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Research Article

FORMULATION AND EVALUATION OF MUCOADHESIVE MICROCAPSULES OF ACECLOFENAC USING METHYL CELLULOSE AND CARBOPOL AS MUCOADHESIVE POLYMERS

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ABSTRACT

Mucoadhesive microencapsulation has been accepted as a process to achieve controlled drug delivery by prolonging the residence time of the dosage form at the site of absorption, thereby improving and enhancing the bioavailability of drugs.Aceclofenac is a non-steroidal anti-inflammatory drug used for relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.Since it has a short biological half life of 3-4h, a sustained release is needed to give a prolonged action and thereby to reduce the dosage frequency. The mucoadhesive microcapsules of Aceclofenac were formulated by orifice ionic gelation technique employing polymers like Methyl cellulose, Carbopol in the ratio 1:1 and 1:2 along with Sodium alginate. The microcapsules prepared were discrete, spherical and free flowing. Microcapsules were evaluated for particle size, percentage yield, flow properties, drug content, drug entrapment efficiency, percentage moisture loss, swelling property, *in vitro* drug release, drug release kinetics, *in vitro* wash-off test, stability study and drug polymer interaction study by FT-IR. The microencapsulation efficiency was found relatively high with Sodium alginate-Carbopol microcapsules (77.4%). Average particle size was found in the range of 951.4±2.9 to 977.5±5.21µm. Drug release from microcapsules was sustained in the following manner MC < Carbopol. Drug release was diffusion controlled and followed first order kinetics. The *in vitro* wash-off test indicated that the microcapsules had good mucoadhesive properties. Hence prepared mucoadhesive microcapsule may be an effective strategy for the development of easy, reproducible and cost effective method for safe and effective oral drug therapy.

Keywords: Aceclofenac, Carbopol, Methyl cellulose, Microcapsules, Mucoadhesion.

INTRODUCTION

In the early 1980s, the concept of mucoadhesives was introduced into the controlled drug delivery area[1].Many concepts have been proposed in recent years to provide a dosage form with a longer transit time and therefore more efficient absorption. The concept of bioadhesion or more specifically mucoadhesion is one of them to increase gastric retention of drugs. Among the various approaches for controlled systems, microencapsulation process have gained good acceptance as a process to achieve controlled release and drug targeting. Though several studies reported, mucoadhesive drug delivery systems in the form of tablets, films, patches and gels for oral, buccal, nasal, ocular and topical routes, however, very few reports on mucoadhesive microcapsules are available[2, 3].

The conventional Aceclofenac tablets administered 2 to 3 times a day due to its short biological half life produces side effects like gastric ulceration and bleeding[4]. The side effects of conventional Aceclofenac tablet have been attenuated by designing the drug in the form of mucoadhesive microcapsules which includes advantages like, maximized absorption rate due to intimate contact with the absorbing membrane, improved drug protection by polymer encapsulation, longer gut transit time resulting in extended periods for absorption. The objective of this study is to prepare and evaluate the sustained release mucoadhesive microcapsules of Aceclofenac, thus reducing the frequency of dosing, side effects and increasing patient compliance. The novelty of this work is in combining the advantage of particulate system (microcapsule) and mucoadhesive drug delivery system by taking sodium alginate and mucoadhesive polymers.

MATERIALS AND METHODS

Materials

Aceclofenac was obtained from Micro Labs, Hosur, India. Methylcellulose (65 cps) and calcium chloride dihydrate were procured from Leo Chem, Bangalore, India. Carbopol 934P was obtained from Loba Chemie Pvt. Ltd, Mumbai, India. Sodium alginate was procured from Reachem Lab. Chemicals Pvt. Ltd, Chennai, India. All other reagents used were of analytical grade.

Methods

Orifice-Ionic Gelation Method

Sodium alginate (1.0 g) and the mucoadhesive polymer (1.0 g) were dissolved in purified water (32 ml) to form a homogeneous polymer solution. The active core material Aceclofenac (2.0 g) was added to the polymer solution and mixed thoroughly with a stirrer to form a smooth viscous dispersion. The resulting dispersion was then added dropwise into calcium chloride (10%w/v) solution (40 ml) through a syringe with a needle of size No: 18. The added droplets were retained in the calcium chloride solution for 30 min to complete the curing reaction and to produce spherical rigid microcapsules. The microcapsules were collected by decantation and the product thus separated was washed repeatedly with water and dried at 45°C for 12 h[5]. The microcapsules prepared along with their coat composition are listed in Table 1.

Table 1: Formulation of mucoadhesive Aceclofenac microcapsules

Formulation code	Drug - Polymer Ratio	Quantity		Quantity of Mucoadhesive Polymers	
		Drug(g)	Sodium alginate(g)	MC(g)	Carbopol(g)
F_1	1:1	2	1	1	-
F_2	1:1	2	1	-	1
F_3	1:2	2	2	2	-
F_4	1:2	2	2	-	2

FT- IR Analysis

FT-IR analysis of pure drug, individual polymer, combination of drug and polymers in higher concentration were taken for the study. Samples were compressed with potassium chloride and transformed into disk[6]. The disk was scanned between 4000-400 cm^{-1} in SHIMADZU FT-IR (IR Affinity-1) spectrophotometer.

Evaluation of microcapsules

Micromeritic properties

The Micromeritic properties of microcapsules were studied by determining various parameters like the angle of repose, bulk density, tapped density and Carr's index. The angle of repose was determined by the fixed-base cone method. Bulk and tapped density were determined using digital bulk density apparatus[7].

Percentage yield

The percentage yield of microcapsules of various batches were calculated using the weight of final product after drying with respect to the initial total quantity of the drug and polymer used for preparation of microcapsules[8, 9].Percentage yield was calculated as per the formula mentioned below.

$$\text{Percentage yield} = \frac{\text{Practical yield} \times 100}{\text{Theoretical yield}}$$

Surface morphology (SEM Analysis)

Shape and surface morphology of microcapsules were studied using scanning electron microscopy (SEM). The microcapsules were mounted on metal stubs using double sided adhesive tape and the stub was then vacuum coated with gold film using sputter coater attached to the instrument[10]. The photographs were taken using a Jeol scanning electron microscope (JEOL-JSM-6390LV, Japan).

Drug content

Aceclofenac content in the microcapsules was estimated by UV spectrophotometric method based on the measurement of absorbance [8,11]of 10µg/ml solution at 275 nm in phosphate buffer solution pH 7.4.

Microencapsulation efficiency

Microencapsulation efficiency was calculated using the formula [8],

$$\text{Microencapsulation efficiency} = \frac{\text{Estimated percent drug content} \times 100}{\text{Theoretical percent drug content}}$$

Particle size analysis

Microcapsules were separated into different size fractions by sieving for 20 minutes using mechanical sieve shaker containing standard sieves of different mesh numbers arranged in a nest with the coarsest at the top and finest at the bottom[12]. The microcapsules retained on each sieve were weighed and the average diameter of microcapsules were determined.

Melting point

The melting point test of the microcapsules were carried out by using melting point apparatus to find out if there is any change in the nature of the coated drug due to the process of preparation. Small amount of microcapsules were taken and ground for the removal of coating material and it was placed in glass capillary tube whose one end was sealed by flame. The capillary tube containing samples was kept in the melting point apparatus and the melting point was noted[13].

Percentage moisture loss

The microcapsules weighed (W1) initially were kept in desiccator containing calcium chloride at 37ºC for 24 h14. The final weight (W2) was noted when no further change in weight of sample was observed.

Percentage moisture loss was determined using the following formula:

$$\text{Percentage moisture loss} = [(W_1-W_2)/W_2] \times 100.$$

Where, W_1= Initial weight of microcapsules;

W_2 = Final weight of microcapsules.

Degree of swelling

The swelling ability of microcapsules in physiological media was determined by swelling them in PBS. Accurately weighed amount of microcapsules was immersed in little excess of PBS for 24 h and washed[15, 16].

The degree of swelling was calculated using the following formula:

$$\alpha = (Ws-Wo) / Wo$$

Where,

α is the Degree of swelling,

Wo = Weight of microcapsules before swelling,

Ws = Weight of microcapsules after swelling.

Mucoadhesion testing by *in vitro* wash-off test

The Mucoadhesive property of the microcapsules was evaluated by an *in vitro* adhesion testing method known as wash-off test. The test was performed in simulated gastric fluid (0.1 M HCl, pH 1.2) and in simulated intestinal fluid (PBS, pH 7.4). Pieces of intestinal mucosa (2 × 2 cm) were mounted onto glass slides of (3 × 1 inch) with cyanoacrylate glue. Two glass slides were connected with a suitable support. About 50 microcapsules were spread on to each wet rinsed tissue specimen and immediately thereafter the support was hung on to the arm of USP tablet disintegration test apparatus. The disintegration apparatus containing tissue specimen was given a slow regular up and down movement in a test fluid at 37 ºC taken in a 1L beaker of the disintegration test apparatus. At different time intervals up to 8 h the apparatus was stopped and the number of microcapsules, still adhering to the tissue was counted[11, 17, 18].

The adhesion number was determined by the following formula

$$Nn = (N/No) \times 100$$

Where, Nn = Adhesion number.

N = Number of microcapsules attached to the mucosa after washing.

No = Initial number of microcapsules in the intestinal mucosa.

***In vitro* drug release studies**

In vitro drug release of Aceclofenac from microcapsules was carried out by using USP Type-I dissolution test apparatus. 900 ml of simulated gastric fluid (0.1M Hydrochloric acid buffer, pH 1.2) was used as dissolution medium for first 2 h and simulated intestinal fluid (phosphate buffer, pH 7.4) was used for next 8 h. A quantity of microcapsules equivalent to 200 mg of Aceclofenac was filled in empty capsule shells and placed in the basket and rotated at 50 rpm. Bath temperature was maintained at 37±0.5ºC throughout the study. Aliquots of samples (10 ml) were withdrawn at an interval of every 1 h. Samples withdrawn were replaced with equal volumes of the dissolution medium[12, 19, 20. The] absorbance of samples was measured using UV Double beam spectrophotometer at 275 nm after suitable dilution with the buffer.

Drug release kinetics

In order to understand the mechanism and kinetics of drug release, the results of the *in vitro* drug release study were fitted with various kinetic models like zero order kinetic model, first order kinetic model, Higuchi model and Korsmeyer-Peppas model[21].

Stability studies of microcapsules

Stability studies of Aceclofenac microcapsules were performed at 25 ± 2ºC/60 ± 5% RH and 40 ± 2ºC/75 ± 5% RH for a period of 3 months. The samples were withdrawn after every month and were analyzed for its appearance, drug content and the drug release[22].

RESULTS AND DISCUSSION

The IR spectral studies of pure Aceclofenac, Methyl cellulose, Carbopol, sodium alginate and combination of drug and polymers

containing highest proportion were carried out. When the characteristic peaks of Aceclofenac were compared with the combination of Aceclofenac and polymers, it was found that the same fundamental peaks were also present in the drug-polymer combinations indicating there was no interaction between Aceclofenac and polymers used.

It was observed that percentage yield of formulations F_1, F_2, F_3 and F_4 were 90.2%, 87.3%, 88.3% and 84.8%, respectively. The formulation F_1 showed maximum yield. The melting point of pure Aceclofenac and Aceclofenac microcapsules were found to be in the range of 149^{0}C to150^{0}C respectively. This reveals that the nature of drug was not affected due to the process of preparation. Scanning electron micrographs of formulations F_1 and F_2 were shown in Fig-1. The microcapsules were found to be discrete, uniform and spherical in shape. The surface of the microcapsules was found to be smooth and the core was completely covered by the coating.

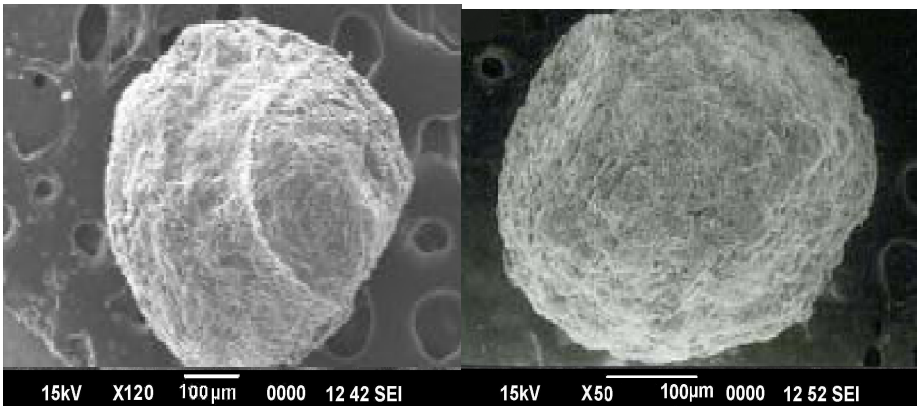

Fig. 1: SEM of formulation F_1 SEM of formulation F_2

The results showed that the angle of repose was found in the range of 21.7±1.7 to 24.5±2.6, which confirmed that the microcapsules were having excellent flow properties. The micromeritic studies revealed that the microcapsules have excellent flow property which indicates the microcapsules produced are spherical and non-aggregated. All the formulations showed excellent flowability as expressed in terms of micromeritic parameters (Table 2).

Table 2: Micromeritic properties of Aceclofenac microcapsules

Formulation code	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
F1	23.5±1.5	0.3875±0.27	0.4273±0.04	9.30	1.10
F2	24.1±1.4	0.4783±0.01	0.5341±0.02	10.44	1.12
F3	21.7±1.7	0.4153±0.03	0.4786±0.04	13.22	1.15
F4	24.5±2.6	0.4463±0.05	0.4985±0.04	10.47	1.11

*All the values are expressed as mean ± standard deviation; n=3.

Three samples were tested from each batch and the drug content was determined by UV spectrophotometric method. The standard deviations among the three values were found to be less. This indicates that the drug was distributed almost uniformly throughout the batch of microcapsules. The microencapsulation efficiency was in the range of 54.4±0.56 to 77.4 ±0.72 %. The average particle size was found to be in the range of 951.4±2.90 to 977.5±5.21 µm as shown in Table 3. The average particle size of microcapsules were found to be increased as the concentration of the polymer was increased. This may be due to increased coat thickness with increasing polymer proportion.

The percentage moisture loss of formulations F_1, F_2, F_3 and F_4 were 10.42±0.61%, 4.74±0.13%, 2.56±0.16% and 3.81±0.41% respectively. The results ensure the presence of diminutive water content which can be due to the involvement of water in process and hydrophilic property of mucoadhesive polymers. The degree of swelling of formulations F_1, F_2, F_3 and F_4 were 52±1.52%, 61±2.64%, 54±3.51% and 72±2.51% respectively, which indicates the hydrophilicity property of the polymers with establishing the fundamentals that the increase in degree of swelling depends on the polymer concentration in formulations. The formulation F_4 exhibited good degree of swelling.

Table 3: Evaluation of Aceclofenac microcapsules

Formulation Code	Drug content (mg)		Microencapsulation efficiency (%)	Particle size (µm)
	Theoretical	Practical		
F1	50	27.2±0.56	54.4±0.56	951.4±2.90
F2	50	30.2±0.72	60.4±0.72	960.2±4.71
F3	33.33	22.4±0.51	67.2±0.51	977.5±5.21
F4	33.33	25.8±0.72	77.4±0.72	965.7±3.47

*All the values are expressed as mean ± standard deviation; n=3.

Microcapsules with a coat consisting of Sodium alginate and a mucoadhesive polymer exhibited good mucoadhesive property in the *in vitro* wash-off test when compared to non-mucoadhesive material, ethylene vinyl acetate microcapsules (EVA). The wash-off test was relatively rapid in phosphate buffer (pH 7.4) than in Hcl buffer (pH 1.2). The rapid wash-off, observed in phosphate buffer pH 7.4 may be due to ionization of carboxyl and other functional groups in the polymers at this pH, which increases their solubility and reduces adhesive strength. The results of wash off test indicated that the microcapsules had fairly good mucoadhesive properties in both acidic and alkaline pH. The results are shown in Table- 4.

Table 4: *In vitro* mucoadhesion wash-off test

Formulation code	Percent of microcapsules adhering to tissue at different time interval (h)									
	In 0.1N HCL, pH 1.2					In phosphate buffer, pH 7.4				
	1	2	4	6	8	1	2	4	6	8
F1	77 (2.1)	75(3.0)	65(2.3)	61(0.57)	48(1.5)	45(2.5)	39(0.57)	28(3.0)	21(1.5)	08(1.5)
F2	85(2.3)	76(2.0)	68(2.1)	62(2.0)	51(2.1)	47(2.3)	42(1.5)	31(3.0)	24(3.0)	10(0.57)
F3	81(2.0)	79(2.5)	70(3.0)	67(3.1)	63(2.1)	57(3.0)	48(1.5)	41(3.0)	27(2.5)	09(1.5)
F4	88(1.5)	82(2.0)	73(1.5)	69(2.3)	66(1.5)	65(2.5)	55(1.3)	43(1.5)	35(2.3)	19(2.0)
EVA	54(2.0)	37(2.0)	12(2.5)	__	__	51(1.5)	32(2.3)	09(2.5)	___	___

*All the values are expressed as mean ± standard deviation; n=3.

The *in vitro* study results revealed that Aceclofenac release from the microcapsules was slow and spread over extended period of time. The percentage drug release from F_1, F_2, F_3 and F_4 formulations were 48.29±1.3, 43.99±1.5, 44.24±3.0, 42.09±1.5% respectively in 10 h. As the proportion of polymer increased, the drug release decreased. This may be due to increased coat thickness with increasing polymer proportion. The order of increasing release rate observed with various microcapsules was alginate-Carbopol < alginate- Methyl cellulose. The cumulative percentage drug release Vs. time profile was represented graphically in Fig 2.

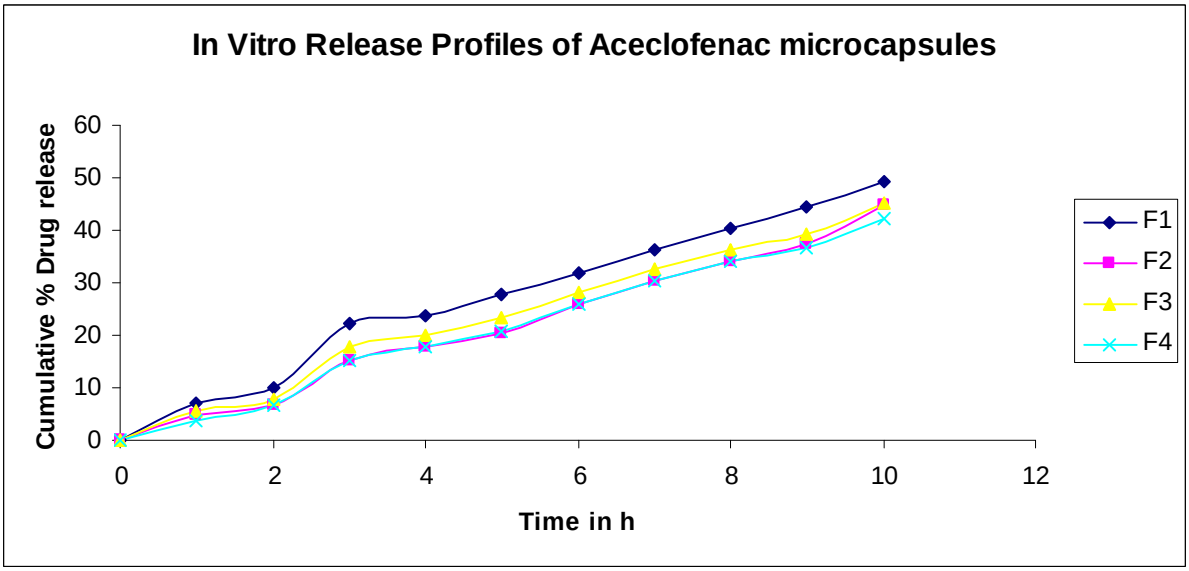

Fig. 2: *In vitro* release profiles of Aceclofenac microcapsules (1:1and 1:2 Ratio)

The drug release data was subjected for mathematical treatment to check the release order kinetics. Plots of log cumulative percent drug remaining Vs time were found to be linear (r > 0.98) with all the microcapsule formulations indicating that the drug release was according to the first order kinetics. To evaluate the drug release mechanism from microcapsules, Higuchi's plots were constructed and these plots were found to be linear with all microcapsules indicating that the drug release mechanism from the microcapsules was diffusion controlled. The results of all microcapsules showed 'n' values more than 0.5 which indicates that it follows Non-Fickian diffusion. The Kinetic data of release profiles of Aceclofenac microcapsules are shown in Table 5.

Table 5: Kinetic data of release profiles of Aceclofenac microcapsules

Formulation code	Zero order	First order	Higuchi	Korsmeyer -Peppas	
	Regression coefficient (r)				n
F1	0.9650	0.9821	0.9788	0.9614	0.8265
F2	0.9729	0.9863	0.9823	0.9670	0.8216
F3	0.9825	0.9917	0.9864	0.9672	0.8540
F4	0.9897	0.9902	0.9759	0.9536	0.8673

The stability study results revealed that there was no significant changes found in appearance and drug content of microcapsules, stored at 25 ± 2°C /60 ± 5% RH and 40 ± 2°C/75 ± 5% RH, after 3 months. The cumulative percentage drug release of Aceclofenac from microcapsules after 3 months showed that there was no significant effect of storage temperature on the drug release.

CONCLUSION

Microcapsules of Aceclofenac with a coat consisting of Sodium alginate and mucoadhesive polymers namely Methyl cellulose and Carbopol in 1:1 and 1:2 ratio could be prepared by the orifice-ionic gelation process. The microcapsules of all the formulated batches were spherical, discrete and free flowing. The drug content was found to be uniform throughout the batch of microcapsules. Aceclofenac release from the microcapsules was slow, spread over extended periods of time and depended on the composition of coat. Microcapsules of sodium alginate – methyl cellulose gave relatively faster release when compared to sodium alginate – carbopol microcapsules. Drug release was diffusion controlled and followed first order kinetics. The wash off test indicated that the microcapsules had fairly good mucoadhesive properties in both acidic and alkaline pH.Thus the developed formulations could be

used for sustained release of Aceclofenac from sodium alginate–carbopol microcapsules with adequate mucoadhesiveness and swelling properties without the risk of mucosal damage.

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