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Development and Evaluation of Mucoadhesive Algino-HPMC Microparticulate System of Aceclofenac for Oral Sustained Drug Delivery

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ABSTRACT

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Micro-particulate drug delivery of aceclofenac was prepared by ion gelation technique using a blend of sodium alginate and HPMC as release retardant. The gastric residence of conventional dosage form is typically short which transit rapidly through the small intestine in not more than 3h, thus rapid gastrointestinal (GI) transit phenomenon may consequently lead to reduction in the extent of absorption of various drugs. The present study was to develop mucoadhesive microsphere of aceclofenac and evaluate the effect of polymer concentration on drug release kinetics. The formulations were investigated for various evaluation parameters like particle size, flow behavior, swelling properties, surface morphology study by SEM and *in vitro* drug release etc. All the formulations showed good flow behavior as compared to the pure drug. It was observed that by increasing the polymer concentration the drug release of all the formulations were gradually decreased and the optimized formulation (F7) was able to sustain the drug release for 12 hours. The drug release mechanism showed that all the formulations revealed higher coefficient of determination (R2 = 0.992 to 0.999) with the Korsmeyer-Peppas model whereas release exponent value (n) ranged from 0.572 to 0.843. So, It can be suggested all the formulations follow anomalous non-Flicking diffusion mechanism.SEM study has revealed that the spheres were almost spherical in shape with rough outer surface. Ex- vivo mucoadhesion study depicts that when the polymer concentration was increased the extent of mucoadhesion also increased. DSC and FTIR study showed that the major peaks of pure drug were almost intact in the formulation. Therefore, it was concluded that aceclofenac loaded alginate-HPMC microspheres can be prepared by gelation technique and used for sustaining the drug release for prolonged period of time.

Keywords: Non Steroidal Anti Inflammatory Drugs, Gastrointestinal Tract, Hydroxy propyl Methyl Cellulose, International Conference of Harmonization

INTRODUCTION

Aceclofenac is a phenyl acetic acid derivative [2-(2',6'-dichlorophenyl) amino] phenylacetoxyacetic acid], and is a novel NSAID indicated for the symptomatic treatment of pain and inflammation[1]. It has higher anti-inflammatory action than conventional NSAIDs and acts by blocking the action of cyclo-oxygenase that is produced by prostaglandins. Aceclofenac has short biological half-life (about 4 h) and is associated with gastrointestinal disturbances. The frequency of administration makes it an ideal candidate for sustained release. But major drawback frequently encountered in SR dosage form is the inability to increase residence time of the dosage form in the gastrointestinal tract (GIT). The gastric residence of a dosage form is typically short, under fasting condition it is not more than an hour and it is also common for dosage forms to transit rapidly through the small intestine in not more than 3h. Thus rapid gastrointestinal (GI) transit phenomenon may consequently lead to reduction in the extent of absorption of various drugs. As quite a lot number of drugs are absorbed exclusively from small intestine or in a confined segment of intestine, it is therefore advantageous to develop mucoadhesive dosage forms, which can remain in intestinal region for a longer duration of time so as to extend the residence time. Several approaches have been adopted in this direction and one of them is to use oral mucoadhesive drug delivery system[2,3]. Different polymers have been investigated for mucoadhesion like polyacrylic acid and derivatives[4], Hydroxypropyl methyl cellulose, various grades of Carbopol as well as natural polymers like sodium alginate, chitosan, starch[5] have been tried. Alginates are one such polymer that has got abundant use in drug delivery systems. This polymer is a naturally derived polysaccharide block composed of regions of sequential β-D-mannuronic acid monomers (M-blocks), regions of α-L-guluronic acid (G-blocks), and regions of interspersed M and G units (Stevens et al.,2004). Alginates undergo gelation in aqueous solution under mild conditions through interaction with divalent cations such as calcium that can cooperatively bind between the G-blocks of adjacent alginate chains creating ionic inter-chain bridges.

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Moreover, alginate as an anionic polymer with carboxyl end groups is a good mucoadhesive agent[6]. Hydroxypropyl methyl cellulose which is a synthetic high molecular weight cross-linked polymer of acrylic acid has been investigated extensively by the pharmaceutical researchers as a mucoadhesive polymer because of its high viscosity at low concentration and low toxicity[7].

OBJECTIVE

The present study was to develop mucoadhesive microsphere of aceclofenac and evaluate the effect of polymer concentration on drug release kinetics and estimate the physicochemical properties and the mucoadhesive strength of the formulations through Ex *vivo* models. It is also attempted to optimize the formulation based on the above evaluation tests and based on the above studies subject the optimized formulation for accelerated stability studies.

MATERIALS AND METHODS

MATERIALS:

Aceclofenac (AC) was obtained as a gift sample from Unicure Remedies India Ltd, India. Sodium alginate (viscosity ≈ 3500 cps) was received as a gift from Rancem lab, India. HPMC was a gift sample from Medley pharmaceuticals. Calcium chloride was purchased from Rancem lab, India. All other chemicals used were of analytical reagent grade.

METHOD:

Preparation of Sodium-alginate microspheres[9]:

Sodium alginate microspheres were prepared by ionic cross-linking process. Sodium alginate was dissolved in distilled water to obtain different concentrations. Then aceclofenac was added to the sodium alginate solution and mixed (Ultraturrax, Jahnke and Kunkel, Germany) for 2 min at 8000 rpm. This dispersion was added in drop wise to a 5% calcium chloride solution using a 24 G needle with continuous stirring at 200 rpm. The stirring was continued for 30 minutes for complete reaction. After 30 minutes microspheres were collected, washed with distilled water and dried overnight at room temperature.

Preparation of Sodium alginate microspheres with HPMC[9]:

HPMC (K100M) and Sodium alginate solutions of different concentrations (Table I) were separately prepared by dissolving both the polymer in water under gentle agitation. Then HPMC (K100M) solution was added into Sodium alginate solution and mixed for 2 min at 4000 rpm for uniform mixing. Then, aceclofenac was added to the polymer solution and proceed are continued as above.

EVALUATION OF MICROSPHERES:

Production yield (% w/w):

The percentage yield of each batch was calculated on weight basis with respect to the weight of starting material. All experiments were carried out in triplicate.

Particle size analysis[11,12]:

The particle sizes of the prepared microspheres were determined by using optical microscopy fitted with an ocular micrometer. The ocular micrometer was calibrated with stage micrometer. The mean diameter reported was arrived from a total of 100 microspheres.

Entrapment efficiency[10]:

The entrapment efficiency of the prepared formulations was determined by the method of extraction of the drug present in the microsphere. The dried microspheres (100 mg) were taken and extracted in 100 mL of phosphate buffer (pH 6.8) for 4 hours. Then the dispersion of microspheres was sonicated for 30 min (Imeco Sonifier, Imeco Ultrasonics, India) and the solution was filtered through a 0.45μm filter. Finally, the polymeric debris was washed twice with fresh solvent (phosphate buffer) to extract any adhering drug. The drug content of filtrate and washings was determined spectrophotometrically at 274 nm (UV-2450, Shimadzu, Japan). Each determination was made in triplicate. . Finally, drug encapsulation efficiency is calculated by

$$\text{Drug Entrapment Efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Micromeritic properties of microspheres:

Flow Properties: The flow properties of microspheres were studied by determining various parameters like the angle of repose, Carr's index, and bulk density and tapped density. The angle of repose was determined by the fixed-base cone method[11,12]. Bulk and tapped densities were determined using digital bulk density apparatus (Electrolab, India). Each experiment was conducted in triplicate.

Swelling Index:

The swelling studies were carried out for the prepared microspheres. The pre-weighed microspheres were immersed in 100 ml of the medium (phosphate buffer, pH 6.8) and maintained at 37.0 ± 0.5°C for 6h of the study period. At predetermined time intervals (0, 1, 2, 3, 4, 5 and 6h), the swollen microspheres were removed from the solution, immediately wiped with a paper towel to remove droplets on the surface, and weighed. The swelling index (SI) was calculated according the equation that follows below.

$$\text{Swelling Index} = Wt - W_0 / W_0$$

Where Wo and Wt represent the initial weight of the dry microspheres and the weight of the swollen microspheres at time t, respectively.

***Ex-vivo* mucoadhesion study:**

The mucoadhesive property of the microspheres was evaluated by using phosphate buffer, pH 6.8. The freshly excised pieces of intestinal mucosa (2x3 cm) from chicken were mounted on to polyethylene plate. About 50 nos. of microspheres were spread onto each wet rinsed tissue specimen and immediately thereafter the slides with suitable support were hung onto the arm of a USP tablet disintegrating test machine. When the disintegrating test machine was operated, the tissue specimen was given a slow, regular up and down movement in the test fluid at 37^0C contained in a one liter vessel. At different time intervals up to 6 h the machine was stopped and the number of microspheres still adhering to the tissue was counted and % mucoadhesion was calculated[9].

***In vitro* drug release study:**

In-vitro release profile of aceclofenac from the microspheres was examined in phosphate buffer (pH 6.8) using USP (XXI) six stage dissolution rate test apparatus I (Thermolab®, Mumbai, India). Microspheres equivalent to 100 mg of drug was suspended in dissolution medium at 50 rpm and 37 ± 0.5°C. An aliquot of 5 ml was withdrawn periodically at intervals of one hour and same volume of fresh medium was replaced. The samples were filtered through Whatman filter paper and analyzed spectrophotometrically at 273 nm for amount of drug released[13].

Analysis of release profiles:

The rate and mechanism of drug release from the prepared matrix tablets were analyzed by fitting the dissolution data into the Zero-order equation: $\mathbf{Q = k_0 t}$

Where Q is the amount of drug released at time t and k_0 is the zero order release rate constant, First order equation: $\mathbf{ln\ (100-Q) = ln100 - lnk_1 t}$

Where k_1 is the first order release rate constant and Higuchi's equation: $\mathbf{Q = k_2 t^{1/2}}$

Where k_2 is the diffusion rate constant.

Drug release data was further analyzed with the help of the Peppas equation: $\mathbf{M_t/M_\infty = kt^n}$

Where n is the release exponent indicative of the mechanism of release, M_t/M_∞ is the fractional release of the drug, t is the release time, k is the kinetic constant[14,15].

Morphological Examination:

The surface texture and shape of the microspheres were investigated by using Scanning electron microscopy (JSM 5610 LV SEM, JEOL, Datum Ltd, Tokyo, Japan). The sample (optimized formulation F7) was spread on stub and coated for 120 s with a layer of gold using a sputter coater. The stub containing the sample was then placed in the scanning electron microscope chamber. The scanning electron photomicrograph image was taken at the acceleration voltage of 20 kV with a chamber pressure of 0.6 mm Hg.

Drug Polymer Interaction (FTIR) Study[22]:

FTIR spectra of pure drug, pure polymers and formulations containing both drug and polymers were performed to study the drug polymer interaction. FTIR study was performed by using Fourier transformer infrared spectrophotometer (Prestige-21, Shimadzu, Japan).

Differential scanning calorimetry (DSC)[22]:

DSC was performed using DSC-60 (Shimadzu, Tokyo, Japan) calorimeter to study the thermal behavior of drug alone, mixture of drug and polymer or prepared co-crystals. The instrument comprised of calorimeter (DSC 60), flow controller (FCL60), thermal analyzer (TA 60) and operating software (TA 60).The samples were heated in hermetically sealed aluminum pans under nitrogen flow (30 ml/min) at a scanning rate of 5°C/min from 24±1°C to 250°C. Empty aluminum pan was used as a reference. The physical mixture of drug with excipients for compatibility studies was prepared by triturating the drug with excipient in a dried mortar for 5 min.

Stability study:

Stability studies of the microspheres formulation were carried to study the effect of storage conditions on the formulation properties. For the stability studies the formulations were placed in airtight containers at freeze temperature (2-8° C) as per ICH guidelines. The stability studies were carried out for 3 months for microspheres formulation. The samples were placed in USP type-1 flint vials and hermetically sealed with bromobutyl rubber plugs and aluminum caps. Five milligrams of the stored microsphere were taken out at 30, 60,and 90 days, and the various parameters evaluated to check the stability of the formulations were:

1. Drug content
2. Particle size of the formulation
3. In vitro release profile of the formulations[16]

RESULTS AND DISCUSSION

All the microspheres were prepared by ionic gelation process. Calcium chloride was selected as cross linking agent to prepare the microspheres. This method was selected to formulate the microspheres because it is quick, easy and cost effective. The composition of all prepared formulations is depicted in Table-1.

Table 1: Composition of prepared microspheres

Formulation Code	Polymer level (% w/v)	Drug level (% w/v)	Cross- linking agent/level (%w/v)	Yield (%)
F1	Sodium alginate, 1%	1%	5%	92.5 ± 2.17
F2	Sodium alginate, 2%	1%	5%	90.7 ± 3.01
F3	Sodium alginate, 3%	1%	5%	96.3 ± 3.18
F4	Sodium alginate, 4%	1%	5%	98.8 ± 2.55
F5	Sodium alginate, 1% + HPMC, 1%	1%	5%	97.7 ± 3.11
F6	Sodium alginate, 1% + HPMC, 2%	1%	5%	98.4 ± 2.98
F7	Sodium alginate, 1% + HPMC, 3%	1%	5%	95.6 ± 4.03
F8	Sodium alginate, 1% + HPMC, 4%	1%	5%	96.7 ± 2.16

Mean ± SD, n=3

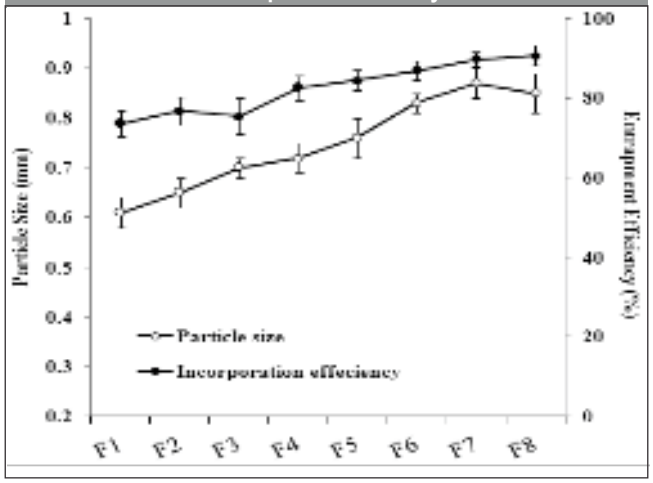
Production Yield:

The yield of all the formulations was within the range of 90.7 ± 3.01 to 98.8 ± 2.55. The low percentage yield in some formulation (F1 and F2) may be due to microspheres lost during the washing process and recovering process. The values of production yield are depicted in Table-1.

Particle size and entrapment efficiency:

The effects of polymer concentration on the particle size and entrapment efficiency of the prepared microspheres are shown in Figure-1. It was observed that the size of the prepared microspheres were in the size range of 0.63 ± 0.03 mm to 0.87 ± 0.04 mm. The entrapment efficiency was found within the range of 76.6 ± 3.21% to 90.7 ± 2.48%.It was found that when the polymer concentration increases, particle size as well as encapsulation efficiency increased. It may be due to higher concentration of the polymer producing much larger particles. Higher concentration of the polymer increases the viscosity of the medium as well as greater availability of calcium binding sites in the polymeric chains. As a result degree of cross-linking also increases[17] and larger droplets were formed entrapping a greater amount of drug.

Fig. 1: Effect of Polymer Concentration on Particle size and Entrapment Efficiency



Micromeritic properties of microspheres:

Bulk density and Tap density:

Interparticulate interaction is one of the most important parameter that affects the bulk and flow characteristics of powder[18]. The studies of flow characteristics suggested that an improvement was found in values of bulk density, tap density as described in Table-2 on developing microsphere formulation of aceclofenac, and indicated that the microspheres had good packability and enhanced flowability.

Angle of repose, Carr's index:

Angle of repose and Carr's index of pure drug and prepared formulations are summarized in Table-2. Angle of repose and Carr's index of pure drug was found 40.2 ±1 and 37.8 ± 1.3 respectively which indicated poor flow property of the pure drug. The angle of repose and Carr's index of all the formulations (F1to F8) were found from 12.4 ± 1.7 to 19.5 ± 1.2 and 8.92 ± 0.8 to 19.6 ±1.4 respectively. So it is concluded that by formulating microsphere formulation of the drug, the flow property of the poorly flowing drug can be improved

Swelling Index :

Figure-2 shows the percentage swelling of different microsphere formulations at different time intervals. The results revealed that all the formulations shows rapid swelling when immersed in phosphate buffer (pH 6.8). The adhesive and cohesive properties of mucoadhesive polymers are generally affected by their swelling behavior[19]. It is also expected that mucoadhesive polymers take up solvent from the rudimentary mucosal surface by capillary effect and swell up[20]. The percent swelling of alginate microsphere (Figure-2a) (F1 to F4) was found to be within the range of 86.9 ± 4.71% to 117.8 ± 3.79% whereas, in case of algino-HPMC microsphere it was found from 108.7 ± 3.56% to 153.7 ± 4.66% (Figure-2b). It was found that by increasing the polymer concentration, swelling of all the formulation was also increasing. This could be due to high ionization of HPMC due to of carboxyl acid group present in the polymer, at pH 6.8, which is capable of absorbing a high amount of solvent[21]

Table 2: Micromeritic study of prepared microsphere formulations

Formulation	Bulk density (g mL-1)	Tapped density (g mL-1)	Angle of repose (°)	Carr's index
PD	0.61 ± 0.12	0.98 ± 0.13	40.2 ± 1.1	37.8 ± 1.3
F1	0.45 ± 0.08	0.56 ± 0.05	19.5 ± 1.2	19.6 ± 1.4
F2	0.53 ± 0.18	0.65 ± 0.13	18.2 ± 1.1	18.5 ± 1.3
F3	0.55 ± 0.03	0.64 ± 0.11	18.7 ± 2.1	14.1 ± 2.0
F4	0.56 ± 0.11	0.65 ± 0.07	17.6 ± 2.3	13.8 ± 1.1
F5	0.65 ± 0.06	0.74 ± 0.07	16.1 ± 1.4	12.2 ± 1.0
F6	0.46 ± 0.07	0.52 ± 0.08	15.0 ± 1.3	11.5 ± 1.3
F7	0.49 ± 0.10	0.54 ± 0.05	14.2 ± 2.0	9.26 ± 1.2
F8	0.51 ± 0.09	0.56 ± 0.07	12.4 ± 1.7	8.92 ± 0.8

Mean ± SD, n=3, PD = Pure Drug.

Fig. 2a: Swelling Study of alginate microsphere

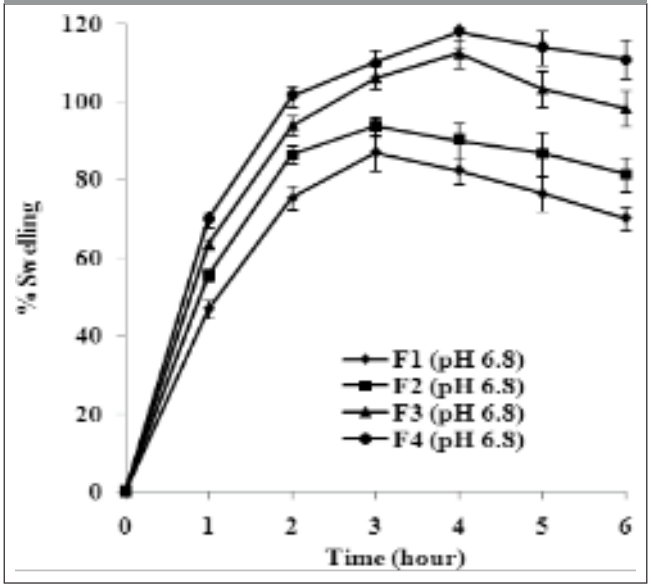
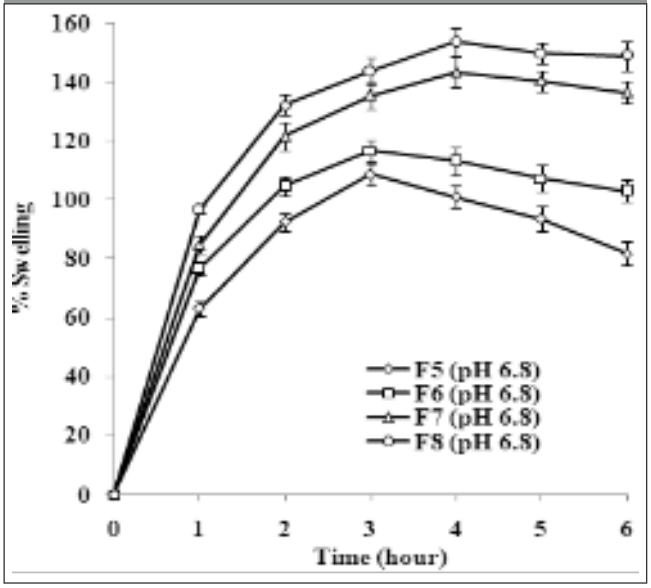


Fig. 2b: Swelling Study of algino-HPMC microsphere



***Ex-vivo* mucoadhesion study of microspheres :**

The results of the ex-vivo mucoadhesion study indicated that all microspheres had good mucoadhesive properties. The percentage of microspheres attached to the mucosa up to 6 hours has been shown in Figure-3a and 3b. It was found that Sodium alginate microspheres (F1-F4) show less mucoadhesion property (Figure-3a) as compared to algino-HPMC microspheres (Figure-3b).This is because in simulated intestinal fluid Sodium alginate solubility, hydration and mucoadhesive property was increased due to ionization of carboxyl acid group present in the polymer. This increases its solubility and shows less mucoadhesion property as compared to algino-HPMC microspheres. In combination both the polymers (F5-F8) increase the viscosity, produce more viscous gel which help to increase adhesion with intestinal mucosa. As a result prepared microspheres adhere to the intestinal mucosa for a prolonged period where they release drug in a sustained manner before being eroded off.

***In vitro* drug release study:**

The effect of polymer concentration on the release of aceclofenac from the prepared microspheres was studied (F1-F8). Alginate formulation F1, F2, F3 and F4 were able to sustain the drug release for 4, 5, 6 and 7 hours (Figure- 4a), respectively whereas algino-HPMC microspheres (F5 to F7) were able to sustain the drug release for more than 7 to 12 hours (Figure-4b). In case of formulation F8 (HPMC 4 %), the release of the drug was too slow and only 81.2 % of the drug was released after 12 hours. Formulations F1 to F4 (Na.-alginate alone) undergo erosion before complete swelling could take place, resulting in faster release of drug. Algino-HPMC microspheres (F5 to F8) were more efficient in sustaining the drug release as compared with alginate

Fig. 3a: Mucoadhesion Study of alginate microspheres

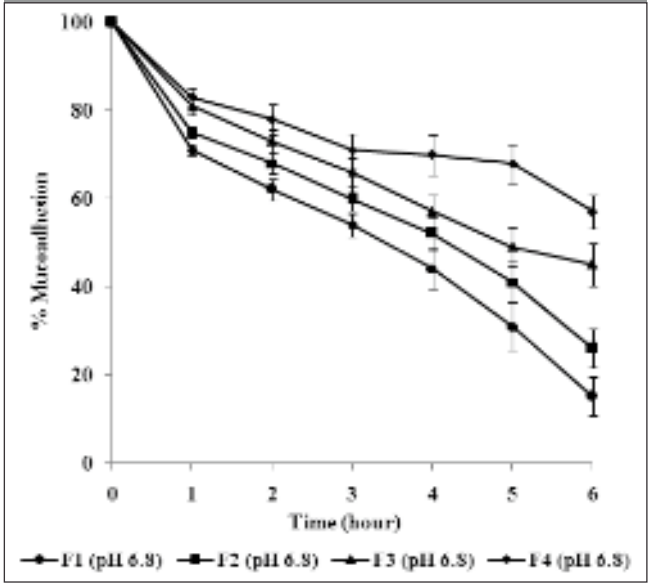


Fig. 4a: In-vitro drug release study of alginate microspheres

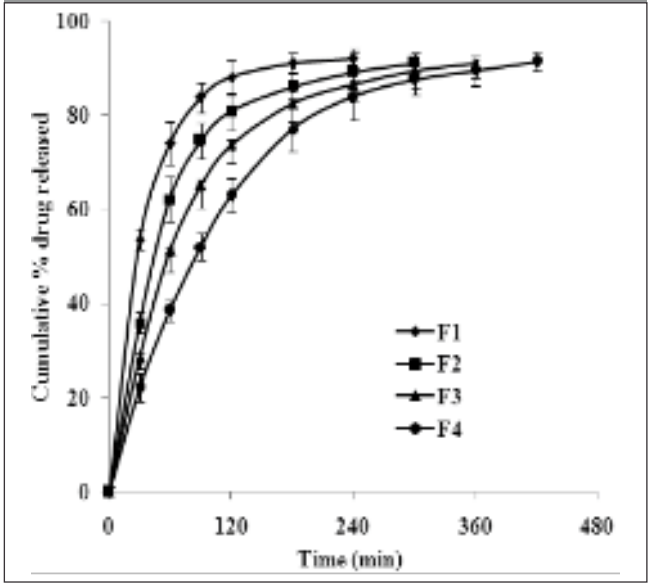


Fig. 3b: Mucoadhesion Study of algino-HPMC microspheres

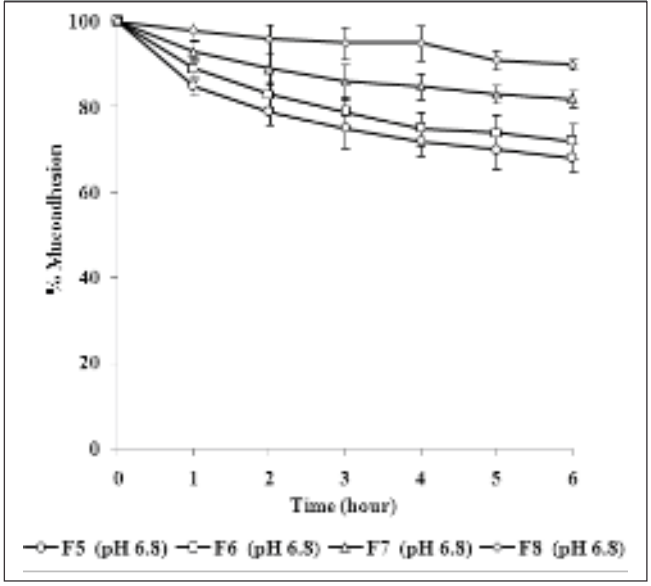
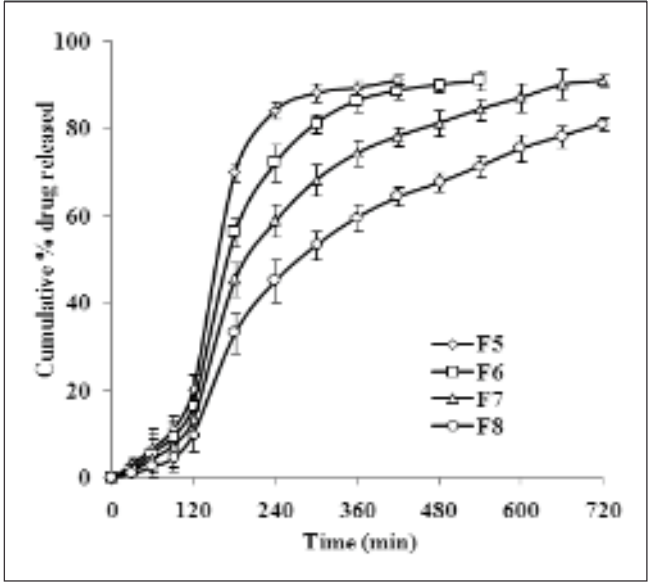


Fig. 4b: *In-vitro* drug release study of algino-HPMC microspheres



microspheres because HPMC could form rigid coat as compared to Sodium alginate. Among all the formulations F7 showed better dissolution profile (more than 90 % drug was released in 12 hours), so it was selected as optimized formulation for further study.

The coefficient of determination (R^2) (Table-3) for all the formulations revealed a higher coefficient of determination (R^2 = 0.992 to 0.999) with the Korsmeyer-Peppas model whereas release exponent value (n) ranged from 0.572 to 0.843. So, it can be suggested all the formulation follow anomalous non-Fickian diffusion mechanism. In conclusion a combined release mechanism of drug diffusion and spheres erosion would be appropriate.

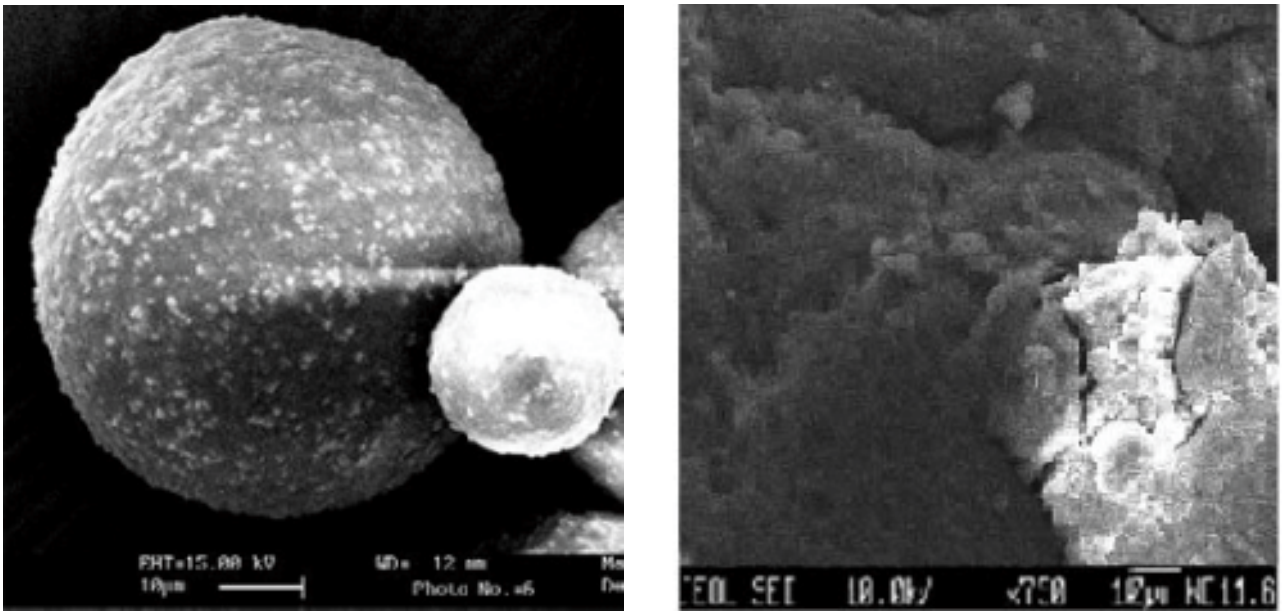
Morphological examination:

The morphological evaluation of the optimized microsphere formulation (F7) was done by scanning electron microscopy (Figure-6a, 6b). SEM study revealed that the microspheres were almost spherical in shape with rough outer surface.

Table 3: Kinetics of drug release from aceclofenac microspheres

Formulation	Drug release kinetics Coefficient of determination (R^2)				exponent (n)
	Release Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Korsmeyer-Peppas (R^2)	
F1	0.993	0.932	0.979	0.999	0.843
F2	0.990	0.956	0.983	0.996	0.821
F3	0.987	0.977	0.978	0.993	0.744
F4	0.983	0.962	0.973	0.995	0.762
F5	0.989	0.958	0.984	0.992	0.675
F6	0.992	0.978	0.991	0.996	0.762
F7	0.994	0.975	0.989	0.997	0.611
F8	0.991	0.958	0.979	0.994	0.572

Fig. 4: SEM Micrographs of optimized formulation (F7)



A (X 50) **B (X 750)**

Drug polymer interaction (FTIR) study:

FTIR spectra are shown in Figure-5. Pure aceclofenac showed various characteristic peaks at 3319.24, 2936.04, 1717.71, & 1286.96 cm-1.The major peaks are 3319.24 for stretching vibration of OH of COOH group, 2936.04 for stretching vibration of NH group, 1717.71 for stretching vibration of C=O of ester carbonyl group, 1286.96 for C-N stretching vibration of secondary aromatic amine, It was observed that all the major peaks of aceclofenac were intact when it was incorporated in the microspheres formulation and no considerable changes in the IR peaks were observed. So FTIR spectra are helpful to the stable nature of aceclofenac in the prepared formulations.

Differential scanning calorimetry (DSC)

The results of DSC studies are given in Fig. 6. Pure aceclofenac showed a sharp endotherm at 154.49°C corresponding to its melting point while into a microsphere, whose thermogram shows two endotherm peaks at the temperature 99.82°C it's probably related to dehydration, and at 155.15°C, so, there was no appreciable change in the melting endotherms of microsphere as compared to pure drug. This observation further supports the IR spectroscopy results, which indicated the absence of any interactions between drug and excipient used in the preparation.

Fig. 5: FTIR spectra

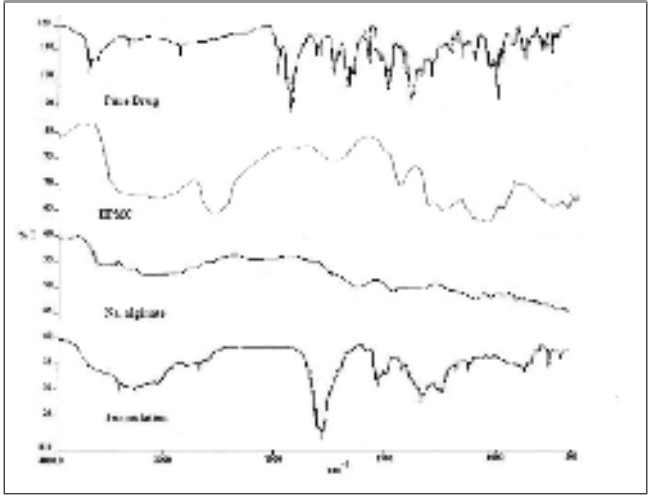
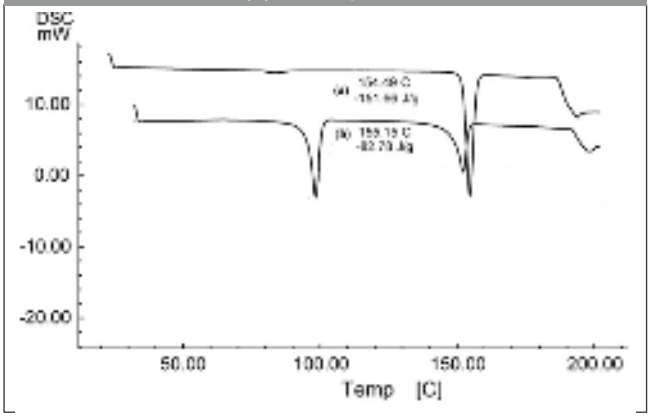


Fig. 6: DSC thermograms: (a) pure drug (aceclofenac) ; (b) microsphere



Stability study of the formulation:

The stability study of the formulation (F7) was performed for 3 months and the effect on the various parameters was studied and is reported below.

1. Drug content:

After 1, 2, and 3 months the formulations under stability study was assayed for the drug content and compared with the content of the initial formulation. The results obtained shown in Table 4.1.

2. Particle Size:

After each month of storage, formulations stored for stability study were tested for particle size and compared with initial particle size.

3. In vitro drug release profile:

One batch was tested for in vitro release by the same method prior used in *In vitro* release method after each month of storage and compared with the initial *In vitro* release.

Table 4.1: % Drug content before and after 3 months storage

Formulation No.	% Drug Content (Assay)			
	Initial	After 1 month	After 2 month	After 3 Month
F7	90.7	89.61	88.75	87.57

Table 4.2 : Particle size before and after 3 months storage

Formulation No.	Particle Size (mm)			
	Initial	After 1 month	After 2 month	After 3 Month
F7	0.87	0.873	0.875	0.88

Table 4.3 Comparison of *In vitro* release of formulation freshly made and after storage

Formulation No.	% Cumulative Drug Release			
	Freshly made	After 1 month	After 2 month	After 3 Month
1	5.66	4.89	5.87	6.98
2	11.27	10.57	10.76	11.65
4	58.81	55.76	58.43	59.67
6	70.51	68.89	69.86	71.85
8	79.76	76.44	81.57	83.76
10	85.65	81.54	86.64	87.47
12	90.47	86.45	92.55	92.85

CONCLUSION

Controlled release mucoadhesive microspheres were successfully prepared employing ionotropic gelation technique. Microspheres prepared are spherical in shape with rough outer surface. The drug entrapment capacity was found to be within the range of 76.6 to 90.7%.The microspheres were found to be effective in sustaining the drug release. Among all the formulations F7 showed better dissolution profile with more than 90 % drug released in 12 hours. The mucoadhesive microspheres were also able to restrict the drug release in stomach and adhere themselves in to the intestinal region. Stability studies reviewed that there was no significant change in drug content and dissolution profile of microspheres. The drug release mechanism indicated that drug release from the microspheres was triggered by drug diffusion and erosion of spheres.

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