ISSN: 0975-766X
Research Article
Available Online through
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FORMULATION, CHARACTERISATION OF ACECLOFENAC MICROSPHERES AND EVALUATION OF COMMERCIAL BRANDS OF MODIFIED RELEASE ACECLOFENAC TABLETS

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Received on 13-05-2011 *Accepted on 25-05-2011*

Abstract

Microspheres are one of the multiparticulate delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites. Aceclofenac is a potent analgesic, anti-pyretic and anti-inflammatory agent used in the management of moderate-to-severe pain and in rheumatic disorders such as rheumatoid arthritis and ankylosing spondylitis. The primary aim of this study is to formulate and characterize the aceclofenac loaded microsphere using Eudragit RL100, Eudragit RSPO and Ethyl Cellulose. Another objective of this study is to evaluate the marketed brands of modified release aceclofenac tablets. The formulated microspheres showed the percentage yield of 69.1 – 76.56%, mean particle size of 86.32 – 114.3 µm and drug entrapment efficiency as 79 – 88%. The *invitro* release of microspheres at phosphate buffer pH 7.4 showed 66.37 – 74.03% after 6 hours. The commercially available marketed brands of modified release aceclofenac [Zerodol CR (IPCA), Aceclo SR (Aristo) and Aceclan SR (Anthus)] were evaluated for uniformity of weight, friability and hardness all the results were within the acceptable limit. The *invitro* release studies with 0.1N HCl for 2 hours showed 10% release and further upto 24 hours in phosphate buffer pH 7.4 showed 61.18 – 66.68% release.

Keywords: Aceclofenac, Eudragit, Ethyl Cellulose, Microspheres.

Introduction

Osteoarthritis, rheumatoid arthritis and ankylosing spondylitis are a group of related, but distinct, disorders of the cartilage of osteoarticular joints. Osteoarthritis predominantly affects the large weight-bearing joints and the

clinical characteristics include morning stiffness of short duration, stiffness or gelling on rest, pain on use, joint inflammation and bone deformity. Rheumatoid Arthritis is less common than osteoarthritis, although no less debilitating. Fatigue, malaise, subcutaneous nodules and fever are common systemic symptoms of Rheumatoid Arthritis. Ankylosing spondylitis is characterized by inflammation, predominantly of the spine, but in some cases, also of the large peripheral joints. Systemic symptoms can include fever, fatigue and anorexia and in some cases pericarditis and pleuritis may occur. NSAIDs have become widely used in the treatment of these illnesses for their pain-relieving and anti-inflammatory properties[1]. Since long-term NSAID treatment is indicated for osteoarthritis, the ideal agent should have good efficacy and a low propensity to cause adverse events. Aceclofenac appears to be particularly well tolerated among the NSAIDs, with a lower incidence of gastrointestinal adverse effects. This good tolerability profile results in a reduced withdrawal rate and greater compliance with treatment[2]. Aceclofenac is a phenylacetic acid derivative related to diclofenac. It is a practically insoluble in water drug with a molecular weight of 354.19, a pKa value of 4.7 and a log p-value of 1.23. It is a potent analgesic, anti-pyretic and anti-inflammatory agent used in the management of moderate-to-severe pain and in rheumatic disorders such as rheumatoid arthritis and ankylosing spondylitis[3]. Aceclofenac is probably metabolized via Cytochrome P450 2C9 to the main metabolite 4-hydroxyacefenac with negligible contribution to clinical activity. Its adverse reactions, as with other NSAIDs taken by mouth, are indigestion, heartburn, nausea and diarrheoa[4]. Microspheres are one of the multiparticulate delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites[5]. They can distribute in the GI tract homogeneously, thus maximizing drug absorption and reducing peak plasma fluctuations, minimizing the risk of local GI tract irritation and dose dumping, decreasing dosing frequency and increasing patient compliance, improving the safety and efficacy of the active ingredient[6]. The primary aim of this study is to formulate and characterize the aceclofenac loaded microsphere. Another objective of this study is to evaluate the marketed brands of modified release aceclofenac tablets.

Materials and Methods

Aceclofenac and Ethyl Cellulose were a generous gift sample from Biotrans Pharmaceutical Pvt., Ltd., Chennai. Eudragit RL100, Eudragit RSPO were received as gift samples from Evonik Degussa Industries, Mumbai, India.

All other chemicals were of A.R grade. Three brands, Zerodol CR (IPCA), Aceclo SR (Aristo) and Aceclan SR (Anthus) of Modified release Aceclofenac 200mg tablets were purchased from the local market.

Preparation of Microspheres by O/W Solvent Evaporation Method[7-9]

Being insoluble in water aceclofenac loaded microspheres can be well formulated using O/W type solvent evaporation method. Drug and polymer dissolved in DCM to obtain a clear solution. This solution was added drop wise through the needle to the aqueous medium containing 1.5% PVA. Solution was stirred using three bladed stirrer for 4 hour at 600 rpm. The formed microspheres were then filtered and washed with water, dried at dessicator until further used. Details of the formulation tabulated in Table 1.

Table 1: Formulation of Microspheres.

Ingredients	Formulations		
	F1	F2	F3
Drug	100mg	100mg	100mg
Polymer	Eudragit RL 100-200mg	Eudragit RSPO - 200mg	Ethyl cellulose -200mg
Solvent	DCM-10 ml	DCM-10 ml	DCM-10 ml
Aqueous Phase PVA (1.5%)	100ml	100ml	100ml

Percentage Yield

The percentage yield of the formulated microsphere was calculated using the following formula and the yields were tabulated on Table 2.

Table 2: Characterisation of Formulated Microspheres

S.No	Formulations	DEE	Percentage Yield	Mean particle size (µm)
1	F1	88	76.56	86.32
2	F2	80	72.33	92.81
3	F3	79	69.1	114.3

Percentage Yield = (weight of the dried microspheres / theoretical yield) X 100

Size Distribution

Microscopic analysis was performed to determine the average size of the microsphere. A sample of microspheres were mounted in the glass slide and examined microscopically. Calibrated eyepiece micrometer and stage micrometer were utilized for the size analysis and the mean sizes were shown on Table 2.

Drug Entrapment Efficiency

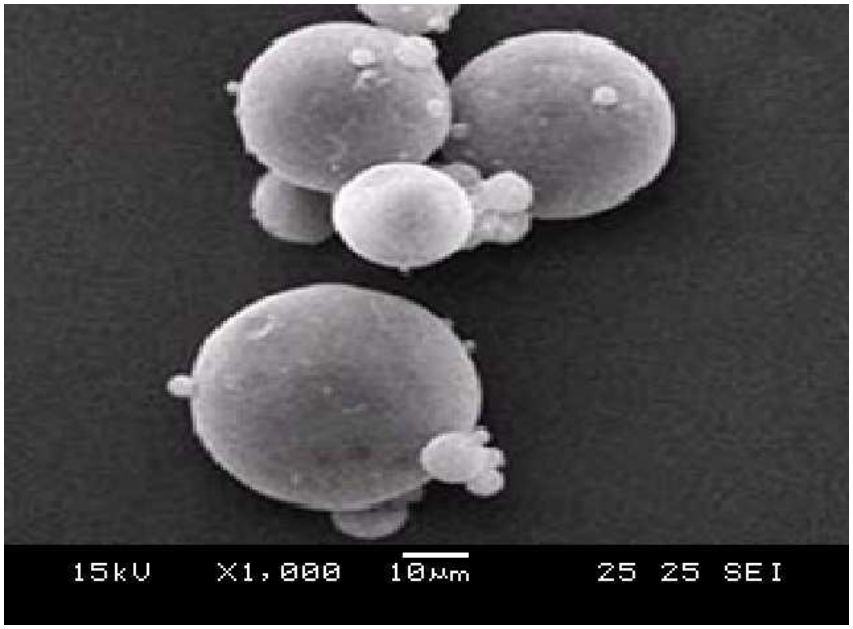
Microspheres equivalent to 25 mg of drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microsphere and extracting with Dichloromethane. The extract was diluted suitably with solvent and the absorbance was measured spectrophotometrically at 275 nm against appropriate blank. The drug entrapment efficiency was calculated according to the following relationship and the results were shown on Table 2.

Percent Entrapment = (Actual Content / Theoretical Content) X 100

Surface Morphology Characteristics

Scanning electron microscopy was performed to characterize the surface morphology of the formed microspheres at angle of 90^0 with accelerating voltage 20KV after gold coating. Morphology characteristics were studied for formulation F1 (Figure 1).

Figure 1: SEM image of F1 Microsphere



Marketed Product Evaluation

Three Commercially marketed brands of modified release Aceclofenac tablets were selected to study the quality of tablets.

Uniformity of Weight[10]

The uniformity of weight was determined for randomly selected twenty tablets of each brand and the results were shown on Table 3 as the relative standard deviation. Indian Pharmacopoeia allows ±5% deviation for the tablets weighing 250mg or more.

Table 3: Evaluation of Commercial Brands

S.No	Tablet Brand	Uniformity of weight (mg)	Friability	Hardness of tablets (kg/cm^2)
1	Zerodol CR	300.8 ± 1.728	0.126%	7.1±0.962
2	Aceclo SR	418.7 ± 2.119	0.055%	11.4±0.802
3	Aceclan SR	411.1 ± 2.857	0.066%	8.7±0.652

Friability

Friability was determined using Roche Friabilator this test subjects a number of tablets to combined effect of shock abrasion by utilizing a plastic chamber which rotates at a speed of 25 rpm after 4 minutes the tablets then dedusted and reweighed. A loss of less than 1% in weigh in generally considered acceptable. Percent Friability was calculated as follows.

Percent Friability = [(Initial weight of Tablets – Final weight of the tablets) / Initial weight of Tablets] X 100

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets were determined using Monsanto hardness tester. The results above three parameters were tabulated in Table 3.

***Invitro* release of Microspheres and Marketed products[11]**

The *Invitro* dissolution studies of formulated microspheres were carried out using paddle type dissolution test apparatus (USP XXIII) rotating at 100 rpm using phosphate buffer pH 7.4 as the dissolution medium. For the commercial brands 0.1N HCl used for the first 2 hrs and then followed by phosphate buffer pH 7.4. The

temperature of the medium was maintained at 37 ± 0.5^{0}C. At specific time intervals aliquots were withdrawn and analysed at 275nm spectrophotometrically after suitable dilution. The withdrawn volume was replaced with an equal volume of fresh medium. The *invitro* release profiles of microspheres and marketed brands were shown on Figure 2 and Figure 3.

Figure 2: *Invitro* release characteristics of Microspheres.

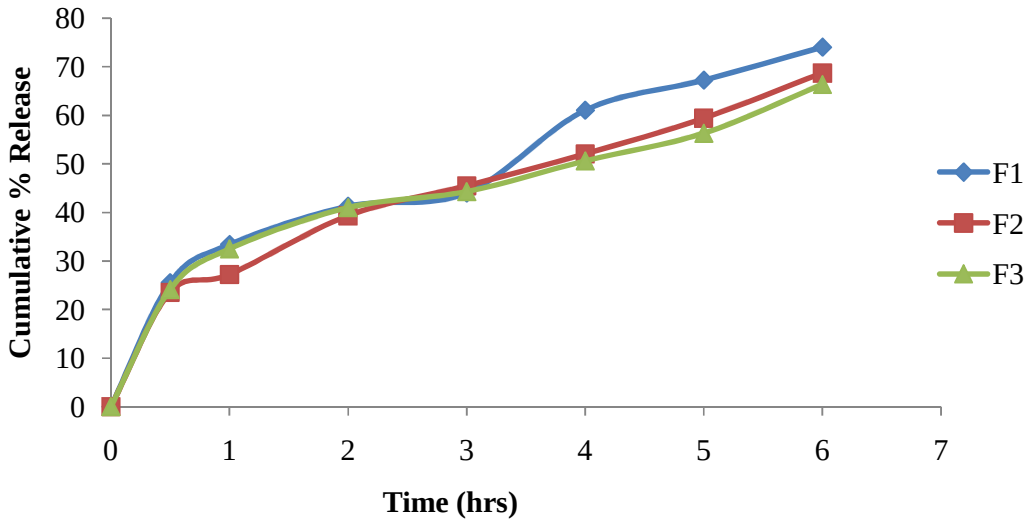
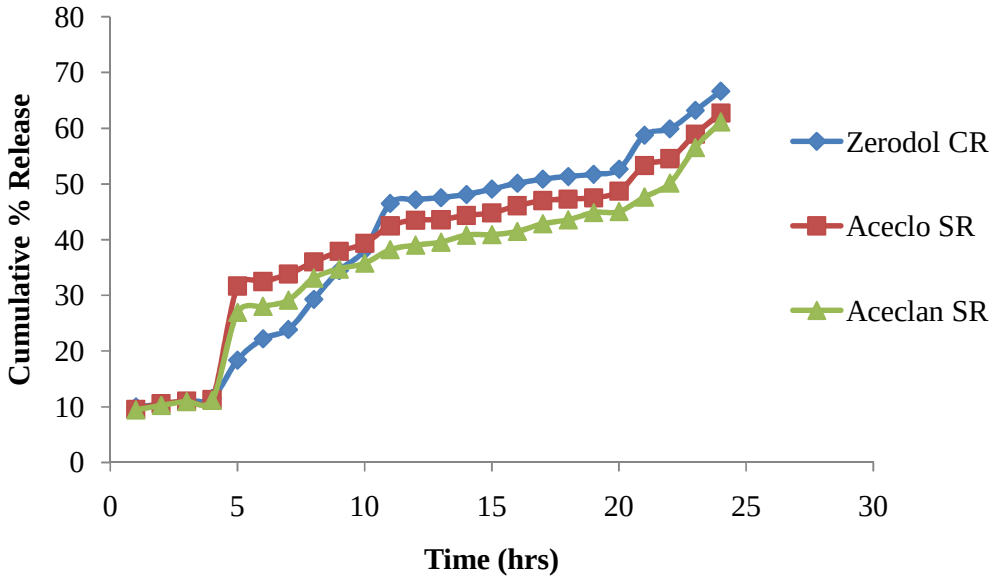


Figure 3: *Invitro* release characteristics of commercial brands.



Results and Discussion

Aceclofenac loaded microspheres were successfully prepared by O/W solvent evaporation method using Eudragit RL100, RSPO and Ethyl Cellulose as polymers. Percentage yield of the formulated microspheres of Eudragit RL100 was found to be high 76.56% followed by 72.33% for Eudragit RSPO and 69.1% for Ethyl Cellulose. Entrapment efficiency were found to be high for all the three formulations 79 – 88%. Mean particle size was found to be 86.32 µm – 114.3 µm Eudragit RL100 shows 86.32 µm as the least size, 92.81 µm for Eudragit RSPO and for Ethyl cellulose it was found to be 114.3 µm as the larger in these three formulations. Surface morphology of formulation F1 containing Eudragit RL100 microspheres was found to be smoother and discrete there are few particles are adhered at the surface of microspheres this could be reason for the initial burst effects of *invitro* release. The cumulative percentage of drug release of the microspheres after 6hrs at phosphate buffer pH 7.4 were found to be 74.03% for Eudrgait RL100, for Eudragit RSPO 68.70% and 66.37 for Ethyl cellulose. These high percentages of release after the 6 hours could be due to the lower amount of polymer concentration added in the formulation. Three brands were chosen in order to study the quality of the marketed brands of modified release aceclofenac tablets. The evaluated brands within their shelf life during the time of the study. Uniformity of weight, Friability and Hardness were evaluated and these results were shown in Table3. From the results obtained it was found that all the three parameters were found to be satisfactory. The *invitro* release of the tablets at 0.1N HCl for first 2 hours of all the three brands showed 10% release and at the pH 7.4 phosphate buffer after 24 hours it was found to be 61.18% for Aceclan SR, 62.72% for Aceclo SR and Zerodol CR showed 66.68%.

Conclusion

Aceclofenac loaded microspheres were prepared successfully by utilizing the Eudragit RL100, RSPO and Ethyl cellulose. The formulated microspheres were shown good results for the evaluated parameters. Further evaluations with these polymers are to be done to bring out stable once daily formulations. The evaluated marketed brands of modified release Aceclofenac tablets shows a sustained release effect over a period of 24 hours and the other evaluated parameters are with in the acceptable limit.

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