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EFFECT OF THE ADDED EXCIPIENTS ON THE RELEASE CHARACTERISTICS OF ACECLOFENAC FROM ALGINATE MICROCAPSULES

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ABSTRACT
Aceclofenac is analog of the potent non-steroidal anti-inflammatory drug Diclofenac with low gastric damage. It belongs to class II according to the Biopharmaceutical classification system (BCS) that has poor aqueous solubility. The aim of this study was to investigate the potential of microcapsule of Aceclofenac with different polymers, to enhance dissolution rate of the drug and minimize gastric release. Alginate based micro-pellets were prepared to contain Aceclofenac in addition to other polymers to impart enteric effect. The selected polymers were Eudragit L100-55, Eudragit S100 and polyvinylpyrrolidone K90 (PVP) at different drug:alginate:polymer ratios. Microcapsules were prepared using ionotropic gelation method where the polymer was dispersed in sodium alginate solution. This liquid was then added drop wise to a solution containing divalent cations (calcium chloride solution). The resultant beads were separated, washed and dried. Before monitoring the dissolution pattern, the obtained beads were characterized using Fourier–transform infrared spectroscopy (FTIR) spectroscopic, X-ray diffraction and differential scanning calorimetry (DSC). The dissolution studies were conducted in acidic and alkaline media. Physical state characterization reflected no interaction between the drug and excipients with possible reduction in the drug crystalline nature. The release of Aceclofenac from the polymeric matrices was considerably reduced in the gastric phase. While the modified crystalline state was associated with a considerable enhancement in the dissolution rate in the intestinal phase, therefore, this technique is considered simple and promising eco-friendly strategy to enhance the dissolution rate of the drug with expected reduction in its deleterious effect on gastric mucosa.

KEYWORDS: Aceclofenac, ionotropic gelation, enhance dissolution, Eudragit S100.

INTRODUCTION
Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs in the world[1], but their use is associated with significant unfavorable effects on the gastrointestinal tract. The bleeding and ulceration induced in the stomach by NSAIDs, commonly referred to as 'NSAID-gastropathy', is the most common adverse reaction to medication and has a significant financial impact on health care systems.[2,3]

The GI intolerance of NSAIDs is not only related to the inhibition of the prostaglandin synthesis but also to acute local contact of the drug with gastric mucosa when taken orally. Attempts have been made to improve therapeutic efficacy and reduce the severity of upper GI side effects associated with various NSAIDs through modified release dosage forms such as enteric-coating, sustained release formulations or fast disintegrate tablet.[4]

Aceclofenac is a non-steroidal anti-inflammatory drug, widely used in the management of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.[5] As with most NSAIDs, irritation of the gastrointestinal (GI) tract is one of the major side effects reported after oral administration of Aceclofenac.[6] Aceclofenac belongs to class II drugs in BCS classification characterized by poor aqueous solubility and high absorption. This means that dissolution of Aceclofenac is rate limiting step for its absorption.

Microcapsulation can be defined as a process by which tiny particle or droplets are surrounded by polymeric, waxy or other protective materials to give small capsules in spherical or semi spherical forms with uniform wall ranging in size from one micron to several hundred microns.[7]

Ionotropic gelation technique is the most widely utilized technique with the most of researchers employing syringes manually or mechanically via pump to simply drip alginate solution into a solution of divalent action this is expected to form beads.[8]

In this work, Eudragit L100-55 and S100 were used. Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylate's, methacrylic acid, and methacrylic acid esters in varying ratios. Several types are commercially available and may be obtained as the dry powder, aqueous dispersion, and organic solution.[9]

Polymethacrylates are primarily used as film-coating agents in tablet and capsule dosage forms. Eudragit are generally regarded as nontoxic and nonirritant materials. Also we use hydrophilic polymer PVP K90.

The aim of our work was improve dissolution of Aceclofenac in the intestinal environment meanwhile minimize release in gastric environment. This was achieved by microencapsulation technique employing the ionotropic gelation technique.

MATERIALS AND METHODS

Materials

Aceclofenac was a gift sample from European Egyptian pharmaceutical Company, Alexandria, Egypt. Eudragit® S100 was a gift sample from Amoun pharmaceutical company, Al-Obour city, Egypt. Polyvinyl pylrolidone K 90 and Sodium alginate was kindly supplied by Sigma Company for pharmaceutical industries, Quesna, Egypt. Eudragit® L100-55 was a gift sample kindly supplied by Pharco pharmaceutical industries, Alexandria, Egypt.

Methods

Construction of calibration curves

An accurately weighed quantity of Aceclofenac was dissolved in 95% ethanol to obtain a stock solution of 1mg/ml concentration. Standard solutions were prepared by dilution of the stock solution with phosphate buffer (pH 7.4) or 0.1N HCL (pH 1.2). Ultraviolet absorbance of the solutions was determined spectrophotometrically (Thermo, Evo300pc, USA) at the wavelength of maximum absorbance at 275 nm for pH 7.4 and 1.2.

The obtained standard curve displayed linear relationship (R^2=0.999) between the concentration and the absorbance (y =0.0263x -0.0009) in pH 1.2 and (R^2=0.999), (y =0.0252x +0.0091) in pH 7.4.

Preparation of microcapsule formulations

Three types of microcapsules containing Aceclofenac were prepared by employing sodium alginate as the coat material in combination with either Eudragit L 100-55, Eudragit S100 or polyvinylpyrrolidone PVP K90 in ratios of 1:0.5:0.5, 1:1:1 and 1:1.5:1.5, respectively, adopting ionic-orifice gelation method (Table 1). Briefly, sodium alginate were dissolved in purified water under steering at 40°C to form a homogenous solution to which core material Aceclofenac and polymer were added and mixed thoroughly to obtain smooth viscous dispersion. The resulting dispersion was then added drop wise to 100 ml calcium chloride (10% w/v) solution through a syringe with a needle of No. 22 size. The added droplets were retained in the calcium chloride solution for 15 min to complete the curing reaction and to produce spherical rigid microcapsules. The microcapsules were then separated by decantation and the product was washed with water and petroleum ether and dried at 45°C for 12 h. Each formulation was labelled and stored in a desiccator for further studies.[10]

Table 1: Composition of different microcapsule formulations.

Formula	Drug	Sodium alginate	Eudragit L100-55	Eudragit S100	PVP K90
pure Drug	1	_	_	_	_
M1	1	0.5	0.5	_	_
M2	1	1	1	_	_
M3	1	1.5	1.5	_	_
M4	1	0.5	_	0.5	_
M5	1	1	_	1	_
M6	1	1.5	_	1.5	_
M7	1	0.5	_	_	0.5
M8	1	1	_	_	1
M9	1	1.5	_	_	1.5

Characterization of microcapsule system

Fourier–transform infrared spectroscopy (FTIR)

FTIR spectra of Aceclofenac sodium, Eudragit L100-55, Eudragit S100, PVP K90 and their microcapsule were recorded using FTIR (Bruker tensor 27, Ettlingen, Germany). Samples were blended with potassium bromide (Spectroscopic grade) and compressed into disks using hydraulic press before scanning in the range of 4000 to 400 cm^{-1}.

Differential scanning calorimetric analysis (DSC)

The thermal behaviour of unprocessed drug, excipients and different formulations were analysed by differential scanning calorimeter (Shimadzu DSC-50, japan). The thermograms of the samples were obtained at a scanning rate of 10°C/min conducted over a temperature range of 25-400°C.

Powder X-ray diffraction analysis (XRD)

Powder X-ray pattern were recorded using a powder X-ray Diffractometer (GNR X-ray Diffractometer, model

APD 2000 PRO) under the following condition: target Cu; filter Ni; voltage 40 kV; current 40 A; receiving slit 0.2 inches. The data were collected in the continuous scan mode utilizing a step size of 0.05° at 20/s. the scanning range was 5-40° at a wave length of 1.54°A.

***In vitro* drug release**

The dissolution studies were carried out using USP II dissolution apparatus (USP paddle type, Copley, England) for the unprocessed drug or different Aceclofenac microcapsule systems containing an amount equivalent to 100 mg of drug. The dissolution medium was 900 ml of 0.1 N HCL (pH 1.2) and phosphate buffer of pH value of 7.4. The dissolution was conducted for 2 hrs in either media at a paddle speed of 75 rpm and Temperature of 37±0.5°C. Samples (5 ml each) were withdrawn at predetermined time intervals along the period of 2 hours at 5, 10, 15, 20, 30, 45, 60, 90, and 120 minutes, filtered using Millipore filter (0.45µm) and were assessed spectrophotometric at a wavelength of 275 nm with a UV spectrophotometer. Sample volume used for analysis was replaced by equal volumes of fresh dissolution medium preheated at 37°C to maintain the sink conditions. Each batch was analyzed in triplicate and the calculated mean percentage drug release values were used to plot the dissolution curve.

From the dissolution profiles, the amount dissolved in first 20 min (Q20) and the percentage of the amount dissolved in last 120 min (Q 120) were calculated for all formulations and compared.

Statistical analysis

All experiments were conducted in triplicates and statistical analysis employed Student t-test. Results were quoted as significant when $P< 0.05$.

RESULTS AND DISCUSION

Infrared spectral analysis (FTIR)

FTIR was used to investigate the effect of co-processing of Aceclofenac with excipients on the structural pattern of the drug. The recorded FTIR spectra are shown in Figure 1.

The IR spectrum of the pure drug showed characteristic bands at 3318 cm^{-1} (N-H stretching), 2970 and 2930 cm^{-1} (O-H stretching), 1719 cm^{-1} (C=O stretching), 1585 cm^{-1} (aromatic C=C stretching), 1506 cm^{-1} (in plane bending for N-H), 965 cm^{-1} (O-H out plane bending) and 750cm^{-1} (N-H out plane bending). This spectrum is in good agreement with the published spectrum for the same drug.[11] Eudragit S 100 produced a characteristic absorption bands at 3481 cm^{-1} for O-H stretching and 1728 cm^{-1} for C=O stretching. For Eudragit L 100, the spectrum characterized by the absorption at 3473 cm^{-1} (O-H stretching), 1738 cm (C=O stretching). In case of PVP K90 the spectrum revealed the absorption band at 3444 cm^{-1} (O-H stretching), 1659 cm^{-1} (C=O stretching). For sodium alginate, the spectrum showed absorption band at 3445 cm^{-1} (OH stretching), 2168 cm^{-1} (CH stretching), 1613 cm^{-1} (C=O stretching), 1423 cm^{-1} and 1031 cm^{-1} for (COO) and (C-O-C), respectively.

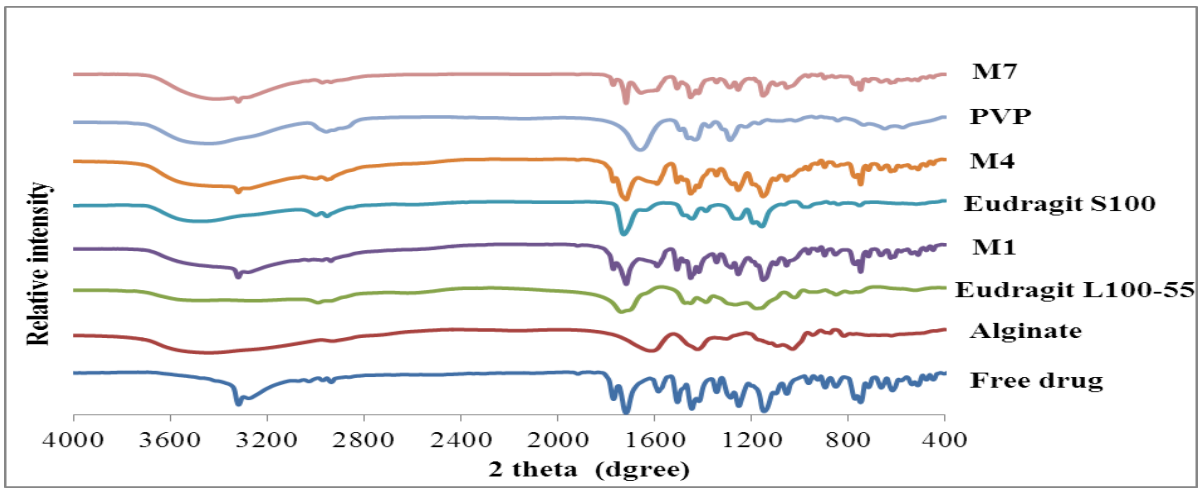

Figure 1: FTIR spectrum of unprocessed Aceclofenac sodium, Sodium alginate, Eudragit L100-55, Eudragit S100, PVP and selected microcapsule formulations. For detailed composition refer to Table 1.

Regarding the selected formulations M1, M4 and M7, the FTIR spectra showed no inter action between drug and the used excipient. Thus, the spectra alleviate any possible incompatibility between the polymers and Aceclofenac.

Differential scanning calorimetric analysis (DSC)

The thermal behaviour of Aceclofenac, pure polymers and selected microcapsule formulations was monitored using DSC. Figure 2 shows representative thermograms of these systems. The DSC trace of the drug showed a sharp endothermic peak at 153.46 °C, representing its melting transition and reflects its crystalline nature. Another small endothermic peak was noticed at about 201 and can be attributed to drug decomposition. This thermogram is similar to published data.[12] For pure PVP, the thermogram showed a broad endothermic peak starting at 30.27 °C and ending at 101.46 °C (Figure 2) due to evaporation of bound moisture.

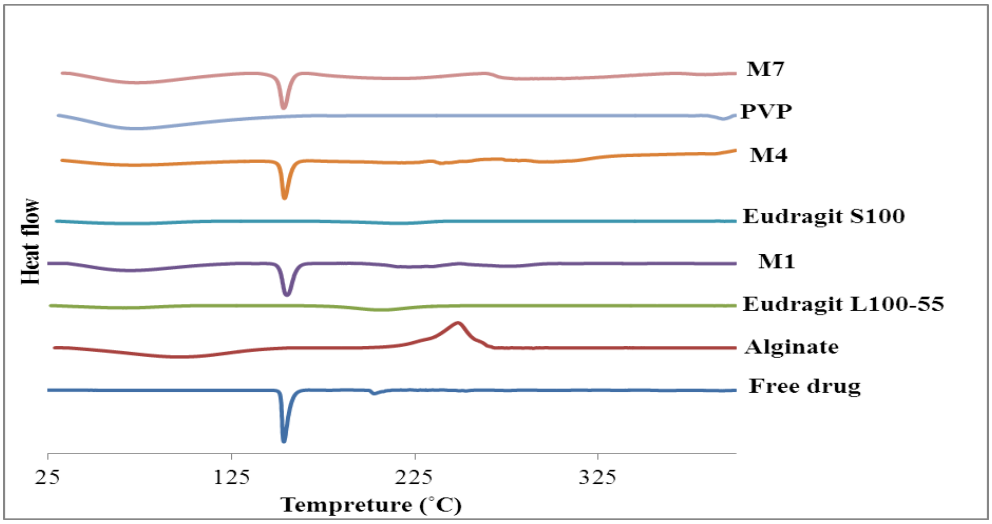

Figure 2: DSC thermogram of unprocessed drug, Sodium alginate, Eudragit L100-55, Eudragit S100, PVP and selected microcapsule formulations. For detailed formulations refer to Table 1.

This thermogram is similar to that published by other authors.[14] For the prepared formulations, the thermograms showed a slight reduction in the endothermic peak appearing at 155.33°C, 153.94°C and 153.39°C for microcapsule prepared using Eudragit L100-55, Eudragit S100 and PVP, respectively. This reduction was accompanied by slight peak broadening. This would suggest that there was partial transformation of the drug to the amorphous form.

Powder X-ray diffraction analysis (XRD)

In order to emphasize the physical state of the drug in the microcapsule systems, X-ray powder diffraction was studies.[13] Representative Diffractograms of Aceclofenac, polymers and selected formulations are shown in Figure 3.

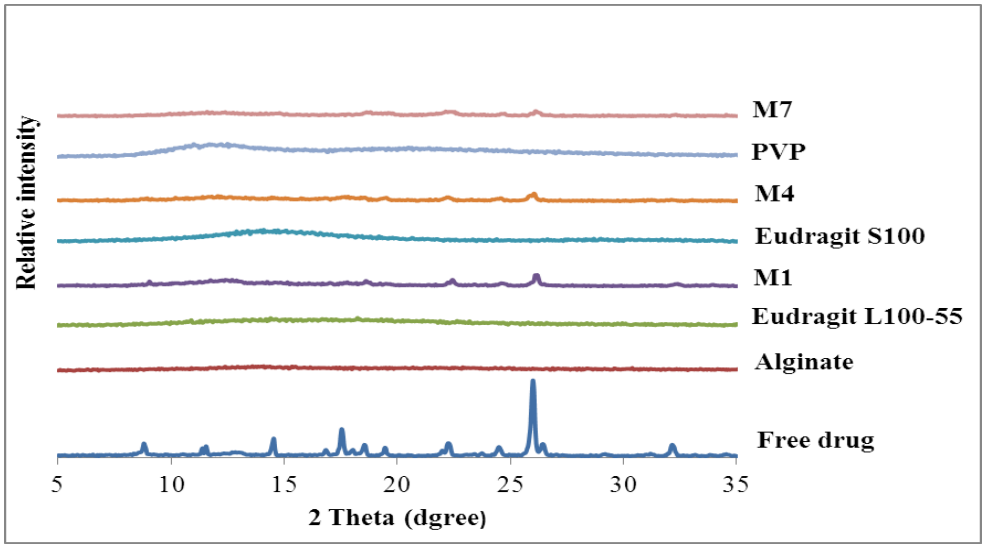

Figure 3: Diffractograms of unprocessed drug, Sodium alginate, Eudragit L100-55, Eudragit S100, PVP and selected microcapsule formulations. For detailed formulations refer to Table 1.

The diffraction pattern of pure drug showed numerous clear peaks at a diffraction angle (2theta) of 11.25˚, 14.45˚, 17.5˚, 22˚, 24.2˚ and 25.27˚. This indicates the crystalline nature of Aceclofenac. This is in good agreement with the published diffractogram of the same drug by other authors.[17] The diffractograms of Eudragit S100[16], EudragitL100-55[12], PVP K90[14] and alginates show their amorphous structure with no distinct peaks.

For the prepared microcapsules, the diffractograms of the selected formulations showed reduced peak intensity. This could be attributed to possible dispersion of the drug in the polymeric matrix in very fine state of subdivision.

***In vitro* drug release studies**

Release studies were performed at various pH values (pH 1.2 and 7.4) as the drug has pH dependent solubility corresponding to physiologic pH of the GI tract segments.[6]

The dissolution profiles were constructed as the cumulative amount release versus time plots and are presented in Figures 5. The dissolution parameters were calculated as the percentage amount released after 20 and 120 minutes in both 0.1 N HCL and phosphate buffer at pH 7.4 and are presented in Table (2).

At the acidic environment (pH 1.2), unprocessed drug showed slow release with a percentages released after 20 minutes of 0.56% with a total release of about 2% after 2 h of release study (Figure 4). In case of microcapsules using Eudragit L100-55 and alginate, there was a marked reduction in the amount of drug released compared to control pure drug. There was no detectable drug release in the first 60 minutes for all formulations (M1 through M3). The percentage released after 20 minutes of Aceclofenac-Eudragit L100-55 and alginate microcapsule (1:0.5:0.5) (M1) was decreased significantly ($P < 0.05$) than free drug at the same pH value. This could be explained by the poor solubility of Eudragit L100-55 in the acidic medium. According to the inventor of the polymer (Evonik), Eudragit L100-55 requires pH value more than 5.0 to dissolve. Another reason for such retarded drug release could be due to crosslinking of alginate in the acidic medium. This crosslinking can lead to shrinking with subsequent reduction in drug release.[10] Upon exposure to alkaline media alginate chains.

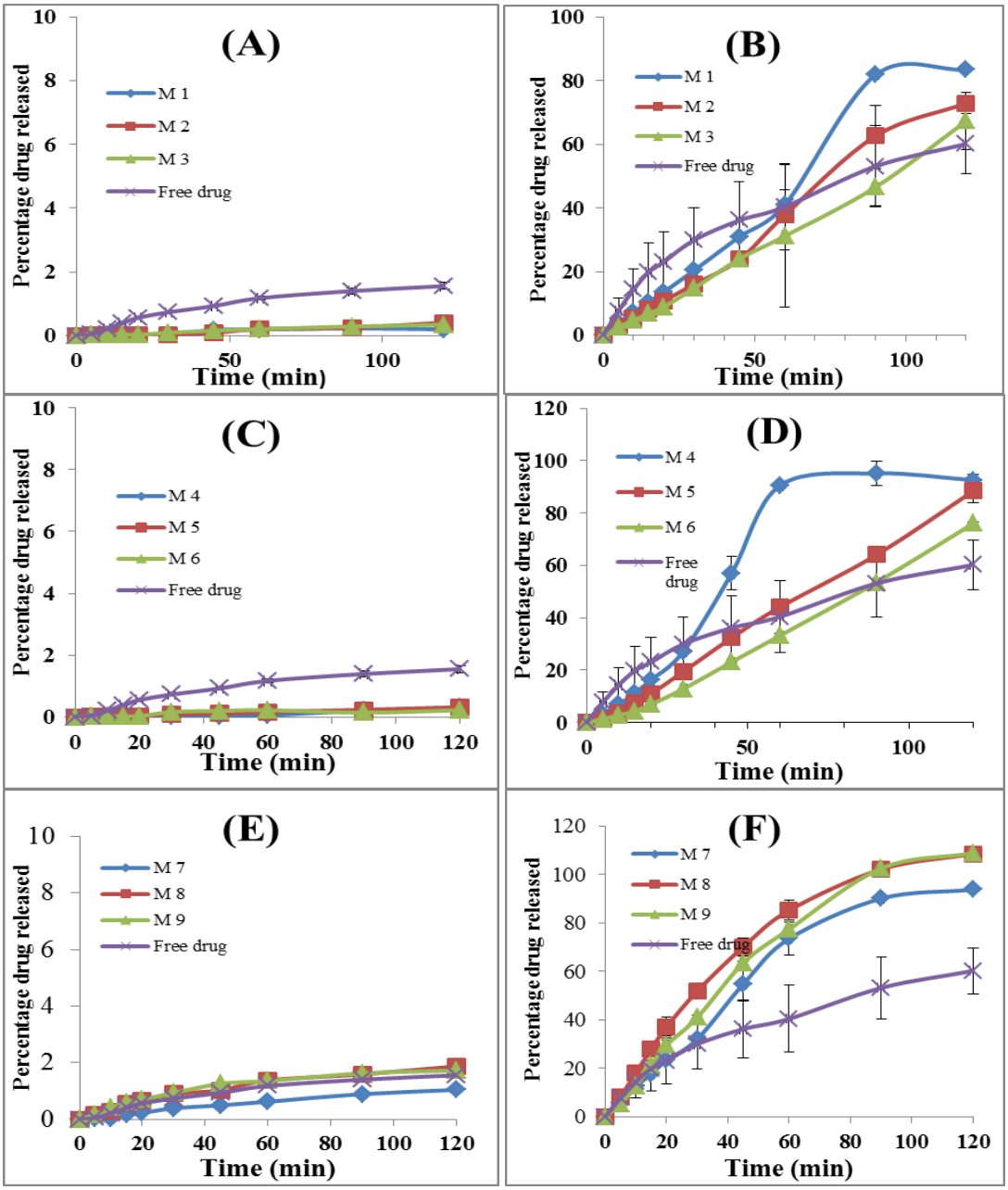

Figure 4: The dissolution profiles of Aceclofenac from pure drug and microcapsules prepared using Alginate with either Eudragit L100-55 at acidic (A) and alkaline (B) media; or using Eudragit S100 at acidic (C) and alkaline (D) media: or using PVP K90 at acidic (E) and alkaline (F) media. For detailed formulations refer to Table1.

Table 2: Dissolution parameters of Aceclofenac from different microcapsule formulations at acidic (pH 1.2) and alkaline (pH 4.7) media.

Formula	pH 1.2		pH 7.4	
	% released at after 20 min	% released at after 120 min	% released after 20 min	% released after 120 min
Pure drug	0.56 ± 0.11	1.56 ± 0.09	23.07 9.51	60.17 ± 9.50
M1	0.03 ± 0.00	0.19 ± 0.02	13.57 ±0.17	83.51 ±6.24
M2	0.03 ± 0.00	0.41 ± 0.00	10.79 ±0.15	72.99 ±1.79
M3	0.03 ± 0.00	0.34 ± 0.00	8.91 ± 0.02	67.36 ±9.07
M4	0.03 ± 0.00	0.31 ± 0.03	16.25 ±0.26	92.57 ±1.98
M5	0.03 ± 0.00	0.32 ± 0.05	10.99 ±0.16	88.37 ±4.43
M6	0.03 ± 0.00	0.23 ± 0.02	6.91 ± 0.13	76.04 ±0.68
M7	0.23 ± 0.02	1.04 ± 0.09	23.25 ±1.00	93.68 ±0.65
M8	0.66 ± 0.04	1.87 ± 0.04	37.01 ±3.96	108.43±1.14
M9	0.70 ± 0.09	1.72 ± 0.02	29.55 ±2.12	108.71±0.83

(*) An amount equivalent to 100 mg of Aceclofenac was utilized in the study.

Open due to ionic interaction with the release of the entrapped drug. To control over the drug release, the polymer contents of the microcapsules was increased (Formulations M2 and M3). However, this did not significantly affect the release rate where the profile was similar to that of M1.

The release study at simulated intestinal fluid (pH 7.4) showed different dissolution pattern. For pure drug, there was a considerable release of the drug with a percentages release of about 23% after 20 minutes with a total release of about 60% after 120 minutes (Figure 4B). For microcapsules, the percentage released was slightly lower than that of the pure drug at the same pH value. However this reduction was statistically non-significant ($P > 0.05$). Microcapsules with higher polymeric ratios showed a similar dissolution pattern. This indicates that lower polymers concentration (ratio 1:0.5:0.5 drug:alginate:Eudragit L100-55) is enough to produce the required control over drug release and M1 is considered as the optimum formula.

It is generally taken that when microspheres of hydrophilic polymers are immersed in water; they swell and form a gel diffusion layer that hinders the outward transport of the drug, hence, producing a controlled release effect. However, at acidic pH the alginate microspheres shrink due to tightening of the gel meshwork. The polymer is eroded at alkaline pH and the contents are released in a sustained manner by both diffusion and slow erosion of polymer matrix.[10]

The dissolution behaviour was noticed for microcapsules prepared using Eudragit S100 (M4 through M6) was similar to those prepared using Eudragit L100-55 (Figure 4 C and D and Table 2). In the acidic medium, increasing the microcapsule content of both alginate and Eudragit produced significant reduction of drug release. This suggests the enteric effect of the polymer that reduced drug release in the stomach and its solubility in the alkaline pH value. This would overcome the possible damaging effect of the drug to gastric mucosa.

For microcapsules prepared using PVP (M7 through M9), the dissolution profiles are presented in Figure 4 E and F and dissolution parameters are in Table 2, Microcapsules prepared using PVP showed slight , but insignificant, enhancement in drug dissolution in the acidic medium (Figure 4E). Though PVP is known to be hydrophilic polymer, this could be explained by the hydrophilic nature of the polymer. It worth noting that the release was reduced from M9 compared to other two formulations, this could be due to increase PVP concentration.

In alkaline medium, there was enhancement in the drug released with percentage release of 23, 37 and 29% after 20 minutes for formulations M7, M8 and M9, respectively. This was due to the solubility of alginate polymers in the alkaline medium. Additionally, the hydrophilic nature of PVP polymer would assist in coat dissolution. It worth noting that there was a reduction in Aceclofenac release from M9 compared to M8. This could be due to the higher content of PVP that may increase the viscosity of the diffusion layer providing hindrances for drug diffusion.[14] The total amount released at the end of the time course of the released study was 93% for M7 with complete release of drug for M8 and M9.

CONCLUSION

Microcapsules of Aceclofenac were successfully prepared using ionotropic gelation technique. Microcapsules were prepared using different polymers namely Eudragit L100-55, Eudragit S100 and PVP in presence of alginate. Beads prepared with sodium alginate and Eudragit S100 at 1:0.5:0.5 drug:alginate:polymer ratio was optimum formula as it enhance dissolution in the simulated intestinal fluid. Therefore, this technique is considered simple and promising eco-friendly strategy to enhance the dissolution rate of the no steroidal anti-inflammatory drug with expected reduction in its deleterious effect on gastric lining.

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