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Formulation and characterization of Piroxicam floating microspheres for prolonged gastric retention

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ABSTRACT

Present study involves preparation and evaluation of floating microspheres with piroxicam as model drug for prolongation of gastric residence time. The microspheres were prepared by solvent evaporation method using polymers hydroxypropylmethyl cellulose and ethyl cellulose. The shape and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy, (SEM) respectively. In-vitro drug release studies were performed and drug release kinetics was evaluated using linear regression method. Effects of the stirring rate during preparation, polymer concentration and dissolution medium on the size of microspheres and drug release were also observed. Prepared microspheres exhibited prolonged drug release (>8 h) and remained buoyant for >10 h. The mean particle size increased and the drug release rate decreased at higher polymer concentration. It was observed that there is no significant effect of the stirring rate during preparation on drug release was observed. In-vitro studies demonstrated diffusion- controlled drug release from the microspheres.

Keywords: Floating microspheres, piroxicam, *in-vitro* release, gastric retention.

INTRODUCTION

Most of the orally administered dosage forms have several physiological limitations such as variability in gastrointestinal time (GI) time, incomplete drug release from devices and short residence time of pharmaceutical dosage forms in absorption region of GI tract. This leads to low bioavailability of sustained release dosage forms and even if slow release of drug is attained, the drug release passes the absorption site and therefore lowering the efficacy of drugs. To overcome these problems several attempts have been made to develop oral dosage forms, capable of having prolonged retention time in stomach to extend the duration of drug delivery. One approach is floating drug delivery system (FDDS) which remain buoyant because of their lower density than the gastric and intestinal fluids. Both single and multiple units have been developed [1,2]. Multiple unit FDDS such as microspheres have the advantage that they are not subjected to 'all or nothing' gastric emptying nature of single unit systems [3]. A growing proportion of elderly

patients suffering from diseases like osteoarthrirtis or rheumatoid arthiritis and they require non steroidal anti inflammatory drugs (NSAIDS) therapy treatment for treatment of it. But NSAIDS are well known for their gastrotoxic and duodenotoxic effects [4]. Piroxicam, a non steroidal anti inflammatory drug exhibit better tolerance than aspirin, indomethacin and naproxen [5]. Poly lactic acid microspheres of piroxicam have been prepared by solvent evaporation method and by spray-drying method [6].

Both natural and synthetic polymers have been used to prepare floating microspheres. Kawashima *et al.* prepared hollow microspheres or microballoons of ibuprofen by the emulsion-solvent diffusion method using acrylic polymers [7]. The microspheres exhibited good *in-vitro* floatability and drug release decreased drastically with increasing polymer concentration. Floating microspheres of cellulose acetate loaded with four different drugs were prepared using the solvent diffusion-evaporation method [8]. The microspheres remained buoyant for more than 12 hours. Methylcellulose and chitosan micro pellets loaded with lansoprazole had a lower density than gastric contents and exhibited better encapsulation efficiencies [9]. The objective of the present study was to develop floating microspheres of Piroxicam in order to achieve an extended retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability. The prepared microspheres were evaluated for size, *in-vitro* drug release, buoyancy and incorporation efficiency. The effect of various formulation variables on the size and drug release was investigated.

MATERIALS AND METHODS

Piroxicam was obtained as a gift sample from IPCA laboratories (India). Hydroxypropylmethyl cellulose (HPMC), ethyl cellulose (EC) and Tween 80 were obtained from Central Drug House (P) Ltd. (India). All other chemicals/reagents used were of analytical grade. A UV/Vis spectrophotometer (Shimadzu 1801, Japan) was used for drug analysis.

Preparation of microspheres

Microspheres were prepared by solvent evaporation technique as employed by Struebel *et al.* **[10]** with some modifications. Piroxicam, HPMC and EC were dissolved in a mixture of ethanol and acetone at room temperature (Table 1). This was poured into 250 mL water containing 0.03% Tween 80 maintained at a temperature of 30–40°C and subsequently stirred at agitation speed of 1500rpm for 30 min to allow the volatile solvent to evaporate. The microspheres formed were filtered, washed twice with distilled water and dried in vacuum.

Table 1: Formulation Chart For Prepared Floating Microspheres

Formulation Code	***Polymer ratio (HPMC/EC)****	**Temperature (°C)**
F1[a]	1:1	30–40
F2[a]	1:2	30–40
F3[a]	1:3	30–40
F4[a]	1:4	30–40
F5[a]	1:5	30–40
F6[a]	1:6	30–40
F7[b]	1:2	30–40
F8[b]	1:3	30–40
F9[c]	1:2	30–40
F10[c]	1:3	30–40

*Stirring rate; a = 300 rpm; b = 500 rpm; c = 1000 rpm, *HPMC/EC Hydroxypropylmethyl cellulose/ Ethylcelluose.*

Characterization of microspheres

Size and shape of microspheres

The size of microspheres was determined using a microscope (Olympus NWF 10x, Educational Scientific Stores, India) fitted with an ocular micrometer and stage micrometer. Scanning electron microscopy (SEM) (Philips-XL-20, IISC Bangalore) was performed to characterize the surface of formed microspheres. Microspheres were mounted directly onto the sample stub and coated with gold film (˜200 nm) under reduced pressure (0.133 Pa).

Buoyancy percentage – Microspheres (0.3 g) were spread over the surface of a USP XXIV dissolution apparatus (type II) filled with 900 mL 0.1 mol L^{-1} HCl containing 0.02% Tween 80 [11]. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.

Incorporation efficiency (IE) – To determine the incorporation efficiency, microspheres were taken, well triturated and suspended in a minimal amount of alcohol and, suitably diluted with water and filtered to separate shell fragments. Drug content was analyzed spectrophotometrically at 334 nm using Shimadzu 1801.

Differential Scanning Calorimetry

Differential scanning calorimetry studies (DSC) was carried out using DSC Q1000 V9.4 calorimeter, coupled to a Shimadzu TA-50 analyzer. Approximately 10 mg of sample was weighed into a aluminum pan which was crimped non hermetically, and heated at a scanning range of 10˚ C/min from 0˚ to 300˚ C under nitrogen purge.

***In-vitro* release**. – A USP basket apparatus has been used to study *in-vitro* drug release from microspheres [12–14]. In the present study, drug release was studied using a modified USP XXIV [10] dissolution apparatus type I (basket mesh # 120, equals 125 µm) at 100 rpm in distilled water and 0.1 mol L^{-1} HCl (pH 1.2) as dissolution fluids (900 mL) maintained at 37 ± 0.5 °C. Withdrawn samples (10 mL) were analyzed spectrophotometrically at 334 nm using Shimadzu 1801. The volume was replenished with the same amount of fresh dissolution fluid each time to maintain the sink condition. All experiments were performed in triplicate. Linear regression was used to analyze the *in vitro* release mechanism.

Statistical analysis. – Experimental results were expressed as mean ±SD. Student's *t*-test and one-way analysis of variance (ANOVA) were applied to check significant differences in drug release from different formulations. Differences were considered to be statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Floating microspheres were prepared by the solvent evaporation method using HPMC and EC **(**Table 1**).** Flow properties of prepared floating microspheres were shown in (Table 2).

The SEM photographs showed that the fabricated microspheres were spherical and exhibited a range of sizes within each batch (Fig. 1).

Table 2: Micromeritics Of Floating Microspheres And Pure Drug

Micromeritic Properties	*Microspheres*	Pure drug
Angle of repose (°)	33.60 ± 1.23	52.94 ± 1.38
Tapped density g/cm^3	0.35 ± 0.03	0.46 ± 0.09
True density g/cm^3	0.49 ± 0.02	0.45 ± 0.07
% Porosity	61 ± 2.3	39 ± 1.35

**Each value is ±SD of three independent determinati ons.*

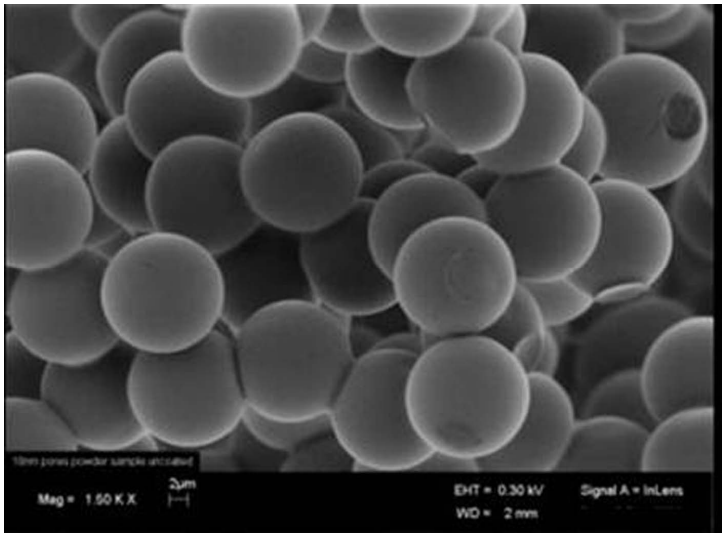

Fig 1: SEM of prepared floating microspheres of Piroxicam (F3).

The microspheres floated for prolonged time over the surface of the dissolution medium without any apparent gelation. Buoyancy percentage of the microspheres was found to be in the range 65.0 ± 2.1 % (batch F9) to 93.7 ± 2.4 (batch F6**)** (Table 3).

Table 3: Various Formulations Parameters For Prepared Microspheres

Formulation Code	*Mean particle size*[a] *(µm)*	*Incorporation efficiency*[b] *(%)*	Buoyancy[b] (%)
F1[a]	227.2 ± 3.5	52.1 ± 1.3	69.0 ± 1.2
F2[a]	253.0 ± 5.7	55.6 ± 2.8	76.7 ± 1.3
F3[a]	280.5 ± 5.6	58.7. ± 1.7	79.0 ± 3.7
F4[a]	329.5 ± 3.2	63.5 ± 2.5	85.7 ± 1.3
F5[a]	363.7 ± 3.9	64.1 ± 2.8	87.7 ± 1.8
F6[a]	396.0 ± 2.8	70.3 ± 2.3	93.7 ± 2.4
F7[b]	203.0 ± 3.7	57.1 ± 2.5	75.0 ± 1.3
F8[b]	233.0 ± 3.9	59.2 ± 1.7	72.0 ± 1.1
F9[c]	199.1 ± 5.1	56.8 ± 2.8	65.0 ± 2.1
F10[c]	197.4 ± 4.2	56.9 ± 3.2	66.7 ± 1.9

a Mean ±SD, n = 10.
b Mean ±SD, n = 3.

Microspheres were prepared using a gradually increasing EC concentration in combination with a fixed concentration of HPMC to predict the effect of polymer (EC) concentration on the size of microspheres. It was found that at low drug polymer concentration, smaller size microspheres was formed and drug released from them are lower then the microspheres prepared from high polymeric content. It is attributed that small sized microspheres provide large surface area for faster drug release. The mean particle size of the microspheres significantly increased with increasing ethyl cellulose concentration ($p < 0.05$) and was in the range 197.4 ± 4.2 µm to 396.0

± 2.8 µm (Table 3). Viscosity of the medium was found to be increasing as we increase the polymer concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities [15, 16]. This results in the formation of larger particles. To observe the effect of agitation speed on the size of the resulting microspheres, formulations were prepared at varying agitation speeds (batches F7–F10). The size of the resulting microspheres was found to be decreased with increasing the agitation but the increase was not statistically significant as shown in Fig. 2.

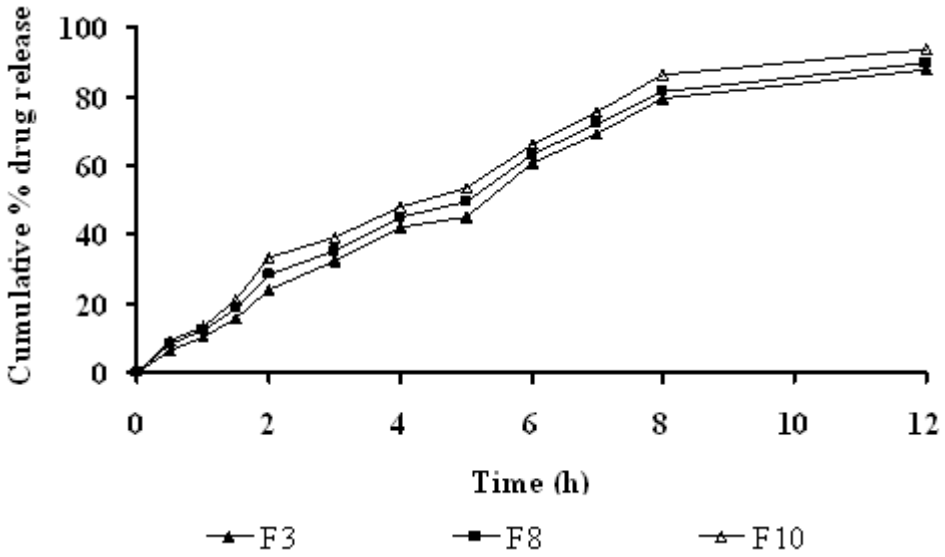

Fig 2: Effect of stirring rate during microspheres preparation on *in-vitro* release of piroxicam from floating microspheres F3(-▲-), F8(-■-),F10(-∆-).

It was found that piroxicam existed completely in amorphous state dispersed uniformly at the molecular level in polymeric microspheres as indicated by characteristics peak patterns of DSC thermograms. *In vitro* drug release studies were performed in 0.1 mol L^{-1} HCl for 12 h. The cumulative drug release of piroxicam significantly decreased with increasing ethyl cellulose concentration ($p < 0.05$, Fig. 3). is because of the increased density of the polymer matrix at higher polymeric concentrations which in turn resulted in an increased diffusional path length. This may decrease the overall drug release from the polymer matrix.

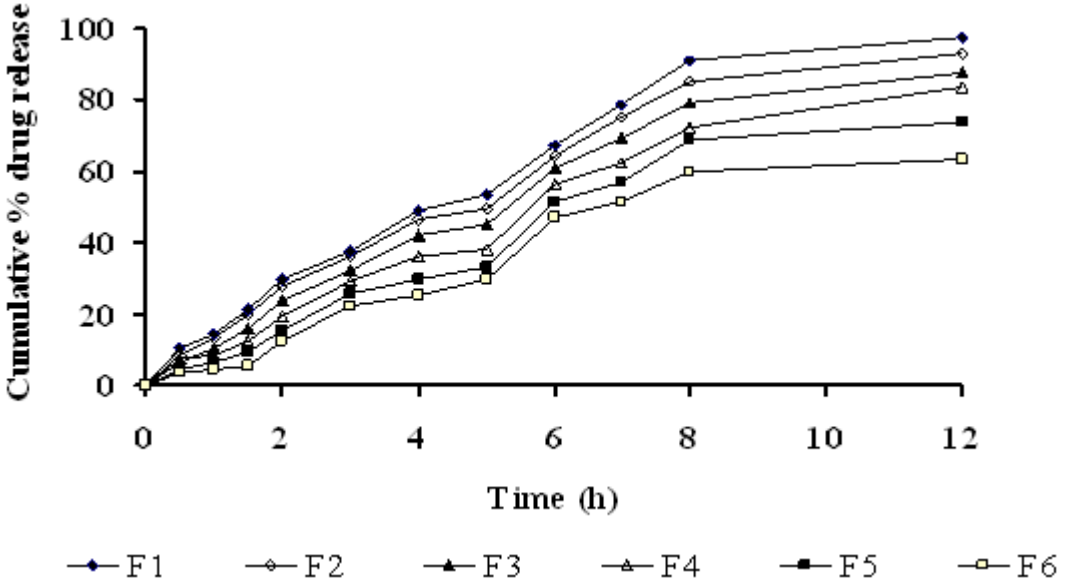

Fig 3: Effect of polymer concentration on piroxicam from floating microspheres.
F1(-♦-) F2(-◊-) F3(-▲-) F4(-∆-) F5(-■-) F6(-□-).

Furthermore, smaller microspheres are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release. The data obtained for *in vitro* release were fitted into equations for the zero-order, first-order and Higuchi release models [17-19]. The interpretation of data was based on the value of the resulting regression coefficients. The *in vitro* drug release showed the highest regression coefficient values for Higuchi's model, indicating diffusion to be the predominant mechanism of drug release.

CONCLUSION

In-vitro data obtained for floating microspheres of piroxicam showed excellent floatability, good buoyancy and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. Diffusion was found to be the main release mechanism. Thus, the prepared piroxicam floating microspheres may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition.

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