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Formulation and evaluation of intragastric floating multiparticulate system of Aceclofenac

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ABSTRACT

The purpose of this research was to prepare and evaluate multiparticulate floating drug delivery system of aceclofenac. The microspheres were prepared by emulsification solvent evaporation technique using eudragit RS 100 as a release rate controlling polymer in the ratios 1:1, 1:2 and 1:3. The prepared microspheres were evaluated for drug-polymer compatibility, micromeritic properties, drug entrapment efficiency, in-vitro buoyancy and drug release studies. The mean particle size increased with increase in the polymer concentration, when compared to pure drug and it was lying between 14.71-25.93 µm. The micromeritic properties were found to be improved when compared to pure drug .Scanning electron microscopy confirmed the hollow structure with smooth external surface. The drug and polymer were found to be compatible as seen in IR studies. The entrapment efficiency considerably decreased with increase in the polymer concentration ranging from 78-36 % respectively. The microspheres floated up to 12 h over the surface of the gastric buffer medium and the buoyancy percentage was found to be in the range of 85-94%. In-vitro drug release studies showed that the prepared microspheres exhibited prolonged drug release for more than 12 hours. The mechanism of drug release was found to be a combination of both peppas and zero order release kinetics. The developed floating microspheres of aceclofenac may be used for prolonged drug release for at least 12 h for maximizing the therapeutic efficacy along with patient compliance.

Key words: Aceclofenac, Eudragit RS 100, Hollow microspheres, Buoyancy.

INTRODUCTION

Oral drug delivery has been known for decade as the most widely used route of administration among all the routes that have been explored for the systemic delivery. Oral route is the most convenient and extensively used route of drug administration. All controlled release systems

have limited applications if the systems cannot remain in the vicinity of the absorption site. The controlled release drug delivery system possessing the ability of being retained in the stomach is called gastroretentive drug delivery system. They can help in optimizing the oral controlled delivery of drugs having "absorption window" continually releasing the drug prior to absorption window for prolonged period of time, thus ensuring optimal bioavailability [1].

Several approaches are currently used to prolong gastric residence time e.g. floating systems, swelling systems, bioadhesive systems and high density systems [2]. One such approach is floating (hollow) microspheres. Hollow microspheres are considered as one of the most promising buoyant systems, as they possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere [3].

Indeed, the gastric emptying of a multiparticulate floating system would occur in consistent manner with small individual variations. On each subsequent gastric emptying, such particles will spread over a large area of absorption sites, increases the opportunity for drug release profile and absorption in a more or less predictable way. Since, each dose consists of many subunits; the risk of dose dumping is reduced [4, 5].

Aceclofenac, a non-steroidal anti-inflammatory drug is used for relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and alkalysing spondylitis. Aceclofenac is rapidly but incompletely absorbed with low bioavailability 60 % from the gastrointestinal tract . The poor bioavailability and short biological half life of 4 h favor the development of controlled release formulation as hollow microspheres.

MATERIALS AND METHODS

Aceclofenac was obtained as gift sample from Unichem Laboratories Goa. All chemicals used were of high quality analytical grade.

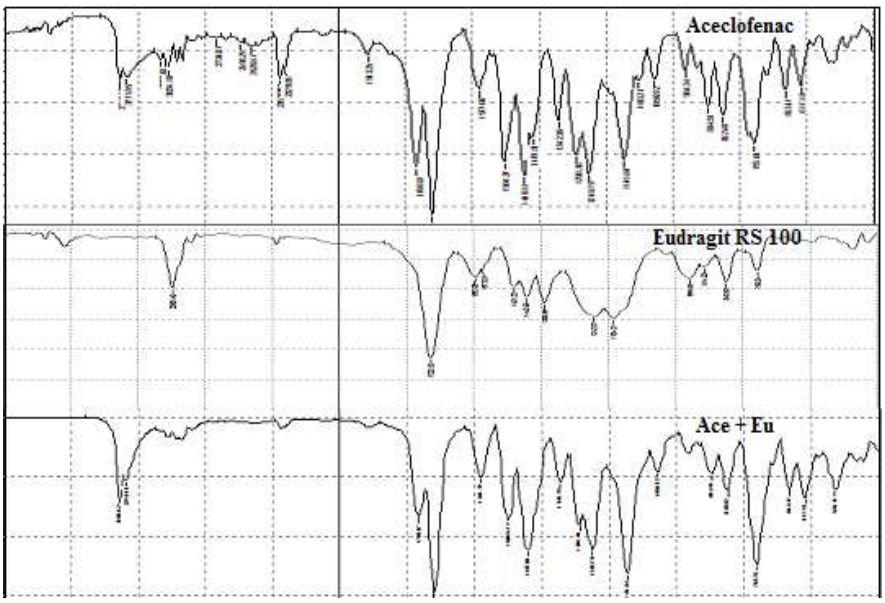
Preparation of microspheres:

The microspheres of aceclofenac using Eudragit RS 100 were prepared by emulsification solvent evaporation technique. Aceclofenac and Eudragit RS 100 were dissolved in ethanol: dichloromethane mixture in1:1 (500 mg: 500mg), 1:2 (500 mg: 1000 mg) and 1:3 (500 mg: 1500 mg) ratios. 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. 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 hollow cavity was formed resulting in floatation of microspheres due to decreased density [6].

Drug-Polymer Interaction Study:

FTIR spectra of pure drug, polymer (Eudragit RS 100), physical mixture of drug and polymer were obtained in KBr pellets at moderate scanning speed between 4000-200 cm^{-1} using a Shimadzu FTIR 1601 PC.

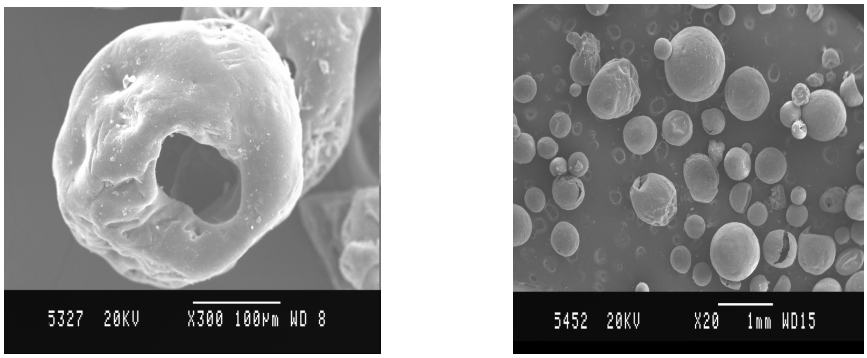
Fig.1- FTIR spectra of pure drug, polymer and physical mixture



Roundness or sphericity:

The morphology (outer surface and sphericity) of hollow microspheres was examined using a scanning electron microscope (GEOL 5400, USA). Completely dried hollow microspheres were coated with gold-palladium alloy for 45 sec under an argon atmosphere in an ion sputter before observation.

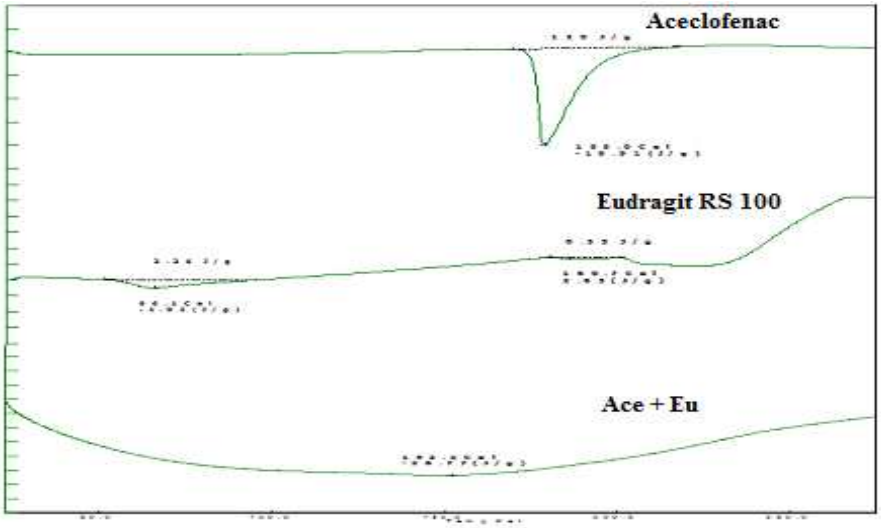
Fig.2 – Scanning electron microphotographs of hollow microspheres



Differential Scanning Calorimetry:

Thermal analysis of aceclofenac, eudragit RS 100 and aceclofenac loaded hollow microspheres were studied by differential scanning calorimeter (Mettler Toledo DSC, USA). Accurate amount of samples were weighed into aluminium pans and sealed. All samples were run at a heating rate of 10°/min over a temperature range of 25-300° in atmosphere of nitrogen.

Fig.3- DSC thermograms of aceclofenac, Eudragit RS 100 and AE+Eu (formulation)



Micromeritic Studies:

The mean size of microspheres was determined using optical microscope (Olympus NWF 40X, Educational Scientific Stores, India) fitted with an ocular micrometer and stage micrometer. The images were taken to characterize the outer surface and for the confirmation hollow formation within the microspheres. The arithmetic mean diameter was determined with MicroLite Image software attached to optical microscope. The flow properties of microspheres were characterized in terms of angle of repose, Carr's index and Hausner's ratio. Accurately weighed microspheres were poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Initial volume was noted. Bulk density (ρ_b) and tapped density (ρ_t) were calculated by tapping method using 10 ml measuring cylinder.

Hausner's ratio (H_R) and Carr's index ($IC_)$ were calculated according to the two equations given below

$H_R = (\rho_t)/(\rho_b)$ and $I_c = (\rho_t \times \rho_b)/(\rho_t)$

Yield of Microspheres:

The prepared microspheres were weighed by using analytical balance and percentage yield was calculated by using the following formula [7]

% Yield = (Actual weight of product / total weight of polymer and drug) x 100

Drug Entrapment Efficiency (DEE):

Accurately weighed microspheres were crushed and transferred into 100 ml volumetric flask. The volume was made up using phosphate buffer pH 7.4. The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically at 273 nm against appropriate blank. The amount of drug entrapped in the microspheres was calculated by the following formula [8]

DEE = (Amount of drug actually present / Theoretical drug load expected) x 100

Table No.1 - Micromeritic properties of hollow microspheres of aceclofenac

Formulation code*	Average particle size (µm)	Angle of repose (θ)	Bulk Density(g/cm^3)	Tapped Density(g/cm^3)	Carr's index(I_C)	Hausner's ratio(H_R)
Aceclofenac	11	39°09′	1.92	0.601	28.00	1.6
AE1	14.71	25°38′	1.51	0.43	10.4.	1.2
AE2	20.7	27°67′	1.69	0.56	16.75	1.3
AE3	25.93	30°12′	1.84	0.62	20.8	1.3

AE- Formulations containing Aceclofenac and Eudragit RS 100*

***In-Vitro* Buoyancy:**

Microspheres (100 mg) were spread over the surface of a USP dissolution apparatus type Π filled with 900 ml of 0.1 N hydrochloric acid containing 0.02% v/v tween 80. The use of tween 80 was to account for the wetting effect of the natural surface-active agents in the GIT. 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 microspheres that remained floating and the total mass of the microspheres [9].

$$Buoyancy\ (\%) = W_f / (W_f + W_s)\ X\ 100$$

Where W_f and W_s are the weights of the floating and settled microspheres. All the determinations are made in triplicate**.**

***In-Vitro* Drug Release Study:**

In-vitro drug release studies were carried out for all formulations using USP dissolution apparatus type Π filled with 900 ml of phosphate buffer pH 7.4. Microspheres equivalent to 50 mg of the drug were taken for the studies. 2 ml of the aliquot was withdrawn at predetermined intervals and equal volume of dissolution medium was replaced to maintain sink condition. The required dilutions were made with buffer and the solution was analyzed for the drug content spectrophotometrically at 273 nm against suitable blank. All the determinations were made in triplicate [10].

Table No.2 - Formulation Code, Composition, Yield, Drug Entrapment and Drug release of hollow microspheres of aceclofenac

Formulation code*	Drug to polymer ratio	Weight of drug (mg)	Weight of polymer (mg)	Volume of ethanol: dichloromethane (ml)	Percentage yield (%)	Drug entrapment (%w/w)	Buoyancy (%)	Percentage Drug Release (%)
AE1	1:1	500	500	10	83.13	78	72.6	90.26
AE2	1:2	500	1000	10	60	63	70.89	84.03
AE3	1:3	500	1500	10	64.5	36	61.25	70.54

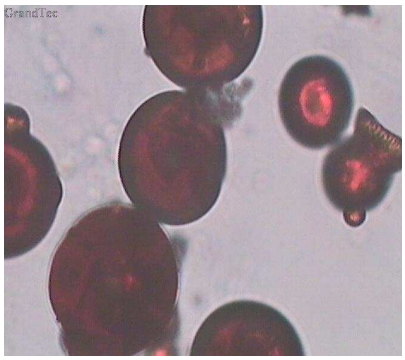
AE- Formulations containing Aceclofenac and Eudragit RS 100*

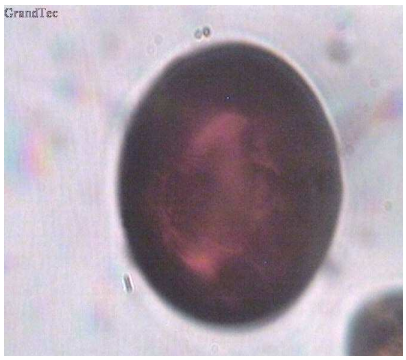
RESULTS AND DISCUSSION

In the present study floating microspheres of aceclofenac were prepared by the emulsification solvent-evaporation technique using eudragit RS 100 as a polymer (Table 2).

The mean particle size of the microspheres significantly increased with increasing eudragit RS 100 concentration and was in the range of 14.71 μm to 25.935 μm. The optical microphotographs taken at 10 x and 40 x magnification confirmed the formation of microspheres as well as the hollow cavity (Fig.4).

Fig.4- Optical microphotographs of hollow microspheres





The viscosity of the medium increases due to enhanced interfacial tension and diminished shearing efficiency. This results in the formation of larger particles. The tapped density values ranged from 0.43 to 0.62 g/cm3, while their true densities ranged between 1.51 to 1.84 g/cm3 of all the formulations, which may be due to the presence of low-density particles in the microspheres. The compressibility index ranged between 10.4 % to 20.8 %. All formulations showed excellent flowability as expressed in terms of angle of repose in the range 25°- 37°. The better flow property indicates that the floating microspheres produced are non-aggregated (Table.1).

The SEM photographs showed that the formulated microspheres were spherical with a smooth external surface (Fig.2).

The IR spectras of pure drug, polymer and physical mixture indicated the absence of any possible drug-polymer interaction as there was no significant shift in the principal peaks of aceclofenac and the drug was found to be stable in all the formulations (Fig.1).

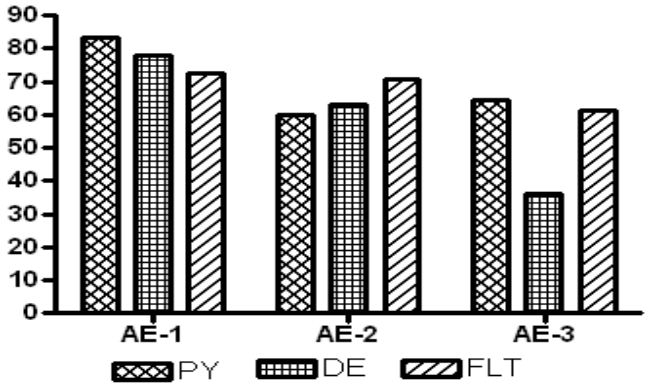
DSC thermograms of aceclofenac, eudragit RS100 and physical mixture were shown in Fig.3. DSC thermogram of aceclofenac showed sharp endothermic peak at 155°, which was around its melting point 156°.The thermogram of formulation also showed the peak near to its melting point indicating that drug was stable in the formulation and absence of any interaction between the drug and the polymer.

Table No.3- The regression-coefficients and rate constants for release of aceclofenac from hollow microspheres

Form.code*	Zero order		First order		Higuchi matrix model		Peppas Korsmeyer		Hixon Crowell	
	R	k	R	k	R	k	R	k	R	k
AE1	0.8278	5.6883	0.9713	0.072	0.9523	24.6	0.9801	0.278	0.9365	0.185
AE2	0.9601	6.886	0.8768	0.0713	0.8879	23.943	0.914	0.7757	0.9108	0.1797
AE3	0.9307	5.1696	0.903	0.045	0.9303	19.428	0.8622	0.375	0.9198	0.1267

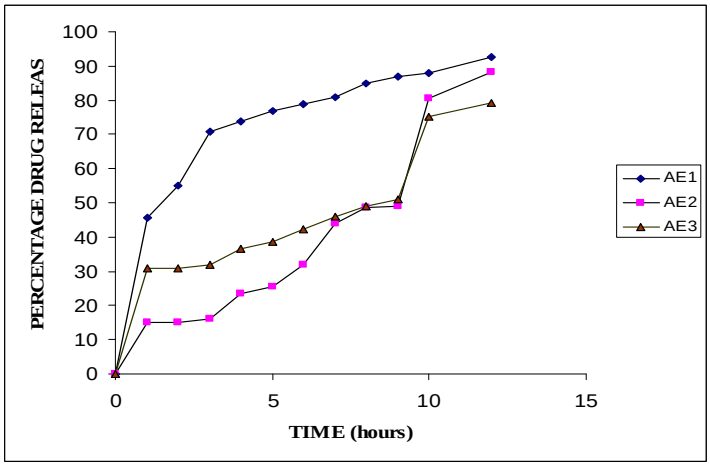
AE- Formulations containing Aceclofenac and Eudragit RS 100*

Fig. 5 - Comparative physical characteristics of formulations AE 1, AE 2 and AE 3



PY-Percentage yeild DE-Drug entrapment FLT- Floatation

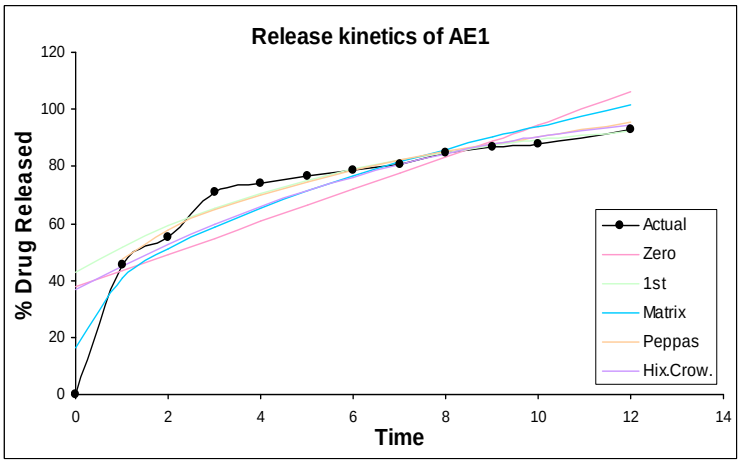
Fig.6-*In-vitro* drug release profile of formulations AE 1, AE 2 and AE 3



The percentage yield of prepared microspheres AE1, AE2 and AE3 were found to be 83.13, 60 and 64.5 % respectively. Drug entrapment efficiency of the microsphere was found to be in the range of 78-36 % (Table 2). 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(Table 2) after 12 h.

The *in-vitro* drug release from the floating microspheres was found to be 90.26, 84.03, and 70.54 % at the end of 12 h for AE1, AE2 and AE3 respectively (Table 2 and Fig.6). From the values, it was observed that on increasing the polymer concentration the release of drug was found to be decreased due to the increase in the thickness of the outer surface of the microspheres. In-vitro dissolution data was fitted to peppas for AE 1 and zero order release kinetics foe AE 2 and AE 3(Table 3 and Fig.7). The increased drug release was recorded for AE1 due to low particle size with greater surface area and thinner outer polymer coating.

Fig.7-Model fitting of *in-vitro* dissolution profile of Aceclofenac for AE 1 hollow microspheres in phosphate buffer pH 7.4



CONCLUSION

The present study reports the development of drug loaded floating microspheres of aceclofenac by using eudragit RS 100 as a rate controlling membrane. AE1 with drug: polymer ratio 1:1 was found to be satisfactory in terms of excellent micromeritic properties, yield of microspheres (83.13 %), incorporation efficiency (78 %), *in vitro* buoyancy (72.60 %) and highest *in vitro* drug release of 90.26 % in sustained manner with constant fashion over extended period of time for 12 h. From the results it was observed that drug: polymer ratio influences the particle size, *in vitro* buoyancy, as well as drug release pattern of floating microspheres.

REFERENCES

[1] CJ Swati ; JA Amit ; VP Sudhir .*AAPS .Pharm. Sci .Tech.*, **2009,** 10,1071.
[2] CR Narayana; BV Basavaraj; V Madhavan. *Int .J .Pharma .Sci .Rev.Res.*, **2010**, 5,135.
[3] R Hetangi; P Vishnu; M Moin. *Int .J. Pharma. Sci. Rev. Res.*, **2010**, 4,183.
[4] S Desai ; S Bolton. *Pharm. Res.*, **1993**, 10,1321.
[5] V Iannucelli; G Coppi; MT Bernabei. *Int.J.Pharm.*, **1998**, 174, 47.
[6] YS Gattani; PS Kawtikwar; DM Sakarkar. *Int .J. Chem. Tech. Res.*, **2009**, 1, 1.
[7] S Shaji; ST Pasha; S Srinivasan. *J. Pharma. Sci. Tech.*, **2009**, 1, 40.
[8] B Singh; J Kanouji; M Pandey. *Int .J.Pharm .Tech .Res.*, **2010**, 2, 1415.
[9] BV Basavaraj; R Deveswaran; S Bharath; V Madhavan. *Pak .J .Pharm .Sci.*, **2008**, 21,451.
[10] P Asha; R Subhabrata; ST Ram. *Daru .*, **2006**,14,57.