERL, 4: 1 (F1), 3: 1 (F2), 2: 1 (F3), 1.5: 1 (F4), 1: 1 (F5), 1: 1.5 (F6), 0: 1 (F7), and 1: 0 (F8). The drug-polymer mixture was dissolved in a solution of ethanol and dichloromethane (1:1), and dropped into 0.2% sodium lauryl sulphate solution. The solution was stirred with a propeller type agitator at room temperature for 1 h at 150 rpm. The formed floating microparticles were filtered, washed with water and dried at room temperature. The floating microparticles were sieved and suitable fractions were collected.

Percent yield. Microparticles dried at room temperature were weighed and the yield of microparticles preparation was calculated (Sahoo *et al.*, 2007).

Measurement of micromeritic properties. The flow properties of prepared microparticles were investigated by measuring the bulk density, tapped density and Carr's index. The mean particle size of the beads was determined by sieving method (Sahoo *et al.*, 2007).

Encapsulation efficiency. About 50 mg of formulation was dissolved in 50 ml of 0.1N HCl (with 2 ml ethanol). The resulting mixture was agitated on mechanical shaker for 24 h. The solution was then filtered and the drug content was estimated spectrophotometrically at 277 nm after suitable dilution (Sahoo *et al.*, 2007).

Buoyancy test. *In vitro* evaluation of floating behavior studies were performed by placing 100 microparticles into 500 ml 0.1 N HCl containing 0.02 % w/v tween 20 in a dissolution vessel (USP dissolution tester) followed by paddle rotation at a speed of 100 rpm maintained at 37 °C (Choi *et al.*, 2002). At predetermined time intervals (2, 4, 6, 8, 10, 12 h) numbers of floating particles were counted by visual observation. The percentage of floating microparticles was calculated by formula:

$$\frac{\text{number of floating microparticles}}{\text{initial number of microparticles}} \times 100$$

Scanning electron microscopy (SEM). Scanning electron microscope (JEOL, JSM-6360) was used to characterize the surface topography of the microparticles after gold coating.

X-ray powder diffractometric (XRD) study. X-ray powder diffractometry was carried out to investigate the effect of micro encapsulation process on crystallinility of drug. Powder XRD patterns were recorded on Rigaku, Japan (Model-Meniflex) X-Ray diffractometer using Ni-filtered, Cuk α radiation, at 30 kV and 25 mA. The scanning rate employed was 2°/min, over 4° to 40° diffraction angle (2θ) range. The XRD patterns of drug powder and drug-loaded beads were recorded.

FTIR study. The IR spectra were recorded for pure drug and drug-loaded microparticles using FTIR JASIO (Model No. 410). Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 400-4000/cm and the resolution was 2/cm.

Drug release study. The drug release rates from floating microparticles were carried out in 500 ml 0.1N HCl maintained at 37 ± 1 °C and stirred using USP basket type dissolution apparatus (LABINDIA, DISSO-2000) at 100 rpm. 100 mg microparticles were used in each test. Samples were withdrawn at suitable time intervals and assayed at 277 nm.

Kinetics of drug release. In order to understand the mechanism of drug release, the first 60 % of the release drug was fitted in Korsmeyer-peppas model (Sahoo *et al.*, 2007; Ritger and Peppas, 1987), wherein:

$$M_t / M\alpha = k\, t^n,$$

where $M_t / M\alpha$ is the fraction of the drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms and is calculated from the slope of the plot of log of fraction of drug released vs. log of time.

Results and Discussion

The percentage yield of floating microparticles determined by weighing after drying to constant weight was found to lounge in the range 32.97-67.92 (Table 1). All formulations

Table 1. Micromeritic properties, yield and floating abilities of various formulations

Batch code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index*	Yield (%)	Floating particle at the end of 12 h (%)
F_1	0.34	0.41	17.07±0.636	32.97	41
F_2	0.33	0.39	15.38±0.811	67.92	42
F_3	0.31	0.36	13.88±0.454	51.27	49
F_4	0.26	0.32	18.75±0.411	55.74	67
F_5	0.29	0.34	14.07±0.442	53.13	50
F_6	0.28	0.33	15.15±0.625	60.97	63
F_7	0.2	0.34	17.64±0.336	56.00	42
F_8	0.36	0.42	14.28±0.144	51.08	23
Drug	0.25	0.36	30.55±0.112	**	**

* = each observation is the mean ± SD of three determinations; ** = the test was not carried out for pure drug

showed excellent flow ability in terms of Carr's Index (all < 18.75). The excellent flow properties suggest that the microparticles can be easily handled during processing. The size distribution varied among the formulations. Most of the floating microparticles were collected above sieve range of 250 µm and the highest amount was retained in the range 250-500 µm (Fig.1). The floating ability varied according to the polymer composition of microparticles (Table 1). Compared to other formulations, the formulation without ERL content, F_8, exhibited lower floating ability. Combination of formulations F_4 and F_6 provided excellent results in terms of floating ability. Formulation F_8 showed highest percentage of drug content and entrapment value and formulation F_7 showed lowest percentage of the retained drug (Table 2). The drug retention decreased with increase in ERL content of floating microparticles. This could be due to high permeation characteristic of ERL that facilitated diffusion of a part of entrapped drug to the surrounding medium during preparation of floating microparticles. Scanning election microscope photographs show the microparticles to be spherical with irregular surface (Fig.2). Cross-sectional view exposed the characteristic open cell structure of microparticles. From X-ray diffraction patterns (Fig.3) it is obvious that the pure drug exhibited crystalline characteristics while in formulations, drug peaks are still visible but with loss of its sharpness which is due to dilution with polymer; hence it may be concluded that the drug retains the crystalline structure in the formulation.

The FTIR report (Fig. 4) shows no significant difference in spectra of drug and formulations confirming absence of drug polymer interaction. The dissolution study was carried out for 6 h in 0.1 N HCl. It was found that drug release was faster in case of formulations containing higher percentage of ERL, whereas release rate was slow for formulations with higher %

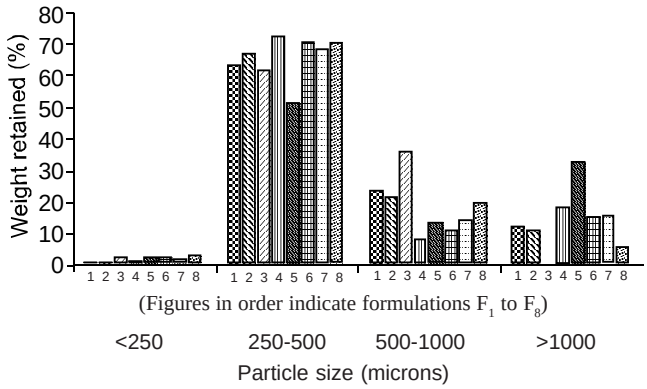


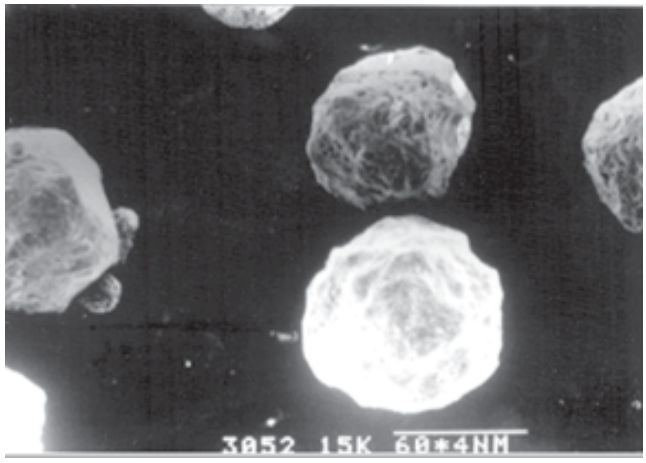
Fig. 1. Particle size distribution of various formulations.

Table 2. Entrapment efficiency and release kinetics of floating microparticles

Batch code	Drug encapsulated (%)*	Korsmeyer-Peppas model		
		n	r	k
F_1	52.56 ± 0.35	0.690	0.970	0.130
F_2	50.21±. 0.02	0.591	0.954	0.159
F_3	49.8± 0.045	0.600	0.976	0.169
F_4	49.48± 0.12	0.538	0.976	0.202
F_5	47.48± 0.866	0.574	0.981	0.224
F_6	45.63±.0.03	0.612	0.987	0.227
F_7	42.33±.0.03	0.563	0.992	0.258
F_8	62.15±.0.045	0.540	0.951	0.136

* = each observation is the mean SD ± of three determinations; diffusion exponent (n), correlation coefficients (r) and kinetic constants (k) are related to the mechanism of drug release, according to equation, $Mt/M\alpha = Kt^n$

(A)



(B)

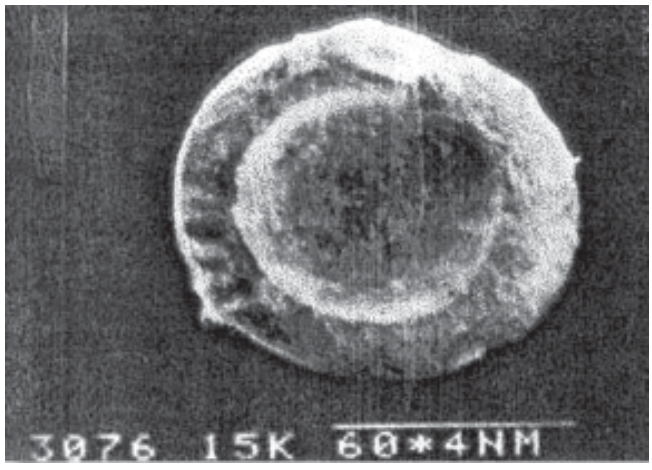


Fig. 2. SEM photographs of floating microspheres (A) with cross sectional view (B) of formulation F_4.

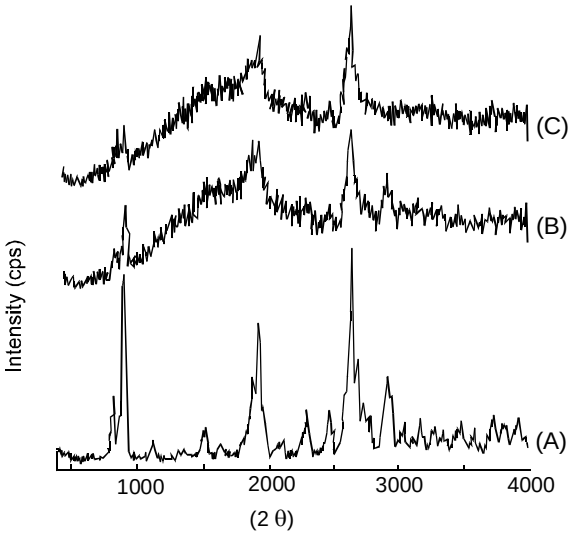


Fig. 3. X-ray diffraction patterns (A): ciprofloxacin; (B): formulation F_1; (C): formulation F_4.

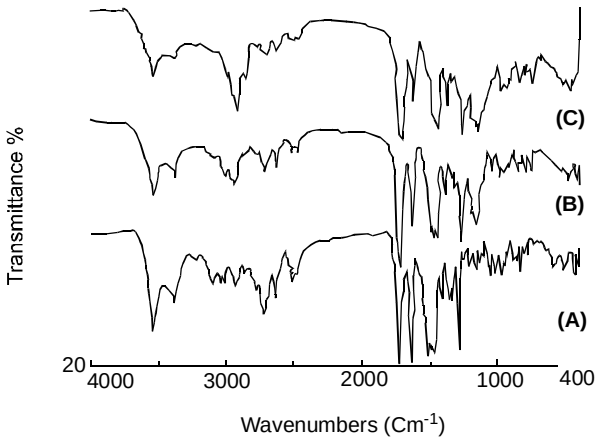


Fig. 4. FTIR spectra (A): ciprofloxacin (B) formulation F_1; (C): formulation F_4.

of ES (Fig.5). This may be attributed to the fact that ERL is a co-polymer of acrylic acid and methacrylic acid esters with a high content of quaternary ammonium groups which makes them more permeable and gives an opportunity to the drug to diffuse out to bulk medium at a faster rate. But ES is of low permeability and insoluble in acidic medium. It is an anionic co-polymer of methacrylic acid and methyl methacrylate containing free carboxylic and ester group. Its very low permeability results from high intermolecular attraction. Hydrogen bonding between the hydroxyl group of carboxylic moiety and the carboxyl oxygen of ester group increases the degree of compactness of polymers and decreases the porosity and permeability, thereby decreasing the release rate. The mechanism of drug release was studied using Korsmeyer-Peppas model. The value of 'n' fell within the range of

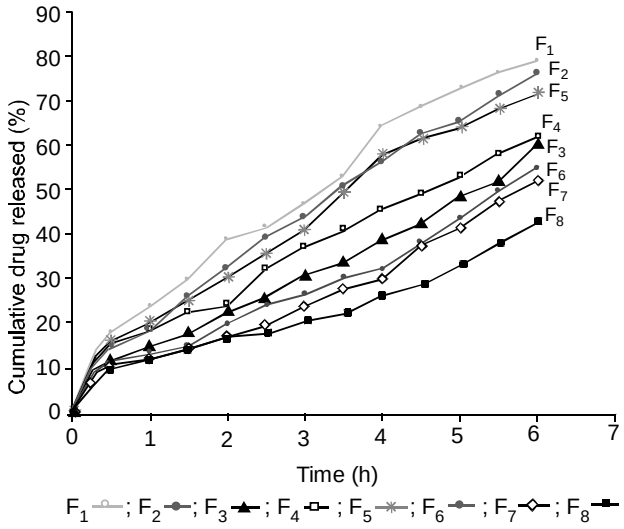


Fig. 5. Dissolution profile of ciprofloxacin from different floating microparticle formulations in 0.1 N HCl (n=3).

0.5-0.7 (Table 2), indicating anomalous or non-fickian type of release, in which the rate of dissolution mediumuptake into the polymer is largely determined by relaxation of polymer chain.

In conclusion, the floating microparticles of ciprofloxacin could be prepared successfully using suitable ratio of ES: ERL by solvent diffusion technique. Formulation F_4 (ES: ERL ratio = 1.5:1) provided better results regarding floating behavior with suitable controlled drug release trait among all other formulations.

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References

Baumgartner, S., Kristl, J., Vrecer, F., Vodopivec, P., Zorko, B. 2000. Optimization of floating matrix tablets and evaluation of their gastric residence time. *Int. J. Pharm.* **195:** 125-135.

Choi, B.Y., Park,H.J., Hwang,S.J., Park, J.B. 2002.Preparation of alginate beads for floating drug delivery system: Effects of CO_2 gas-forming agents. *Int. J. Pharm.* **239:** 81-91.

Deshpande, A.A., Rhodes, C.T., Shah, N.H., Malick, A.W. 1996. Controlled release drug delivery systems for prolonged gastric residence: an overview. *Drug Dev. Ind. Pharm*. **22:** 531-540.

El-Kamel, A.H., Sokar, M.S., Al Gamal, S.S., Naggar, U.F. 2001. Preparation and evaluation of ketoprofen floating oral delivery system. *Int. J. Pharm.* **220:** 13-21.

Groning, R., Cloer, C., Georgarakis, M., Muller, R. S. 2007. Compressed collagen sponges as gastroretentive dosage forms: *In vitro* and *in vivo* studies. *Eur. J. Pharm. Sci.* **30:** 1-6.

Hilton, A.K., Deasy, P.B. 1992. *In vitro* and *in vivo* evaluation of an oral sustained-release floating dosage form of amoxicillin trihydrate. *Int. J. Pharm.* **86:** 79-88.

Hwang, S.J., Park, H., Park, K. 1998. Gastric retentive drug-delivery systems. *Crit. Rev. Ther. Drug Carrier Syst.* **15:** 243-284.

Kawashima, Y., Niwa, T., Takeuchi, H., Hino, T., Ito, Y. 1991. Preparation of multiple unit hollow microspheres (microballoons) with acrylic resin containing tranilast and their drug release characteristics *(in vitro)* and floating behaviour *(in vivo)*. *J. Control Release* **16:** 279-289.

Moes, A.J., 1993. Floating delivery and other potential gastric retaining systems, Current status on targeted drug delivery to the gastrointestinal tract. *Capsugel Library* 95-112.

Ritger, P.L., Peppas, N.A. 1987. A simple equation for description of solute release. II. Fickian and anomalous release from swellable devices. *J. Control Release* **5:** 37-42.

Rouge, N., Buri, P., Doelker, E. 1996. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. *Int. J. Pharm.* **136:** 117-140.

Sahoo, S. K., Dhal, Mohapatro, S. P., Behera,B. Ch., Barik, B. B.2007. Effect of processing temperature on Eudragit RS PO microsphere characteristics in the solvent evaporation process. *Pharmazie* **62:** 638-639.

Sato, Y., Kawashima, Y., Takeuchi, H., Yamamoto, H. 2003. *In vivo* evaluation of riboflavin-containing microballoons for floating controlled drug delivery system in healthy human volunteers. *J. Control Release* **93:** 39-47.

Tripathy, K.D. 2001. *Essentials of Medical Pharmacology*, 890 p., 5th edition, Jaypee Brothers Medical Publishers Pvt. Ltd., New Delhi, India.