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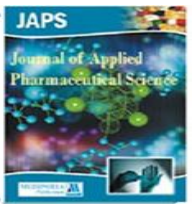

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Formulation design of Aceclofenac microcapsules by inotropic gelation technique, characterization studies and release kinetics

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ABSTRACT

Osteoarthritis predominantly affects the large weight bearing joints and the clinical characteristics include morning stiffness of short duration, stiffness or gelling on rest, pain on use, joint inflammation and bone deformity. Microcapsules of aceclofenac were formulated with methyl cellulose, sodium CMC and hydroxyl propyl methyl cellulose by technique. The microcapsules showed excellent rheological properties for all batches. The formulations showed drug content uniformity with high drug entrapment efficiency. The *in vitro* wash off test revealed the mucoadhesive ability of the micro capsules. Scanning electron microscopy indicated structural and surface morphology uniformity. The *in vitro* release studies indicated sustained release of aceclofenac from the formulations. Kinetic study of the release data indicated the zero order release and non fickian sustained release mode of drug release. The microcapsules showed the correlation between wall thickness and drug release pattern.

Key words: Aceclofenac, Ionic gelation, Entrapment efficiency, *In vitro* release.

INTRODUCTION

Osteoarthritis, rheumatoid arthritis and ankylosing spondylitis are a group of related, but distinct, disorders of the cartilage of osteoarticular joints. Ankylosing spondylitis is characterized by inflammation, predominantly of the spine, but in some cases, also of the large peripheral joints. Systemic symptoms can include fever, fatigue and anorexia and in some cases pericarditis and pleuritis may occur (Pareek et al., 2006). Rheumatoid Arthritis is less common than osteoarthritis, although no less debilitating. Fatigue, malaise, subcutaneous nodules and fever are common systemic symptoms of Rheumatoid Arthritis. NSAIDs have become widely used in the treatment of these illnesses for their pain-relieving and anti-inflammatory properties. Since long-term NSAID treatment is indicated for osteoarthritis, the ideal agent should have good efficiency and a low propensity to cause adverse events. Aceclofenac appears to be particularly well tolerated among the NSAIDs, with a lower incidence of gastrointestinal adverse effects. This good tolerability profile results in a reduced withdrawal rate and greater compliance with treatment. (Legrand, 2004). Aceclofenac is an NSAID of a phenyl acetic acid class. It is indicated in arthritis and osteoarthritis, rheumatoid arthritis, ankylosing spondylitis. Aceclofenac phenyl acetic acid derivative 2-[(2,6-Dichlorophenyl)amino] phenyl acetoxy acetic acid indicated in the symptomatic

treatment of pain and inflammation with a reduced side effect profile especially regarding gastrointestinal complications (Parfitt 1999, Brogden et al. 1996). To reduce the dosing frequency and adverse effects during prolong treatment it is needed to formulate in long acting dosage form. Aceclofenac directly blocks prostaglandin E2 secretion at the site of inflammation by inhibiting IL-Beta and Tumour necrosis factor in the inflammatory cells. Recommended dose of Aceclofenac is 100mg twice daily, due to short biological half-life of the drug 4h makes it suitable candidate for the modified release dosage forms. To reduce the frequency of administrations and to improve patient compliances, aceclofenac is suitable for making sustain release dosage form. (Trivedi P, 2008).

Microcapsules are homogeneous, monolithic particles which improve the treatment by providing localization of the drug at the site of action and by prolonging the drug release. These techniques are widely used in pharmaceutical research (Breghausen SW., 2002). Multiparticulate delivery systems like microcapsules are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites (S Haznedar., 2004). They can distribute in the GI tract homogeneously, thus maximizing drug absorption and reducing peak plasma fluctuations, minimizing the risk of local GI tract irritation and dose dumping, decreasing dosing frequency and increasing patient compliance, improving the safety and efficacy of the active ingredient (Shavi GV., 2009).

Ionic gelation technique for microencapsulation is the method which prolongs the duration of drug effect significantly, provides symptomatic relief to the patient and improves patient compliance. Eventually the total dose and few adverse reactions may be reduced since a steady plasma concentration is maintained. Hence in the current study formulation and *in vitro* evaluation of sustained released Aceclofenac microcapsules with polymers like methyl cellulose, Na CMC and HPMC employing ionic gelation technique. The prepared formulations were studied for their flow properties, encapsulation efficiency, *in vitro* release studies and drug release kinetics. The optimized formulation was subjected for Scanning electron microscopic study.

MATERIAL AND METHODS

Aceclofenac drug was obtained as gift sample from Micro Labs, Bangalore, India. Methyl cellulose, Sodium carboxy methyl cellulose and hydroxyl propyl methyl cellulose were procured from S.D.Fine chemicals, Mumbai. All other chemicals and solvents used in the study were of LR grade.

Ionic gelation process: The ionic gelation processes (Kim C. K., 1992, Hari P. C., 1996) was used to prepare microcapsules. Sodium alginate (1.0 g) and Mucoadhesive polymer like Na CMC (1.0 g), MC (1.0 g) and HPMC (1.0 g) were dissolved in purified water (90ml) to form a homogeneous polymer solution. Core material, Aceclofenac (2.0 g) was added to the polymer solution and mixed thoroughly to form a smooth viscous dispersion. The resulting dispersion was then manually dropped into 10% w/v of 100ml Calcium Chloride solution through a syringe with a needle of size no.18. The added droplets were retained in the Calcium Chloride solution for 15 minutes 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 45^0c for 12 h.

Characterization studies of microcapsules: Particle size distribution and size analysis

For size distribution analysis, different sizes in a batch were separated by sieving, using a range of standard sieves. The amounts retained on different sieves were weighed. The mean particle size of the samples was calculated by the formula. **(**Goudanavar, 2010).

$$d_{average} = \frac{\sum nd}{\sum n}$$

Where n is the frequency weight and d is the mean size.

Determination of flow properties properties: Angle of Repose

The flow properties of different mucoadhesive microcapsules were studied by measuring the angle of repose employing fixed funnel method. The angle of repose was calculated by using the following formula **(**de Souza et al., 2007).

$$\text{Tan } \phi = \frac{h}{r} \text{ or } \phi = \text{Tan}^{-1} \frac{h}{r}$$

Where h = height of the pile, r = radius of the base of the pile.

Bulk density

Accurately weighed amount of the beads and transferred into 50 ml measuring cylinder. It was subjected to tapping for 3 times and the volume occupied by the beads was noted. Bulk density was estimated by using the following formula. Bulk density = Weight of the beads / Bulk volume of the beads **(**Ozyazici et al., 1996).

Tapped density

Accurately weighed amount of the beads and transferred into 50 ml measuring cylinder. It was subjected to tapping for 50 times and the volume occupied by the beads was noted. Tapped density = Weight of the beads / Tapped volume of the beads **(**Ozyazici et al., 1996).

Hausner ratio

It can be calculated by using the formula Hausner's ratio = Tapped density / Bulk density average of three readings were computed. (Vijay Kumar et al., 2001).

Carr's index

It can be calculated by using the following formula

Carr's index (%) = Tapped density – Bulk density / Tapped density X 100.

True density

It was done by using Liquid displacement method by using Specific gravity bottle. This method is possible if the beads

were non porous. For this solvent is selected in such way a loaded beads were insoluble in it. True density = weight of sample/ weight of liquid displaced by solids **(**Ozyazici et al., 1996).

Determination of Moisture content

The formulations were subjected to moisture content study (Indian Pharmacopoeia., 1996); by placing the microcapsules at 60^0C for 10 min in an IR moisture balance.

Surface Accumulation study

This study was conducted to estimate the amount of drug present on the surface of the formulations which may shows immediate release in the dissolution media.50mg of formulation were suspended in 50ml of phosphate buffer (PH6.8). The samples were shaken vigorously for 30 min by hand shaking. The amount of drug leached out from the surface was analyzed spectrophotometrically at 275 nm. Percentage of drug released with respect to entrapped drug in the sample recorded (Abu et al., 1996).

Wall Thickness

Wall thickness of micro capsules was determined by the method of (Luu et al., 1973) using the equation. The wall thickness is correlated with the drug release to study the influence of polymer coat with drug release form microcapsules.

$$h = \frac{\overline{r}(1 - p) d_1}{3[pd_2 + (1 - p) d_1]}$$

Where: h is the wall thickness, r is the arithmetic mean radius of the microcapsules, d_1 is the density of the core material, d_2 is the density of the coat material, p is the proportion of the medicament in the microcapsules.

Drug content evaluation

Aceclofenac content in the microcapsules was estimated by an UV spectrophotometric method based on the measurement of absorbance at 275 nm in phosphate buffer of pH 6.8. Estimated percent drug content was determined from the analysis of 50mg microcapsules and the theoretical percent drug content was calculated from the employed coat: core ratio in the formulation of microcapsules **(**Ozyazici et al., 1996).

Microencapsulation Efficiency

Microencapsulation efficiency was calculated using the following formula. It is used to find the drug entrapment capability of various polymers with respect to the ionic gelation method used for formulation (Sarfaraj et al., 2010).

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

Scanning Electron Microscopy (SEM)

The samples for the SEM analysis were prepared by sprinkling the microcapsules on one side of the double adhesive stub. The stub was then coated with fine gold dust. The microcapsules were then observed with the scanning electron microscope (Leica Electron Optics, Cambridge, USA) at 15 kv (Sarfaraj et al., 2010).

***In Vitro* Release Studies**

Microcapsules (16/22 mesh size (1141.5 µ) containing equivalent to 200 mg of aceclofenac were packed in '5' size hard gelatin capsule and subjected to *in vitro* drug release studies. Release of aceclofenac from the capsule was studied in phosphate buffer of pH 6.8 (900 mL) using a United States Pharmacopoeia (USP) XXIV 8-station dissolution rate test apparatus (Model TDT - 08L, M/s Electro lab, Mumbai, India) with a rotating paddle stirrer at 100 rpm and 37^0C ± 1^0C. Samples of dissolution fluid were wthdrawn through a filter (0.45 µ) at different time intervals and were assayed at 275 nm for aceclofenac content using a Shimadzu UV-1700 double beam spectrophotometer (Shimadzu Corporation, Japan). The drug release experiments were conducted in triplicate (A. Hoffman et al., 1986).

Drug release kinetics

Data obtained from dissolution studies was fitted to various kinetic equations. Were kinetic model used were a zero order equation ($Q=Q_0-k_0t$), first order equation ($\text{Ln } Q=\text{Ln}Q_0-k_1t$) and Higuchi equation($Q=K_ht^{1/2})^{1/2}$), Korsemeyer-peppas equation log Q_t vs. logt, were Q_t, is the cumulative amount of drug released at time t and $Q_0$is the initial amount the drug present in the microcapsules. k_0 is the zero order release rate constant,k_1 is the first order release rate constant and k_h is the diffusion rate constant **(**Chowdary, et al., 2003).

Permeability Studies

The permeability constant P_m of the microcapsules was calculated as described by Koida et al using the equation.

$$P_m = \frac{K \cdot V \cdot H}{A \cdot C_s}$$

Where V is the volume of the dissolution medium (cm^3), H is the wall thickness of the microcapsules (mm), A is the surface area of the microcapsules (cm^2), C_s is the solubility of the core material (mg) in the dissolution medium and K is the release rate constant (mg/hr or hr^{-1}).

For a given microcapsule and under standard testing conditions the values of V, A and C_s remain constant and hence the equation can be written as P_m = K x H where K is the release rate constant and H is the wall thickness of the microcapsule. (Koida Y. et al., 1986).

Evaluation test for mucoadhesion by *In vitro* Wash off test

The mucoadhesive property of the microcapsules was evaluated by an *in vitro* adhesion testing method known as the *in vitro* wash-off method. Freshly excised pieces of intestinal mucosa (2 × 2 cm) from sheep were mounted onto glass slides (3 × 1 inch) with cyanoacrylate glue. Two glass slides were connected with a

suitable support. About 50 microcapsules were spread onto each wet rinsed tissue specimen, and immediately thereafter the support was 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°C contained in a 1 L vessel of the machine. At the end of 30 minutes, at the end of 1 h, and at hourly intervals up to 8 h, the machine was stopped and the number of microcapsules still adhering to the tissue was counted. The test was performed at both gastric pH (0.1N HCl, pH 1.2) and intestinal pH (phosphate buffer, pH 6.8). (Madhusudhana Rao Y. et al., 1998).

RESULTS AND DISCUSSION

Aceclofenac Methyl cellulose (MC) Microcapsules

The ionic gelation process produced uniform microcapsules. Aceclofenac was coated with the mixture of MC and calcium alginate. Microcapsules were developed with 1:1, 1:2 and 1:3 ratios to determine the affect of coating material concentration on the release rate of Aceclofenac. These microcapsules were characterized for diameter, density, flow properties, moisture content, surface accumulation study, drug content and entrapment efficiency. All the formulations indicated fairly good flow property with uniform drug content. The technique also showed good drug entrapment efficiency by the employed polymers. Low coefficient variation in the percent drug content indicated uniformity of the drug content in each batch of microcapsules (Table 1 and 2).

Table 1: Rheological parameters of Aceclofenac microcapsules prepared by ionic gelation method.

Key Polymer used	Core: Coat Ratio	Angle of Repose	Bulk Density (g/cm^3)	Carr's Index	Hausner's Ratio	True Density (g/cm^3)	Average Particle Size (μ)
Methyl cellulose	1:1	25.16	0.29	25.64	1.34	3.63	1073.1
	1:2	19.74	0.43	17.30	1.20	6.45	1127.8
	1:3	15.13	0.53	8.62	1.09	7.63	1224.4
Sodium CMC	1:1	27.49	0.29	32.55	1.45	4.50	1350.58
	1:2	25.13	0.38	26.92	1.36	7.91	1394.51
	1:3	21.43	0.43	23.21	1.28	9.76	1435.51
HPMC	1:1	28.01	0.31	34.0	1.49	6.23	1085.7
	1:2	25.87	0.37	28.8	1.39	10.15	1337.38
	1:3	22.66	0.44	23.2	1.32	11.67	1414.11

Table 2: Drug content, Entrapment efficiency of Aceclofenac microcapsules prepared by ionic gelation method.

Key Polymer used	Core: Coat Ratio	Moisture content (%)	Surface Accumulation study (%)	Drug content	Entrapment efficiency (%)	Wall thickness (μm)	Permeability Coefficient (μm\hr)
Methyl cellulose	1:1	2.0	3.68	43.24	86.48	68.6	1808.98
	1:2	1.0	2.66	41.23	82.47	84.27	1745.23
	1:3	1.6	1.55	38.2	76.40	90.33	1708.14
Sodium CMC	1:1	1.0	4.61	45.68	91.36	60.00	1699.32
	1:2	0.8	3.62	44.08	88.17	72.56	1696.2
	1:3	1.2	3.00	42.36	84.72	81.26	1686.9
HPMC	1:1	1.0	4.96	45.68	91.36	51.36	1488.5
	1:2	1.2	3.93	44.08	88.17	60.12	1484.5
	1:3	1.8	3.15	42.36	84.72	67.45	1451.9

The microcapsules were subjected to *in vitro* release studies by employing 6.8 pH phosphate buffer (Figure 1) and when amount of drug release values were plotted against time straight lines were obtained in all the cases indicating that the rate of drug release from these microcapsules followed zero order kinetics. To ascertain the mechanism of drug release from various microcapsules studied in the present investigation, plots of log fraction of drug released vs log time (peppas plots) were drawn. The plots were found to be linear with all the microcapsules and the exponential coefficient values >0.5 indicating the non-fickian controlled release mechanism (Table 3).

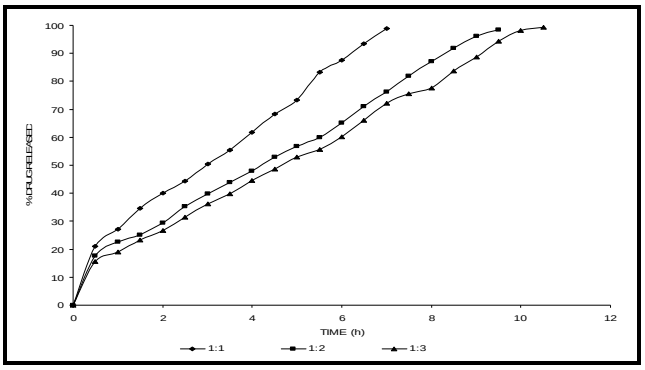

Fig 1. *In vitro* drug release from aceclofenac microcapsule formulations with MC.

Table 3. *In vitro* drug release kinetics from aceclofenac microcapsule formulations prepared by ionic gelation method.

Technique	Core: coat ratio	Correlation coefficient Values				Release Rate Constant K_0 (mg/hr)	T_{50} (hr)	T_{90} (hr)	n
		Zero order	First order	Matrix	Peppas				
MC	1:1	0.9573	0.8389	0.9826	0.9927	26.37	2.7	7.2	0.5958
	1:2	0.9816	0.8670	0.9608	0.9832	20.17	3.8	9.5	0.6470
	1:3	0.9853	0.8179	0.9571	0.9856	18.91	4.3	10.3	0.6701
Na CMC	1:1	0.9433	0.8947	0.9883	0.9949	28.27	2.3	5.9	0.6124
	1:2	0.9405	0.8649	0.9882	0.9961	23.42	2.6	7.1	0.5925
	1:3	0.9715	0.8989	0.9730	0.9917	20.86	3.6	8.9	0.6527
HPMC	1:1	0.9751	0.875	0.9557	0.9686	28.27	2.6	6.5	0.6447
	1:2	0.9775	0.8612	0.9673	0.9861	24.76	3.0	7.5	0.6466
	1:3	0.9725	0.8412	0.9716	0.9917	22.01	3.3	8.5	0.6333

The corresponding correlation coefficients and other release parameters indicated that the release rate was found to decrease with increase in the concentration of coating material applied. The wall thickness of microcapsules was found to be increased with the increase in concentration of coating material applied. There exists a good correlation ship in between wall thickness and release rate constant. The formulation was also subjected to *In-vitro* wash off test in presence of 0.1N HCL and pH 6.8 phosphate buffer. The wash off was relatively rapid in phosphate buffer than in acidic fluid. The results of wash off test indicated fairly good mucoadhesive property of the microcapsules (Table 4).

Table 4: *In vitro* wash-off test to assess mucoadhesive property of aceclofenac microcapsules formulated by employing ionic gelation technique.

Microcapsules	Percent of microcapsules adhering to tissue at 5 times (h)									
	0.1 N HCl, pH 1.2					Phosphate buffer, pH 6.8				
	1	2	4	6	8	1	2	4	6	8
MC	84	81	76	73	71	88	76	66	59	52
NaCMC	78	72	62	57	56	71	62	51	40	33
HPMC	70	64	58	56	54	68	53	41	34	26

Aceclofenac Sodium caboxy methyl cellulose (NaCMC) Microcapsules

This process produced uniform microcapsules with respect to their morphology. Aceclofenac was coated with the mixture of NaCMC and calcium alginate. Microcapsules were developed with 1:1, 1:2 and 1:3 ratios to determine the affect of

coating material concentration on the release rate of Aceclofenac. These microcapsules were characterized for diameter, density, flow properties, moisture content, surface accumulation study, drug content and entrapment efficiency. The results indicated microcapsules good flow property. The technique also showed good entrapment efficiency. Low coefficient variation in the percent drug content indicated uniformity of the drug content in each batch of microcapsules (Table 1 and 2). The microcapsules were subjected to *in vitro* release studies by employing 6.8 pH phosphate buffer and the when amount of drug release values were plotted against time straight lines were obtained in all the cases indicating that the rate of drug release from these microcapsules followed zero order kinetics. To ascertain the mechanism of drug release from various microcapsules studied in the present investigation, plots of log fraction of drug released vs. log time (peppas plots) were drawn. The plots were found to be linear with all the microcapsules and the exponential coefficient values >0.5 indicating the non-fickian controlled release mechanism (Table 3). The corresponding correlation coefficients and other release parameters indicated that the release rate was found to decrease with increase in the concentration of coating material applied. The wall thickness of microcapsules was found to be increased with the increase in concentration of coating material applied. There exists a good correlation ship in between wall thickness and release rate constant. The formulation was also subjected to In-vitro wash off test in presence of 0.1N HCL and pH 6.8 phosphate buffer. The wash off was relatively rapid in phosphate buffer than in acidic fluid. The results of wash off test indicated mucoadhesive property of the microcapsules (Table 4).

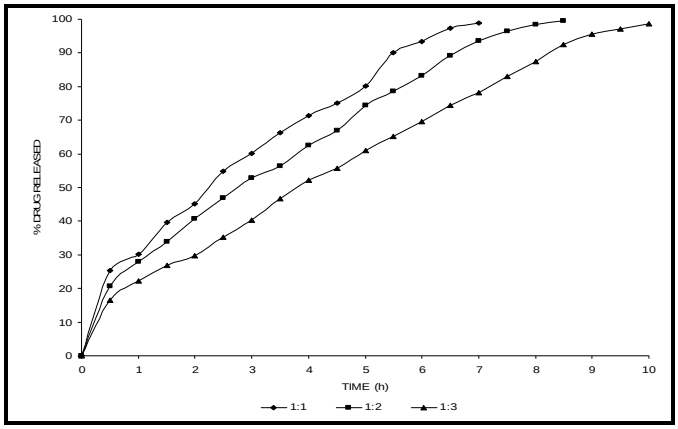

Fig 2. *In vitro* drug release from aceclofenac microcapsule formulations with NaCMC

Aceclofenac Hydroxy propyl methyl cellulose (HPMC) Microcapsules

This process produced uniform microcapsules. Aceclofenac was coated with the mixture of HPMC and calcium alginate. Microcapsules were developed with 1:1, 1:2 and 1:3 ratios to determine the affect of coating material concentration on the release rate of Aceclofenac. These microcapsules were characterized for diameter, density, flow properties, moisture content, surface accumulation study, drug content and entrapment efficiency. The results showed micro capsules with good flow property. The technique also showed good entrapment efficiency. Low coefficient variation in the percent drug content indicated uniformity of the drug content in each batch of microcapsules (Table 1 and 2). The microcapsules were subjected to *In vitro* release studies by employing 6.8 pH phosphate buffer and when amount of drug release values were plotted against time straight lines were obtained in all the cases indicating that the rate of drug release from these microcapsules followed zero order kinetics. To ascertain the mechanism of drug release from various microcapsules studied in the present investigation, plots of log fraction of drug released vs. log time (peppas plots) were drawn. The plots were found to be linear with all the microcapsules and the exponential coefficient values >0.5 indicating the non-fickian controlled release mechanism (Table 3). The corresponding correlation coefficients and other release parameters were indicated that the release rate was found to decrease with increase in the concentration of coating material applied.

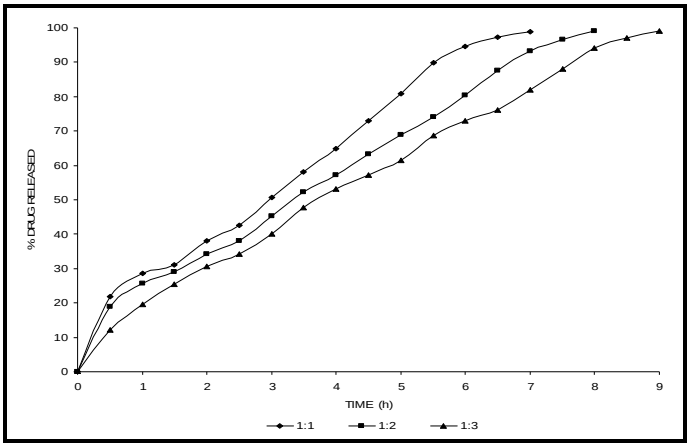

Fig 3. *In vitro* drug release from aceclofenac microcapsule formulations with HPMC

The wall thickness of microcapsules was found to be increased with the increase in concentration of coating material applied. There exists a good correlation ship in between wall thickness and release rate constant. The formulation was also subjected to *In-vitro* wash off test in presence of 0.1N HCL and pH 6.8 phosphate buffers. The wash off was relatively rapid in phosphate buffer than in acidic fluid. The results of wash off test indicated fairly good mucoadhesive property of the microcapsules (Table 4).

To compare the efficacy of these polymers, the formulations has to be formulated with the same technique under similar set of conditions and having same thickness as it is not possible practically to obtain microcapsules having same thickness, Liner regression analysis was applied to obtain the corresponding release rate constants from the microcapsules produced with different polymers. The release rate constants of these microcapsules made with these polymers were found to be permeable to drug and order of drug release form microcapsules was HPMC<NaCMC <MC. (Table 5).

Table 5. Comparison of drug release from MC, NaCMC and HPMC Microcapsules formulated by ionic gelation technique.

Polymer	Regression Equation	Release Rate Constant k_0 (mg/hr) for a wall thickness of 10μ
MC	Y=-0.3469X+50.117	46.6
NaCMC	Y=-0.6274X+66.489	60.12
HPMC	Y=-0.6857X+69.291	62.43

Microcapsules with a coat consisting of alginate and a Mucoadhesive polymer exhibited good Mucoadhesive property in the *in vitro* wash off test .The was-off was relatively rapid in phosphate buffer than in acid fluid. The results represented in (table 4) for wash off test indicated fairly good Mucoadhesive property of the prepared microcapsules. The SEM of the optimized microcapsule batch showed the uniform surface with their morphology (Figure 4 and 5).

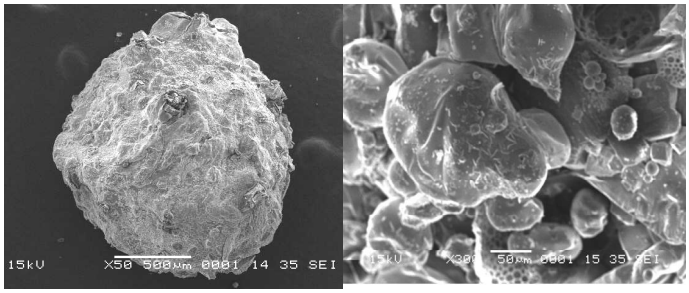

Fig 4 and 5. SEM Photographs of Aceclofenac Microcapsules optimized batch formulated with ionic gelation method.

CONCLUSION

The observations made during study and results obtained showed the suitability of the investigated polymers for microencapsulation of aceclofenac for its sustained release. The ionic gelation method was easy to adopt and also to achieve high drug entrapment efficacy. All the formulations indicated accurate drug content and content uniformity. The *in vitro* drug release studies revealed that the drug release by zero order and non-fickian controlled release mechanism for all the formulations studied. The wash off test showed the mucoadhesive nature of microcapsules that in turn helps for steady and slow drug release which is essential for sustain release dosage form. The studies have further scope for investigation of formulation and process variables with polymer to formulation method to study their influence on drug release at desired rate.

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