International Journal of ChemTech Research
ISSN : 0974-4290
Vol.1,No.1,pp 1-10, Jan – March 2009

Formulation and evaluation of Gastro retentive Multiparticulate Drug delivery system of Aceclofenac

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Abstract: Gastroretentive dosage forms have potential for use as controlled-release drug delivery systems. Multiple unit systems avoid the 'all-or-none' gastric emptying nature of single unit systems. A controlled release system for aceclofenac designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microparticles by the emulsification solvent-evaporation technique consisting of eudragit RS 100 as a polymer. The shape and surface morphology of prepared microsphere were characterized by optical and scanning electron microscopy. The micromeritic properties of microspheres were found to be much improved. *In-vitro* drug release studies were performed and drug release kinetics was evaluated using the linear regression method. Effects of polymer concentration, stirring rate during preparation and effect of temperature on size and drug release was evaluated. The prepared microspheres exhibited prolonged drug release (> 12h) and remained buoyant for > 12 h. The mean particle size increased and the drug release rate decreased at higher polymer concentration. No significant effect of the stirring rate during preparation on drug release was observed. As the temperature increased the release of drug was fast due to shell of the microspheres was very thin and some of the microspheres were broken. *In-vitro* studies demonstrated diffusion-controlled drug release from the microspheres.

Keywords*:* Aceclofenac; Floating microparticles; Eudragit RS 100; Emulsification solvent-evaporation technique; Controlled release.

Introduction

Drugs that are easily absorbed from the gastrointestinal tract (GIT) and have a short half-life are eliminated quickly from the blood circulation, require frequent dosing. To avoid this problem, the oral controlled release (CR) formulations have been developed in an attempt to release the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time. Such oral drug delivery devices have a restriction due to the gastric retention time (GRT), a physiological limitation. Therefore, prolonged gastric retention is important in achieving control over the GRT

because this helps to retain the CR system in the stomach for a longer time in a predictable manner[1]. In recent years, scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short GRT and unpredictable gastric emptying times (GET). The gastro-intestinal residence time determines the time period available for drug release from oral controlled release delivery systems within the GIT. Approaches to increase the GRT include: (i) bioadhesive delivery systems, which adhere to mucosal surfaces; (ii) swellable delivery systems, which increase in size after swelling and retard the passage through the pylorus; and (iii) density-controlled delivery systems, which either float or sink in gastric fluids[2, 3]. Floating drug delivery system (FDDS) is of particular interest for drugs which (a) act locally in the stomach; (b) are primarily absorbed in the stomach; (c) are poorly soluble at an alkaline pH; (d) have a narrow window of absorption; and (e) are unstable in the intestinal or colonic environment[4]. FDDS which remain buoyant due to their having a lower density than the gastric and intestinal fluids. Both single and multiple unit systems have been developed. Multiple unit FDDS such as microspheres have the advantage they are not subjected to 'all or nothing' gastric empting nature of single unit systems[5, 6]. A growing proportion of elderly patients suffer from diseases like osteoarthritis or rheumatoid arthritis and they require nonsteroidal anti-inflammatory drug (NSAID) therapy for the treatment of it. But NSAIDs are well known for their gastro toxic and duodenotoxic effects. Aceclofenac, a nonsteroidal anti-inflammatory drug to achieve the same goal, floating microspheres loaded with aceclofenac was prepared using modified emulsification solvent-evaporation technique. The objective of the present study was to develop floating microspheres of aceclofenac in order to achieve an extended retention in the upper GIT[7], which may result in enhanced absorption and thereby improved bioavailability. The prepared microspheres were evaluated for size, *in-vitro* release, buoyancy and incorporation efficiency. The effect of various formulation variables on the size and drug release was also investigated.

Materials and method

Aceclofenac was obtained as a gift sample from Aarti drugs ltd., Tarapur.Thane. Eudragit RS 100 was obtaining from degussa private ltd, Mumbai. Polyvinyl alcohol, ethanol, dichloromethane and tween 20 were obtained from Loba chemical Mumbai. All other chemicals/reagents used were of analytical grade.

A UV/Vis spectrophotometer (Shimadzu 1700pharma spec) was used for drug analysis.

Preparation of microspheres

The microspheres of aceclofenac using eudragit RS 100 were prepared as follows. Aceclofenac (0.1 g) and eudragit RS 100 were dissolved in ethanol: dichloromethane mixture (1:1 v/v, 10 ml) at room temperature. The drug solution was poured slowly as a thin stream into 200 ml of water containing 1% w/v polyvinyl alcohol. The solution was kept at constant temperature while stirring at 300 rpm. The finely dispersed/emulsified droplets of the polymer solution of drug were solidified in the aqueous phase via diffusion of the solvent[8]. After agitating the mixture for 1 h, the microspheres were filtered, washed several times with water to remove traces of polyvinyl alcohol and dried overnight at 60°. During drying, microsphere cavity became hollow resulting in FDDS.

Characterization of prepared microspheres

Micromeritic properties

The microspheres were characterized by their micromeritic properties, such as particle size, true density, tapped density, compressibility index and flow properties. The size was measured using an optical microscope, and the mean particle size was calculated by measuring 200–300 particles with the help of a calibrated ocular micrometer. The tapping method was used to determine the tapped density and percent compressibility index[9] as follows:

Tapped density = [Mass of microspheres / Volume of microspheres after tapping] × 100

$$\% \text{ Compressibility index} = [1- V/Vo] \times 100$$

Here V and Vo are the volumes of the sample after and before the standard tapping, respectively.

True density was determined using a benzene displacement method. Porosity[9] (e) was calculated using the equation:

$$\varepsilon = (1- P_p / P_t) \times 100$$

Where Pt and Pp are the true density and tapped density, respectively.

Angle of repose θ of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method[10] and calculated as

$$\text{Tan } \theta = 2H / D$$

Where 2H/D is the surface area of the free standing height of the microspheres heap that is formed on a graph paper after making the microspheres flow from the glass funnel.

Morphology

The morphology of microsphere were studied by scanning electron microscopy (SEM) (FEI Philips-XL-30, VNIT, Nagpur) was performed to characterize the surface of formed microspheres. Microspheres were mounted directly onto the sample stub and coated with platinum film.

Determination of percent yield and drug entrapment [11]

Total percentage yield of floating microspheres calculated by weighting of prepared microspheres was divided by the total amount of all the non–volatile components used for the preparation of the microspheres.

The drug content of eudragit RS 100 microspheres was determined by dispersing 50 mg formulation (accurately weighed) in 10 ml ethanol followed by agitation with a magnetic stirrer for 12 h to dissolve the polymer and to extract the drug. After filtration through a 5 μm membrane filter (Millipore), the drug concentration in the ethanol phase was determined spectrophotometrically at 275 nm. Eudragit RS 100 did not interfere under these conditions. Each determination was made in triplicate. The percentage drug entrapment was calculated as follows:

% Drug entrapment = [Calculated drug conc. / Theoretical drug content] × 100

Percentage buoyancy [12]

Fifty milligrams of the floating microparticles were placed in simulated gastric fluid (pH 1.2, 100 ml) containing 0.02 w/v% Tween 20. The mixture was stirred at 100 rpm in a magnetic stirrer. After 8 h, the layer of buoyant microparticles was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\text{Buoyancy } (\%) = W_f / (W_f + Ws) \times 100$$

Where W_f and Ws are the weights of the floating and settled microparticles, respectively. All the determinations were made in triplicate.

***In-vitro* release**

A USP basket apparatus has been used to study *in-vitro* drug release from microspheres. In the present study, drug release was studied using a modified USP XXIV 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 275 nm. The volume was replenished with the same amount of fresh dissolution fluid each time to maintain the sink condition.

Linear regression was used to analyze the *in-vitro* release mechanism.

Result and discussion

Floating microspheres were prepared by the emulsification solvent-evaporation technique using eudragit RS 100 as a polymer. The mean particle size of the microspheres significantly increased with increasing eudragit RS 100 concentration and was in the range 277.2 μm to 407.0 μm. The viscosity of the medium increases at a higher polymer concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities. This results in the formation of larger particles. The tapped density values ranged from 0.41 to 0.64 g/cm^3, while their true densities ranged between 1.62 to 1.92 g/cm^3 of all the formulations, which may be due to the presence of low-density particles in the microspheres. The porosity of all the formulations was found to be in the range of 60–80%. The compressibility index ranged between 20.7% to 26.8%. All formulations showed excellent flowability as expressed in terms of angle of repose in the range 25^0- $37^{0.}$ The better flow property indicates that the floating microspheres produced are non-aggregated (Table 1).

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

The percent yield of prepared microsphere was in the range 80.37 to 95.24. Percent drug entrapment efficiency of the microspheres was in the range 89.70 to 64.80. The microspheres floated for prolonged time over the surface of the dissolution medium without any apparent gelation. Percentage buoyancy of the microspheres was in the range 72.60 to 61.25 after 12 hr. (Table II).

Table 1: Micromeritic properties of different floating microsphere.

Batch code	Drug: Polymer	Stirring rate	Temp (^{o} c)	Mean Particle size[a] (μm.)	True density[b]. (g/cm^3)	Tapped density[b] (g/cm$^{3)}$	Compressibility index [b]	Porosity (%)	Angle of repose [b]
F1[a]	1 : 1	300	37	310.2±5.7	1.62±0.2	0.41±0.1	21.2±1.1	74.60	27.4±2.1
F2[a]	1 : 2	300	37	344.1±7.5	1.64±0.1	0.45±0.2	20.7±1.8	72.56	26.6±1.2
F3[a]	1 :3	300	37	382.7±7.9	1.70±0.2	0.50±0.3	22.8±1.9	70.58	31.2±1.6
F4[a]	1 : 4	300	37	407.0±9.4	1.92±0.3	0.64±0.2	23.1±2.1	66.66	34.4±2.4
F5[b]	1 : 2	500	37	288.4±6.7	1.81±0.2	0.52±0.4	22.5±1.5	71.27	29.1±3.1
F6[b]	1 : 3	500	37	294.8±7.9	1.67±0.1	0.54±0.1	25.3±1.6	67.66	28.6±1.6
F7[c]	1 : 2	1000	37	277.2±8.3	1.75±0.2	0.44±0.7	21.0±1.8	74.85	25.3±1.9
F8[c]	1 : 3	1000	37	287.6±9.7	1.81±0.1	0.49±0.5	26.3±2.1	72.92	26.1±2.1
F9[a]	1 : 2	300	45	302.4±4.6	1.76±0.2	0.57±0.4	24.3±0.9	67.61	34.2±2.4
F10[a]	1 : 3	300	45	297.8±8.3	1.86±0.2	0.46±0.6	26.1±2.1	75.26	31.0±1.6
F11[a]	1 : 2	300	50	325.7±6.5	1.75±0.1	0.52±0.4	24.3±1.8	70.28	37.2±2.4
F12[a]	1 : 3	300	50	309.4±5.7	1.80±0.2	0.48±0.2	26.8±2.4	73.33	34.2±1.6

Temp: Temperature.

Stirring rate; [a] = 300 rpm; [b] = 500 rpm; [c] = 1000 rpm

[a] Mean ± SD, n = 10; [b] Mean ± SD, n = 3.

To observe the effect of agitation speed on the size of the resulting microspheres, formulations were prepared at varying agitation speeds (batches F5–F8). The size of the resulting microspheres decreased with increasing agitation but the increase was not statistically significant. It may be inferred that the agitation speed in the studied range was not able to break up the bulk of the polymer into finer droplets and the released rate also not affected significantly.

To observe the effect of temperature on released rate and on particle size, as the temperature increase (batches F9-F12) [13], the shell of the microspheres was very thin and some of the microspheres were broken. It might be caused by faster diffusion of acetone in the droplet into non-aqueous phase and evaporation of acetone immediately after introducing it into the medium. In that case also release was fast, and size was also decreased.

Table 2: Various formulation parameters for microspheres

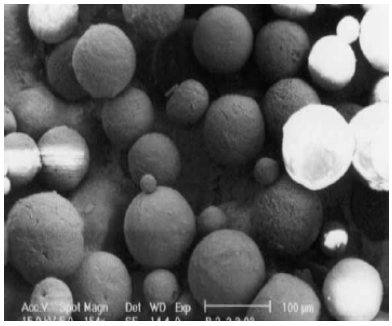
Batch code	Percent yield [b]	Incorporation efficiency [b] (%)	Buoyancy [b] (%)
F1	81.34±3.1	85.10 ± 2.1	63.00 ± 1.9
F2	85.42± 2.8	89.70 ± 2.4	66.80 ± 2.1
F3	80.37 ± 1.4	83.80 ± 2.4	72.60± 3.2
F4	89.24 ± 2.8	79.40 ± 3.2	70.2 ± 0.8
F5	91.24 ± 1.9	85.10 ± 1.4	65.20± 2.4
F6	90.21 ± 4.2	83.65 ± 0.9	68.40± 1.8
F7	87.34 ± 3.4	87.20 ± 1.9	67.20 ± 0.8
F8	95.24 ± 2.4	75.99 ± 3.1	64.31 ± 1.8
F9	91.36 ± 4.5	70.15 ± 1.5	69.12 ± 3.1
F10	92.14 ± 2.9	72.20 ± 2.2	61.25± 2.4
F11	89.29 ± 4.6	67.50 ± 2.8	65.64 ± 3.6
F12	86.67 ± 3.4	64.80 ± 1.4	63.40± 2.8

[b] Mean ± SD, n = 3.

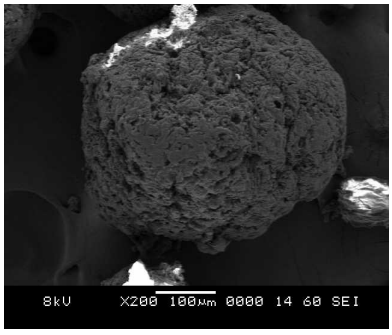
In-vitro aceclofenac release studies were performed 1.2-pH buffer for 12 h. The cumulative release of aceclofenac significantly decreased with increasing eudragit RS

100 concentration (batches F1-F4) (Fig. 2). The increased density of the polymer matrix at higher concentrations results in an increased diffusional pathlength. This may decrease the overall drug release from the polymer matrix. 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. Aceclofenac release was higher in the case of microspheres prepared at a higher agitation speed but the difference in drug release was not statistically significant (Fig. 3). Significant effect of temperature was observed on the *in-vitro* release of aceclofenac as the temperature increase the released rate also increase (Fig. 4).

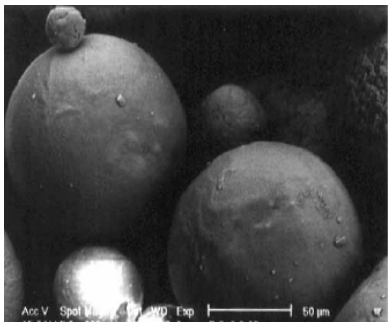
The data obtained for *in-vitro* release were fitted into equations for the zero-order, first- order and higuchi release models [16, 17.] The interpretation of data was based on the value of the resulting regression coefficients. The *in-vitro* drug release showed the highest regression coefficient values for higuchi model, indicating diffusion to be the predominant mechanism of drug release.



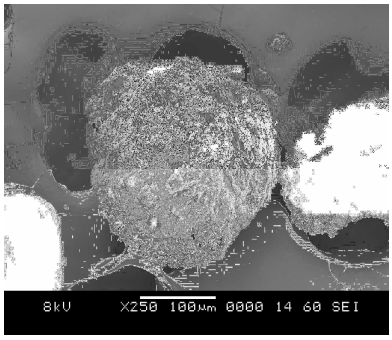
SEM 1



SEM 3



SEM 2



SEM 4

Fig 1: SEM of floating microspheres of A2 batch

SEM 1 shows size range of floating microspheres.

SEM 2 shows smooth texture of floating microspheres.

SEM3 shows dents on the surface.

SEM4 shows surface morphology of floating microspheres

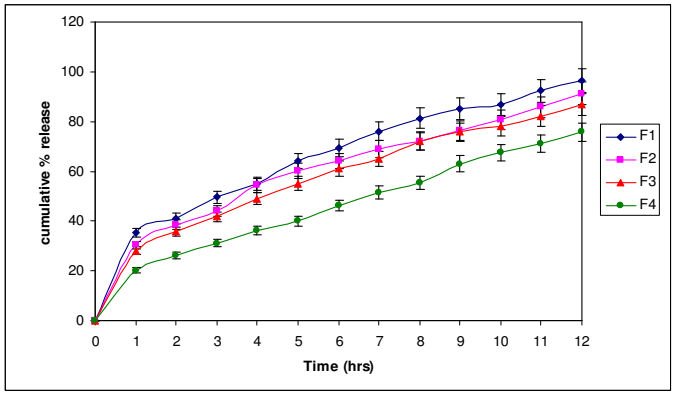


Fig.2: Effect of polymer concentration on *in- vitro* release of aceclofenac from floating microspheres. (Bars represent mean ± SD; n=3)

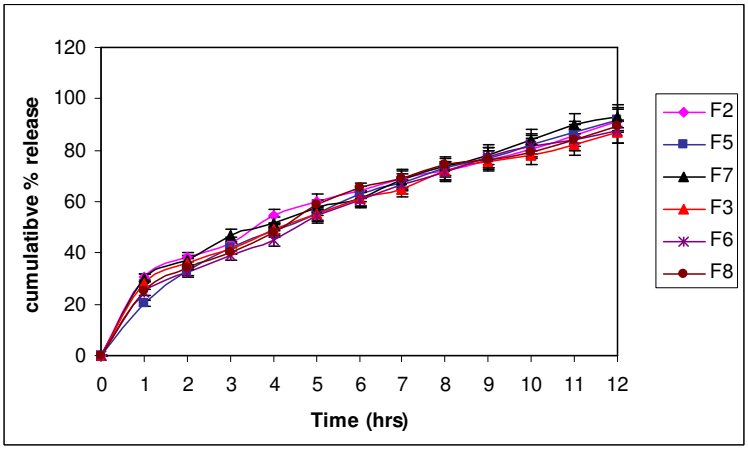


Fig.3: Effect of the stirring rate during microsphere preparation on *in- vitro* release of aceclofenac from floating microspheres. (Bars represent mean ± SD; n=3)

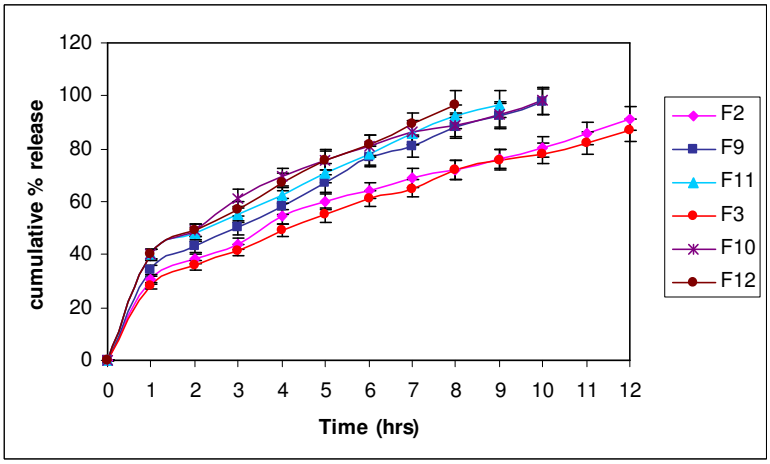


Fig.4: Effect of temperature on *in-vitro* release of aceclofenac from prepared microspheres. (Bars represent mean ± SD; n=3)

Conclusions

In-vitro data obtained for floating microspheres of aceclofenac showed excellent percent yield, good incorporation efficiency, 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 floating microspheres may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition.

Acknowledgement

Authors are thankful to Aarti drugs ltd., Tarapur.Thane for providing drug sample of aceclofenac.

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