ORIGINAL ARTICLE

EFFECT OF PROCESSING VARIABLES ON MICRO PARTICULATE SYSTEM OF ACECLOFENAC

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ABSTRACT

Microparticulate systems of aceclofenac were prepared by modified solvent evaporation method using different variables such as polymer (cellulose acetate): drug ratios (1:9, 1:6, 1:3, and 1:1), agitation speeds (500-1500 rpm) and stirring time (5-15 min). The effects of processing variables were evaluated by microparticle size and entrapment efficiency. The average microparticle size increases from 80.2 ± 1.45 to 97.3 ± 2.06 µm with increase in the polymer concentration while reduces with increase in agitation speed and stirring time; and at the higher speed gives irregular shape of particles. The highest entrapment efficiency, size uniformity, angle of repose (23.6 ± 0.3 degree) and compressibility index (13.8 ± 0.7%) of microparticles were found with 1:6 (polymer: drug ratio), at 1000rpm and 10min stirring time among all microparticles. The *in-vitro* drug release study was carried out with prepared microcapsules (AC-1 to AC-4) of various polymer concentrations and optimized processing variables and compared with conventional and SR tablets. The conventional tablet and SR tablet releases maximum drug within 3 and 6h respectively while microparticulate system releases more than 12h. All formulations followed first order release kinetic and diffusion controlled drug release.

Keywords: Microparticle, sustained and cellulose acetate.

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INTRODUCTION

Aceclofenac [2-(2',6'-dichlorophenyl)amino]phenylacetoxy-acetic acid] is a phenylacetic acid derivative with potent analgesic and anti-inflammatory properties. It is used for inflammatory mediator such as inhibition of production of IL-1β, tumor necrosis factor, basal and IL-1β stimulated IL-6 production, cyclooxygenase activity, basal and stimulated prostaglandin E2 production by blood mononuclear cells, by synovial cells, articular chondrocytes and osteoarthritic cartilage. It rapidly and completely absorbed after oral administration with peak plasma concentration with in 1.25 to 3 hours but highly protein bound (>99%) in plasma having 25 L volume of distribution. The high concentration with rapid absorption of drug causes adverse effect to GIT. To improve the therapeutic efficacy of aceclofenac and reduce the severity of upper GI tract side effect through altering dosage form of aceclofenac can be achieved by modifying release of the formulation to optimize drug delivery. There are variety of sustained release matrix tablets of aceclofenac are available in the market e.g., Dolokind-SR and Hifenac-SR etc. The sustained release formulation such as microparticulate has been tried for present study, which may give one of the efficient means of drug delivery with patient compliance (Akimoto *et al.,* 2000, Hayllar *et al.,* 1994 and Ribeiro *et al.,* 1998).

MATERIAL AND METHODS

Aceclofenac (Gift sample from Ranbaxy Lab. Ltd. Dewas, M.P.), cellulose acetate (Zeim Lab. Nagpur), acetone, liquid paraffin heavy and light, and n-hexane, were of analytical grade supplied by S.d. fine chem. Ltd.

Preparation of microparticles

The microparticles were prepared by modified emulsion solvent evaporation method (Benedetti *et al*., 1990; Abd EI-Hameed and Kellaway, 1997; Satturwar *et al*., 2002). Cellulose acetate was dissolved completely in acetone (10ml) in a glass vessel, and aceclofenac was added. The mixture was stirred at 150 rpm at room temperature (25 ± 1°C) for 15 min. The resultant solution was intermittently sprayed using a spray gun (0.5mm nozzle size, 50 psi pressure) into previously heated (60 ± 1°C) liquid paraffin (500 ml, 1:1 mixture of light and heavy liquid paraffin) with continuous stirring at 1000 rpm. Microparticles of varying polymer: drug ratio (1:9, 1:6, 1:3 and 1:1 i.e., AC-1, AC-2, AC-3 and AC-4 respectively) were prepared by keeping two variables constant i.e., agitation speed (1000rpm) and stirring time (10 min). Similarly, microparticles were also prepared at different agitation speed viz., 500, 1000, and 1500 rpm keeping the polymer: drug ratio 1:6 and stirring time 10 min was constant. In the same way microparticles were prepared using different stirring time i.e., 5, 10 and 15 min at the polymer: drug ratio 1:6 and agitation speed 1000 rpm. The microparticles were separated by filtration through Whatman filter paper (0.45μm), washed three times with 25 ml n-hexane to remove all liquid paraffin stick to microparticles and allowed to dry at room temperature (25 ± 1°C).

Each microparticles of varying polymer: drug ratio was made in triplicate.

Morphological study

The surface morphology of microparticles was performed by a scanning electron microscopy (SEM, LEO 430, London). Microparticles were mounted on stubs and coated for 120 s with a layer of gold using a sputter coater. The size of microparticles was determined by an optical microscopy by using a calibrated ocular micrometer (Erma, Japan).

Entrapment efficiency determination

An accurately weighed quantity of microparticles

Table 1: Regression equation, regression co-efficient(r), first order release rate constant, angle of repose and compressibility index of microparticles

S. No.	Formula-tion	Polymer: Drug Ratio	Regression equation	Regression coefficient (r)	Release Rate Constant K_1 ($_{hr}^{-1}$)	Angle of repose θ(degree) ± SD, n=3	Compressibility Index (I) (%) ± SD, n=3
1.	AC-1	1:9	Y=39.329x-1.2145	0.976	0.404	23.5 ± 0.4	11.1 ± 1.1
2.	AC-2	1:6	Y=8.911x-8.031	0.9944	0.177	23.6 ± 0.3	13.8 ± 0.7
3.	AC-3	1:3	Y=29.491x-13.261	0.991	0.157	23.5 ± 0.4	14.2 ± 0.6
4.	AC-4	1:1	Y=28.213x-14.138	0.990	0.134	34.4 ± 0.6	23.6 ± 0.6
5.	SR Tab.	200 mg	Y=7.9804x+78.967	0.9858	0.338	--	--

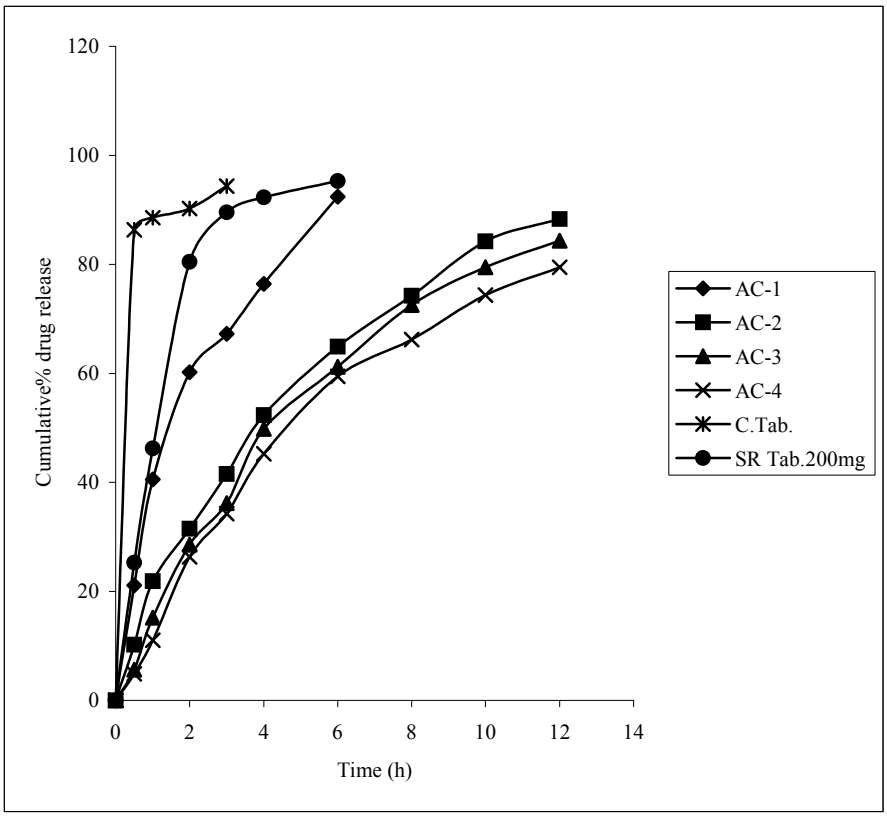

Fig. 1: Release profile of aceclofenac from cellulose acetate microparticles. (AC-1, AC-2, AC-3, AC-4, C.Tab and SR tablet)

(equivalent to 100mg aceclofenac) was first extracted with 30 ml of alkaline phosphate buffer pH 7.4 then consecutive drug extraction was carried out 10 times using 7 ml buffer in each extraction. All filtrates were mixed together and filtered through Whatman filter (0.45µm). The filtrate was assayed spectrophotometrically (UV-1700-Shimadzu Japan) after suitable dilution at 274nm. The drug entrapment efficiency was determined by using (Mingna song *et al.,* 2005) equation (calibration curve equation A=0.0244, R=0.999, n=6). Each determination was made in triplicate.

Flow properties

Flow properties of the microparticles were determined by angle of repose and the compressibility index (Banker and Anderson, 1986). The mean of three determinations was used to calculate the angle of repose and the compressibility index from each of the formulation.

Drug release studies

The USP method II or paddle dissolution test was used with a pH 7.4 alkaline phosphate buffer as the release medium The stirring speed was 100 rpm and the temperature of the release medium was kept at 37 ± 0.5°C. An accurately weighed microparticles equivalent to 100 mg of aceclofenac was added into each dissolution flask (U.S.P. dissolution 6-basket assembly XXI, Model No. USP TDT–06P, Electrolab). Samples (5ml) were withdrawn at programmed intervals and replaced by fresh buffer (preheated at 37 ± 0.5°C) .The samples were filtered through Whatman filter (0.45µm) and assayed spectrophotometrically at 274 nm after suitable dilution. The amount of aceclofenac was calculated from the calibration curve. The mean of six determinations was used to calculate the drug release from each of the formulation.

RESULTS AND DISCUSSION

The effect of processing variables of microparticle; polymer concentration, agitation speed and stirring time were studied on particle size and drug entrapment efficiency. When polymer concentration was increased from 1:9 to 1:1 (polymer: drug) then particle size increases from 80.2 ± 1.45 to 97.3 ± 2.06 µm. The average diameter of the microparticles at various agitation speeds i.e., 500, 1000, and 1500 rpm were found in decreasing order i.e., 94.1 ± 2.05 to 79.1 ± 1.63 µm. At lower speed (500 rpm), the mean

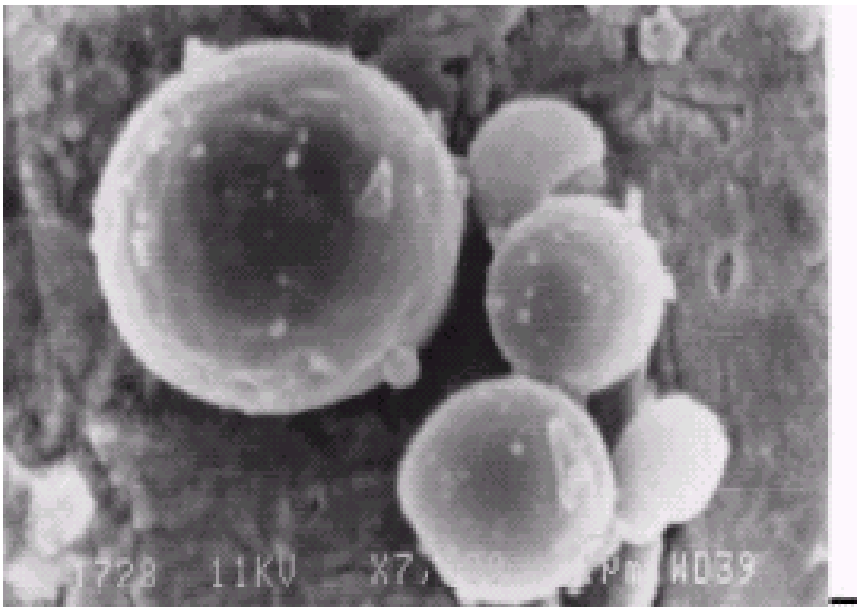

Fig. 2: Scanning electron micrographs of cellulose acetate microparticles containing aceclofenac (polymer: drug ratios, 1:6).

particle diameter and size distribution of the microparticles increased considerably. The irregularly in shape of microparticles occurred at higher speed (1500rpm) but discreet and uniform size of microparticles was obtained at 1000rpm. The average diameter of the microparticles decreases from 91.4 ± 2.05 to 78.23 ± 0.87µm on increasing stirring times viz., 5, 10 and 15 min. The short time (5min) resulted aggregates and less discreet microparticles, where as, high stirring time (15min) resulted smaller microparticles with increased size distribution. The discreet and uniform size of the microparticles was found at 10 min stirring time.

The entrapment efficiency of prepared microparticles of various polymer: drug ratio were found to be 70.31 ± 1.05, 77.66 ± 1.86, 66.46 ± 2.08 and 64.63 ± 3.85% for formulation AC-1 to AC-4 respectively. The maximum entrapment efficiency (77.66 ± 1.86%) was found for AC-2 formulation because at this polymer: drug ratio uniform size of drug globules enveloped with polymer may occur during emulsification process, which was observed under projection microscope (Quasmo, India). The agitation speed affects on drug entrapment efficiency of microparticles and it were found to be 73.66 ± 3.15, 77.63 ± 1.81 and 72.71 ± 3.40% with 500-1500rpm respectively. The lower entrapment efficiency at 500rpm agitation speed may be due to inadequately stirring of droplets, which leads to increased chances of coalescing. At higher agitation speed i.e., 1500rpm, it was observed that most of the globules were forced towards the wall of the flask due to high rotation and it ultimately lowers the contact time between polymer and drug molecules. But at 1000rpm, no sticking of polymeric material around the walls of flask was observed which may leads to improved drug entrapment efficiency (AC-2, 77.63 ± 1.81%). The effect of varying stirring time (5-15min) was also observed for drug entrapment efficiency and found 70.66 ± 1.83 and 73.46 ± 1.95% at lower and higher stirring time. The maximum entrapment efficiency (77.46 ± 0.51%) was observed at stirring time 10 min because of completely tightening of polymeric network around the globules. So, microparticles which prepared under optimized conditions viz., polymer: drug ratio 1:6, agitation speed 1000rpm and stirring time10 min were found to be spherical in shape and exhibited a smooth surface as indicated in the scanning electron photomicrograph (fig. 2)

Data of average diameter and entrapment efficiency of CA microparticles were compared statistically using unpaired t-test and one-way analysis of variance (ANOVA) at a significant level $P \leq 0.05$.

The flowability of microparticles was determined in terms of angle of repose and compressibility index for its application in fabrication of sustained products. The angle of repose was found in the range of 23.5 ± 0.4 to 34.4 ± 0.6 degrees and compressibility indices in the range of 11.1 ± 1.1 to 23.6 ± 0.6 % suggesting good flowability to particles.

The release study of all microparticles of polymer: drug ratios were carried out by dissolution data in alkaline phosphate buffer pH 7.4. It is calculated as cumulative percent drug release and compared with the conventional tablet (fig. 1). The cumulative % drug release in the formulation AC-1, AC-2, AC-3, AC-4 and SR tablet was

found to be 92.43±1.6, 88.32±0.23, 84.33±0.6 79.43±1.8 and 95.29±0.52 %respectively (fig. 1). The study showed that cumulative % drug release is influenced by the microparticle size in all formulation and showed increase in release with decrease in microparticles size. This may be due to the presence of more drug molecules close to their surface in smaller particles for dissolution in the surrounding medium as compared to larger microparticles. The drug release from SR tablets and conventional tablet was exhausted with in 6 and 3 h respectively while micrparticles sustained the drug more than 12 h. To observe the kinetic of drug release, the logarithm of percent drug retained verses time was plotted and found straight line. It indicates that all microparticles follows first order release rate kinetic pattern (table 1) while marketed ST tablet follows after 2 h.. The dissolution data of all microparticles and SR tablets were fitted in Higuchi's model and found, that was linear (r^2 value, table 1) indicating diffusion controlled release from the polymer and best release profile was obtained with AC-2 formulation (1:6 polymer: drug ratio, agitation speed 1000rpm and stirring time 10min). The release kinetics of AC-2 formulation was compared with marketed SR tablet, and found that AC-2 formulation have slow release (K_1= 0.177 h^{-1}) than marketed SR tablet (K_1= 0.338) as required for aceclofenac SR formulation. The r-value of AC-2 formulation also showed more controlled diffusion as compared to marketed SR tablet.

CONCLUSION

It concluded that the processing variables; polymer: drug ratio, agitation speed and stirring time affects the successful preparation of sustained release aceclofenac microparticles by an emulsion solvent evaporation process. These variables not only influenced the morphology but also affects on release of drug from the microparticles. The cellulose acetate is a suitable polymer to give diffusion-controlled microparticles. These microparticles also have flexibility to develop suitable dosage form for desired period of drug delivery as compared to available marketed formulation and improve safety, efficacy and patient compliance. These microparticles may reduce high dose absorption at once, which causes GI side effect as in conventional tablet.

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