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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MICROSPHERES RESIN LOADED ACELOFENAC

Dr. Praveen Ashok, Dr. Yogita Tyagi, Ms Hiba Parveen and Vikash Kumar*

Gyani Inder Singh Institute of Professional Studies Dehradun.

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***Corresponding Author**
Vikash Kumar
Gyani Inder Singh Institute of Professional Studies Dehradun.

ABSTRACT

Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) are seen in almost all organs but GI tract is most frequently affected as they cause GI irritation, bleeding and also peptic as well as duodenal ulceration. Concepts about gastro-duodenal mucosal ulceration have been evolved from the simple theory of topical injury to other theories involving multiple mechanisms with both local and systemic effects. Aceclofenac is one of the commonly used NSAIDs. It belongs to class II drugs in BCS and characterized by poor aqueous solubility and high absorption. Dissolution of aceclofenac is a rate limiting step which affects its onset especially in dental pain, rheumatoid and osteoarthritis. Solid dispersion is a type of solid state material where molecular dispersion of one or more active drugs is carried by an inert carrier. The above mentioned considerations led to the objective of this study, which aimed to prepare and evaluate solid dispersion systems containing aceclofenac and Eudragit Ll00, Eudragit S100, Eudragit RL100, PVP k90 and methyl cellulose 15cps. All formulations were prepared by dissolving the polymer in a mixture of isopropanol and acetone (1:1 V/V), 100mg drug was then dissolved in a minimal amount of the solvents mixture at 40oC. Solvent were evaporated over a period of 24 hrs under stirring conditions (150 rpm) at room temperature, 1:1. 1:2 and 1:3 ratios were utilized for each polymer. The polymer which showed the optimum release conditions was chosen for in-vivo studies using male Wistar rats. The obtained solid dispersion systems were evaluated using FT-IR, DSC and PXRD. Drug content as well as in- vitro drug release studies were determined at different pH values. Drug content in the prepared matrices ranged between 97.98% and 100%. No significant drug-polymer interactions were observed in IR studies. Aceclofenac entrapment efficiency in the different prepared formulations was affected by neither the

polymer type nor drug to polymer ratio. Solid dispersion with Eud S100 1:1 drug to polymer significantly reduced gastric irritations and gastric ulcers compared to free drug as well as the other proposed formulations as proved from histopathological examination of rat stomachs.

KEYWORDS: Solid dispersion; Aceclofenac; NSAIDs; Drug delivery systems; Ulcerogenic activity.

INTRODUCTION

Aceclofenac is a potent analgesic non-steroidal anti- inflammatory agent commonly used in managing inflammatory conditions such as rheumatoid arthritis and ankylosing spondylitis.It is a phenylacetic acid derivative related to diclofenac (Fig. **1**). Chemically, aceclofenac is (2-(2-(2-((2,6-dichlorophenyl)amino)- phenyl)acetyl) oxyacetic acid) (1-2). It is a partially water-insoluble drug that undergoes first-pass metabolism when taken orally. How- ever, aceclofenac is associated with gastrointestinal problems such as dyspepsia (7.5%), abnormal pain (6.2%), nausea (1.5%), diarrhea (1.5%), and ulcerative colitis (0.1%). Aceclofenac is non-steroidal anti-inflammatory drug used e< tensively in the treatment oF rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. AcecloFenac is one oF the emerging NSAID molecules. Aceclofenac is newer derivative oF dicloFenac and having less GIT complication, the short biological half-life 4 h, and dosing Frequency more than are time make it an ideal candidate For modified release multiple unit preparation. To reduce the Frequency of administrations and to improve patient compliances, aceclofenac is suitable For making sustain release dosage Form.

The microencapsulation technique is a commonly used tech- nique for controlling drug release, eliminating or minimizing its- induced adverse reactions, in addition to improving the bioavaila- bility of drugs facing first-pass metabolism as well as increasing patient compliance.[3,4] Polymeric gel beads, which are distinct microspheres, can be manufactured using numerous natural and biodegradable polymers.[5] These formulations can serve as solid.

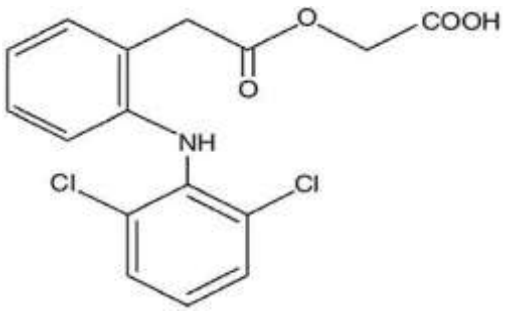


Fig. 1: Chemical structure of aceclofenac.

Substrates on which the drug is coated or encapsulated. Formulating drugs such as polymeric gel vesicular microspheres can control drug release rats and give more even drug distribution. Within the gastrointestinal tract, microspheres can promote the bioavailability of drugs so formulated.

In addition, the microencapsulation technique has been applied numerous drugs to reduce their gastric irritation effect. En- capsulation of NSAIDs prior to their oral administration is expected to minimize gastric and intestinal ulceration normally associated with the administration of these drugs.

Microencapsulation by ionotropic vesicular gelation technique is based on the utilization of cross-linking polymeric chains by polyelectrolytes in the presence of counter ions to form hydrogel vesicular microspheres, called gel spheres or vesicles. These vesicles are spherical cross-linked hydrophilic polymeric entities capable of extensive gelation and swelling in simulated biological flu- ids. In addition, they control the release of drugs through polymer relaxation. The formation of these hydrogel vesicles takes place by dropping a polymeric solution loaded with the drug into the aqueous phase containing polyvalent cations. Polyvalent cations diffuse into the polymeric drops containing the drug, causing cross-linking of the polymeric chains, creating a three-dimensional lattice. Bio- molecules can also be loaded into these gel vesicles under mild conditions to retain their three-dimensional structure.

As a microencapsulation method, ionotropic gelation is basedon the coalescence of the polymeric colloidal particles. For example, ionotropic gelation of the anionic polysaccharide sodium alginate prevails in oppositely charged calcium ions, resulting in the formation of vesicular microspheres. A subsequent curing step in- duces the fusion of colloidal polymer particles into a homogenous matrix. During the coating and drying

process, the colloidal polymer particles coalesce and fuse into the homogenous film. The ionotropic gelation technique is an uncomplicated and versatile method that forms an intimate contact between the encapsulateddrug and the release retardant polymeric matrix.

Against this background, this study aims to develop a con- trolled-release formulation that can reduce drug-induced gastric ulcerogenic activity by microencapsulating aceclofenac in Eudragit L100/alginate, Eudragit S100/alginate, and polyvinylpyrrolidone (PVP)/alginate polymer mixtures using the vesicular ionotropic gelation technique. Analytical tools such as FTIR, DSC, and X-ray diffraction were performed to assess the possibility of solid-state interaction of the encapsulated drug with microspheres forming polymers. The best formula, demonstrated via the *in vitro* release test, was subsequently used in *in vivo* experiments to evaluate its effect on aceclofenac-induced ulcerogenicity.

MATERIALS AND METHODS

Materials

Aceclofenac (GMBH, Germany) was a gift sample kindly supplied by EPICO pharmaceuticals industries, El-Asher, Egypt, Eudragit L100, Eudragit S 100 and Eudragit RL100 were purchased from Sigma- Aldrich, St. Louis, Mo, USA. PVP k90 and MC cp15 were obtained from RÖhm Pharma GMBH, Darmstadt (Germany). All other reagentsand chemicals were analytical grades and were used as received.

Methods

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

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

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:

$$\square = (1 - P_p / P_t) \square 100$$

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

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

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

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

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 □m 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

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.

Buoyancy (%) =W_f / (W_f + Ws) □ 100

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

Drug content determination

The entrapment efficiency of the drug in the proposed drug delivery systems was determined after separation of the drug from soliddispersion. The entrapment efficiency (EE) was calculated usingthe equation: PEE = Drug content in the proposed drug delivery systems was determined by crushing a known amount of solid dispersion in a mortar with a pestle before soaking in 100 ml phosphate buffer (pH 7.4) with continuous stirring using overheat stirrer (Stuart, Germany) for 90 min this provided complete swelling and bursting of the matrices. The resultant dispersions were filtered through 0.45 µm Millipore filterand the concentration of the drug in the solution was determinedspectrophotometrically after appropriate dilution using phosphate buffer (pH 7.4) as a blank.[40] The drug content was calculated as thepercentage drug load as given by the formula [41-43]. % drug load = 100

Where WD is the amount of the drug loaded in the solid dispersionand WB is the weight taken of the proposed matrices. Drug content asperformed in triplicate for each sample and the results were reportedas a mean ± SD.

***In- vitro* drug release studies**

The dissolution of the drug from the proposed drug delivery systemswas carried out according to a united state pharmacopeia (USP) XXIV8- station dissolution rate apparatus (Erweka type DT. Germany). Onehundred mg of aceclofenac or its equivalent from the solid dispersion was packed in 5 size transparent hard gelatin capsules and the drug release was studied in 0.1N HCl (pH 1) and in phosphate buffer ofpH value of 7.4. Samples of 5 ml were withdrawn at predetermined time intervals, filtered through Millipore filter (0.45 µm) and then assessed spectrophotometrically at a wavelength of 275 nm with a UVspectrophotometer (SHIMADZU, UV- 160A, Japan). Sample volume used for analysis was replaced by equal volumes of fresh dissolution medium preheated at 37°C to maintain the sink conditions.

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 □ to 407.0 □m. 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.

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

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	Stirrin g rate	Temp (^{o} c)	Mean Particle size[a] (□m.)	True density[b]. (g/cm^3)	Tapped density[b] (g/cm$^{3)}$	Compress ibility 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.

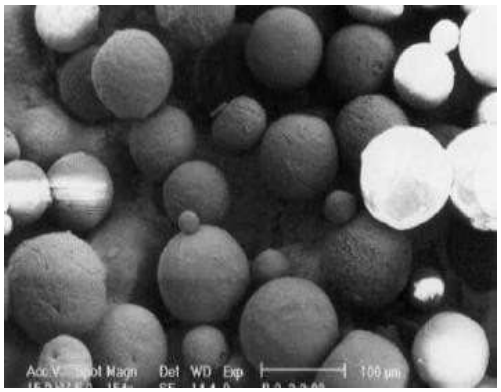
Batch code	Percent yield [b]	Incorporation efficiency [b](%)	Buoyancy [b](%)
F1	81.34±3.1	85.10 ± 2.1	63.00 ± 1.9
F2	85.42± 2.8	89.70 ± 2.4	66.80 ± 2.1
F3	80.37 ± 1.4	83.80 ± 2.4	72.60± 3.2

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

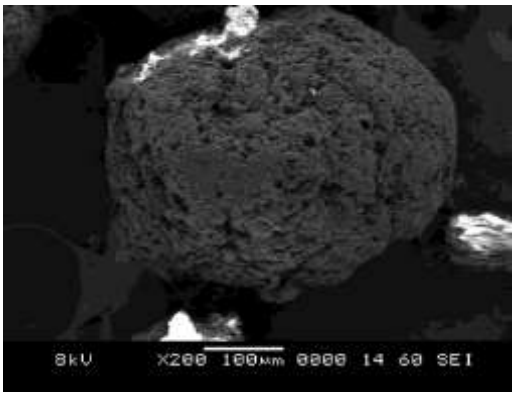
[b] Mean ± SD, $n = 3$.

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).

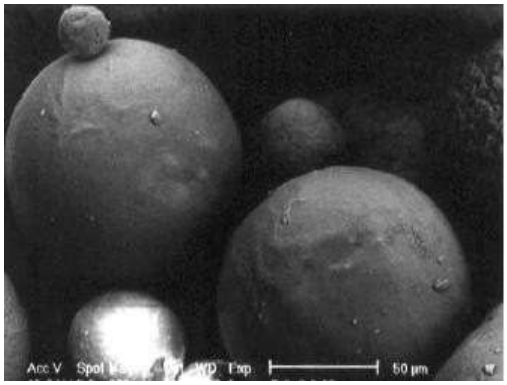
The data obtained for *in-vitro* release were fitted into equations for the zero-order, first- order and higuchi release models.[16,17] The interpretation of data was based on the value of the resulting regression coefficients. The *in-vitro* drug release showed the highest regression coefficient values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



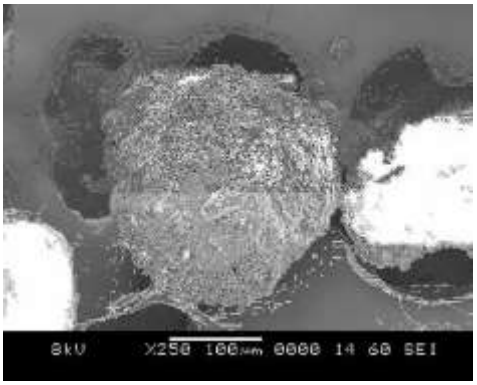
SEM 1



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

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.

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