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An Approach to Design & Development and Evaluation of Aceclofenac Floating Pellets Using Sodium Alginate and HPMC (HPMC K4M & HPMC K100LV) as polymer

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ABSTRACT: The present study was conducted to investigate the effect of Na-alginate and hydroxyl propyl methyl cellulose (HPMC) polymer combination of Aceclofenac floating pellets. The Aceclofenac pellets were prepared with two different grades of HPMC polymers in the ratio of 2:1, 1:2 and 1.5:1.5 respectively while the amounts of Na-alginate used in the formulations was 3.50, 5.25 and 7.0g. Prepared pellets were evaluated by Particle size and Morphology, Contraction ratio, Moisture content, Friability Test, Swelling study, Buoyancy time and floating time of the pellets were examined on the basis of polymer concentration. The contraction ratio of the particle was highest when pellets were prepared with 1.5% Na-alginate solution and the polymer ratio was 1:2 (BX, BY, BZ). In case of Buoyancy of Pellets, When Alginate concentration was 1% and HPMC K4M & HPMC K100LV ratio was 2:1 then, the Aceclofenac pellets were not floated for long time. When the concentration of Na-Alginate increased to 1.5%, 2%, then all pellets were floated. In case of swelling study, CY, BZ, CZ showed highest swelling of approximately 8% when Na-alginate concentration was (1.5 % , 2%, 2 %) and BY and CY batches showed lowest swelling of 2.9% at 4hrs when Na-alginate concentration was 1.5 %. Friability values for each formulation were recorded in table the values of the preferred formulas are within acceptable limit. Thus, the selection and use of suitable polymers in appropriate ratio is very important in designing floating pellets of Aceclofenac.

KEYWORDS: Na-alginate, Aceclofenac, Methocel, Floating Pellet, Polymer.

1 INTRODUCTION

Some solid dosage forms may be designed to release their medication to the body for absorption rapidly and completely. Sustained release, sustained action, prolonged action, controlled release, extended action, time release, depot, and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. The term "controlled release" has become associated with those systems from which therapeutic agents may be automatically delivered at predefined rates over a long period of time. Products of this type have been formulated for oral, injectable, and topical use, and include inserts for placement in body cavities as well [1]. Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID). It is used for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Aceclofenac has higher anti-inflammatory action than conventional NSAIDs [2]. It is a cytokine inhibitor. Aceclofenac works by blocking the action of a substance in the body called cyclo-oxygenase. Cyclo-oxygenase is involved in the production of prostaglandins (chemicals in the body) which cause pain, swelling and inflammation. Aceclofenac shows high anti-inflammatory, antipyretic and analgesic activity with moderate incidence of gastric side effects and a high therapeutic index [3]. Our literature survey revealed that there were no research publications on floating pellets of Aceclofenac using Na-alginate and hydroxy propylmethyl cellulose blend (Methocel® K4M Premium USP & Methocel® K100LV Premium USP) [4]. Hence, the present research study was designed to develop floating pellets of Aceclofenac using

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Na-alginate, Methocel® K4M Premium USP & Methocel® K100LV Premium USP indifferent amounts as polymers and the Aceclofenac Floating Pellets were evaluated with respect to Particle size and Morphological Study by Scanning Electron Microscopy (SEM), Contraction ratio, Moisture content and Friability Test, Swelling study, Buoyancy time and floating time of the pellets.

2 MATERIALS AND METHODS

2.1 CHEMICALS, REAGENTS AND EQUIPMENTS

Aceclofenac was obtained as a gift sample from United Pharmaceuticals Ltd., Chittagong, Bangladesh. Na-alginate (LOBA Chemicals Pvt. Ltd., India), Methocel® K4M Premium USP and Methocel® K100LV Premium USP were received from BASF Bangladesh Ltd. Calcium chloride (CaCl2) (Merck, Germany), disodium hydrogen phosphate (Merck, Germany), potassium dihydrogen phosphate (Merck, Germany) were collected from Glaxo Smith Kline, Chittagong, Bangladesh. All the chemicals and reagents used for the present research work were of analytical grade. The equipments used in the entire study were Scanning Electron Microscopy (Hitachi S-3400N), Dissolution tester (Erweka-DT70), Digital pH meter (WTW-pH 3000), Magnetic stirrer (Heidolh), Electronic balance (Toledo B303-S) and UV-Visible spectrophotometer (Shimadzu, Japan).

2.2 PREPARATION OF ACECLOFENAC FLOATING PELLETS

Drug, polymers **(**Na-alginate, Methocel® K4M Premium USP & Methocel® K100LV Premium USP) and other excipients were weighed separately according to the proposed formulations of floating pellets. In the present study, nine formulations of *Aceclofenac* floating pellets coded as AX, BX, CX, AY, BY, CY, AZ, BZ and CZ were pr*e*pared using various quantities of polymers and other excipients as shown in table 1.

Table 1. Codes & composition of various formulations of Aceclofenac floating pellets (Weights are expressed in g)

Formulation Materials	Formulations								
	AX	**BX**	**CX**	**AY**	**BY**	**CY**	**AZ**	**BZ**	**CZ**
Aceclofenac	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Sodium alginate	3.50	3.50	3.50	5.25	5.25	5.25	7.00	7.00	7.00
Methocel® K4M USP	2.00	1.00	1.50	2.00	1.00	1.50	2.00	1.00	1.50
Methocel®K100LV USP	1.00	2.00	1.50	1.00	2.00	1.50	1.00	2.00	1.50
Calcium Chloride	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11
Water up to	350	350	350	350	350	350	350	350	350

To prepare the *Aceclofenac* floating pellets, Na-alginate (1% w/w) gel was prepared by overnight soaking with sufficient quantity of demineralized water which was homogenized by using electronic stirring at 4000 rpm for half an hour. Then required amount of Methocel® K4M Premium USP & Methocel® K100LV Premium USP for each formulation was added to form suspension and the resultant mixture was homogenized for half an hour. A requisite quantity of Aceclofenac was also added to the obtained mixture which was further homogenized for another 45min. The homogenized solution was sprayed on to cationic solution (CaCl2, 0.1%) and 15min reaction time was provided for the formation of pellets which were collected and washed for four times with distilled water. Finally, they were dried at room temperature for approximately 12h. During the entire experiments, all of the parameters such as stirring time, rpm, reaction time, drying time and temperature were optimized by error and trial method [5],[6].

2.3 EVALUATION OF ACECLOFENAC FLOATING PELLETS BY SCANNING ELECTRON MICROSCOPY (SEM)

The morphology of Aceclofenac pellets was examined by scanning electron microscopy (SEM) at the Bangladesh Center of Scientific and Industrial Research (BCSIR), Dhaka, Bangladesh). The sample was carefully observed with SEM (Hitachi, S-3400N). The particle sizes (n=2) of Aceclofenac pellets were measured with a digital slide calipers and the contraction ratio of the beads was calculated by dividing the mean volume of dried gel (dried pellet) by that of the hydrogel (wet pellet) [7].

Table 2. Diameter of pellets according to slide calipers

Batch No.	Mean Diameter of Dried pellets (n=10)	Standard Deviation (S.D)	Standard Error (S.E)	S.D±S.E
AX	1.244	0.0442	0.052	0.0442±0.052
BX	1.071	0.0438	0.0139	0.0438±0.0139
CX	1.072	0.051	0.0145	0.051±0.0145
AY	1.071	0.044	0.013	0.044±0.013
BY	1.626	0.034	0.010	0.034±0.010
CY	1.492	0.026	0.008	0.026±0.008
AZ	1.072	0.049	0.0156	0.049±0.0156
BZ	1.267	0.015	0.004	0.015±0.004
CZ	1.339	0.041	0.013	0.041±0.013

n= No. of Pellets

Table 3. The contraction ratio of Aceclofenac pellets

Batch no.	Diameter of hydrogel pellets(mm)	Diameter of dried pellets(mm)	Contraction ratio(CR)
AX	2.28	1.367	0.599
BX	2.313	1.396	0.6035
CX	2.27	1.144	0.504
AY	2.390	1.1134	0.467
BY	1.705	1.458	0.856
CY	1.9615	1.369	0.698
AZ	2.071	1.05	0.508
BZ	2.12	1.283	0.6051
CZ	2.106	1.338	0.631

2.3.1 DETERMINATION OF PELLET MOISTURE CONTENT

In order to assess the performance of the drying process, the residual moisture present in the pellets was determined by weighing the samples before and after the drying process using a thermo balance Mettler Toledo (Made by Mettler Toledo Group US).(Claudio Nastruzzi).

2.3.2 FRIABILITY TEST

Resistance to abrasion was determined using a Friability Test Apparatus (Manufactured by Remi Equipments US). To this end, o.1gm of pellets was uniformly tumbled for 10 min at 25 rpm. Weight loss from the tablet was measured afterwards. (*Claudio Nastruzzi*) [8].

$$\% \text{ Loss of weight} = (\text{loss of weight} \div \text{Initial weight}) \times 100$$

Table 4. Percent (%) of weight loss and moisture content

Batch Number	Percent of weight loss (%)	Moisture content (%)
AX	0.5%	0.3
BX	0	0.1
CX	0	0.4
AY	0.5%	0.3
BY	0	0.2
CY	0	0.4
AZ	0.6%	0.3
BZ	0.5%	0.15
CZ	0.6%	0.1

2.3.3 BOUNCY OF THE PREPARATIONS

Specific gravity of the test solution (distilled water, 0.9% NaCl solution & gastric fluid) was previously measured using a standard pycnometer. Sample pellets (ten pellets) were steeped in 50ml of each test solution and their buoyancy was observed visually. The preparation was considered to have buoyancy in the test solution only when all of the granules floated in it [9].

Table 5. Buoyancy time and Floating Time of Aceclofenac Pellets

Batch No.	*Buoyancy Time*	*Floating Time(hr)*
AX	-	12
BX	-	10
CX	-	14
AY	1	14
BY	1.2	8
CY	1.5	10
AZ	1.7	10
BZ	1.8	8
CZ	1.9	10

`-` means pellets were not bounced.

2.3.4 SWELLING STUDY

The extent of swelling was measured in terms of percent (%) weight gained by the beads. The swelling behavior of formulations of AX, BX, CX, AY, BY, CY, AZ, BZ,CZ of Aceclofenac beads were studied. In this test, 10 mg beads from each formulation were kept in petri dishes containing pH 1.2 phosphate buffers. At the end of 1 hour, the beads were withdrawn, soaked with tissue paper and weighed. Then for every 1 hour, weights of the beads were noted, and the process was continued till the end of 4 hours. Percent weight gained by the beads was calculated by the following formula [10], [11].

$$S.I = \{(Mt-Mo) / Mo\} X 100$$

Where, S.I = swelling index, Mt = weight of beads at time 't' and Mo = weight of beads at time, t = 0.

Table 6. Swelling time of Aceclofenac pellet

Batch No.	*Swelling index (%) (at 4 hours)*
AX	2.9
BX	3.1
CX	3.5
AY	3.6
BY	4.0
CY	5.3
AZ	8.4
BZ	8.2
CZ	9.1

3 RESULTS AND DISCUSSION

3.1 PARTICLE SIZE AND MORPHOLOGY OF ACECLOFENAC PELLETS BY SCANNING ELECTRON MICROSCOPY (SEM)

Aceclofenac floating pellets were prepared at different concentration of sodium alginate and HPMC. The magnifications were used for taking micrographs were 10-3500. (SE-Secondary Electron) Morphology and surface properties of the pellets were found to be affected by the extent of core loading and polymer type.

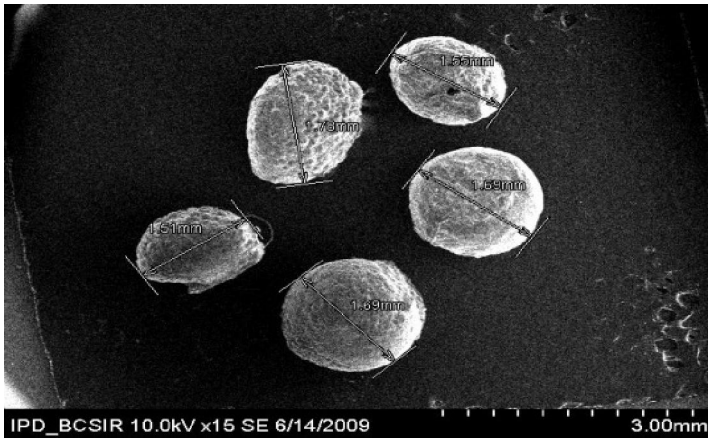

Fig. 1. SEM Photograph showing the diameter of pellets (Batch BY)

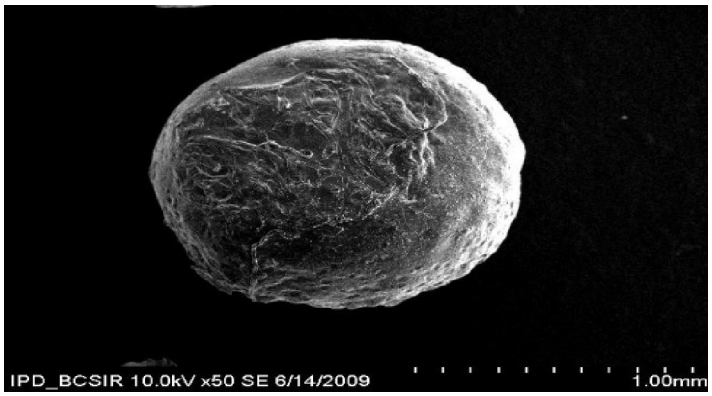

Fig. 2. SEM Photograph showing shape and surface of pellet (Batch BY)

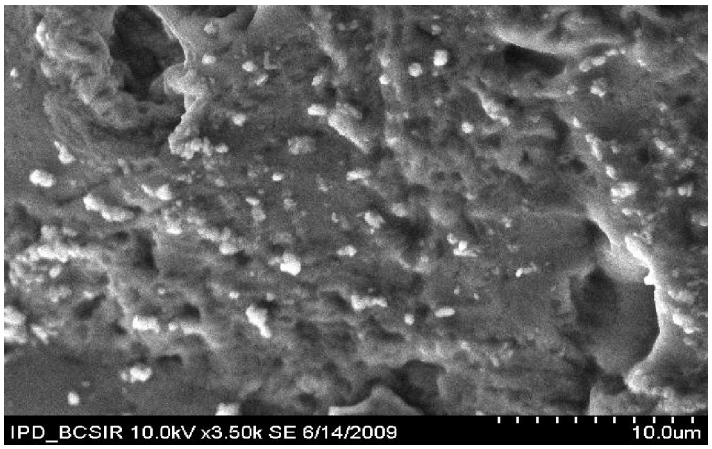

Fig. 3. SEM Photograph showing Drug distribution dried surface (Batch BZ)

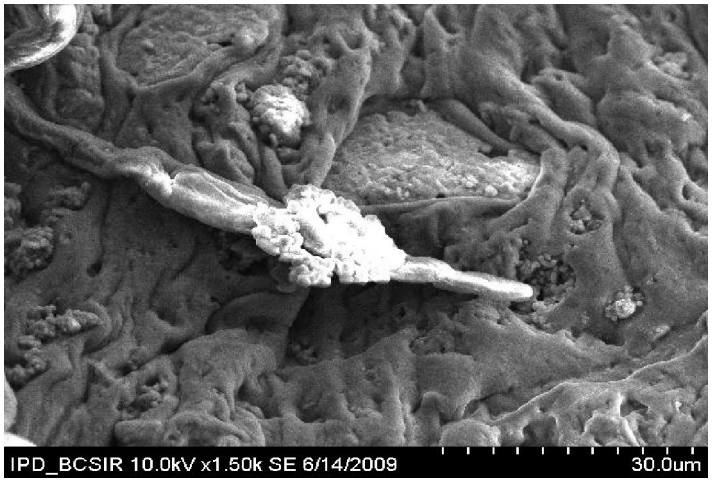

Fig. 4. SEM Photograph showing polymer in dried pellets (Batch AZ)

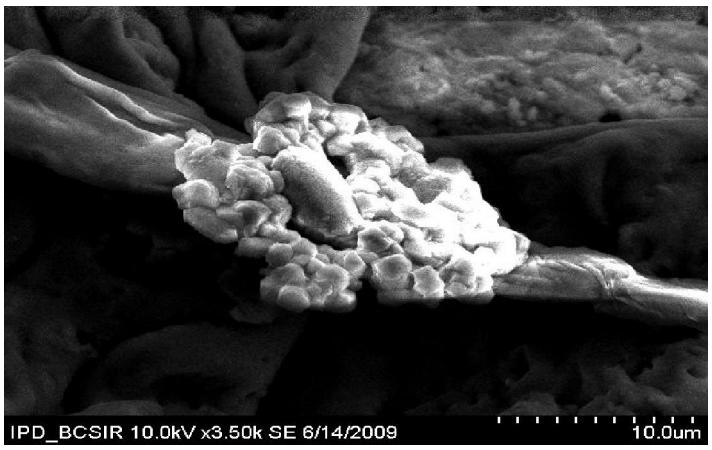

Fig. 5. SEM Photograph showing uncovered drug crystal on the surface (Batch AZ)

It is clear from the figures that magnifications provide the morphology of single pellet with diameter Table 2 and figure 6 and the pellet is roughly spherical in shape [12]. The magnifications also provide the idea of pellet surface, which is relatively smooth. It also showed the drug distribution, though the drug particles are present on the surface but they are scattered and amalgamated. The figures also give the idea of net-work between Na alginate and the polymer for the pelletization and this unique rearrangement satisfy the stability and strength of pellets [13].

SEM was performed on the prepared Aceclofenac pellet to access their surface and morphological characteristics in Figure 1 & 2. These figures also showing the diameter and shape of the pellets. Figure 3 shows the drug distribution in the polymer network. Figure 4 give idea about polymer network in the pellet surface. Figure 5 shows the presence of uncovered drug crystal on the surface could be attributed to formation of drug nucleus in the non-stirred layer surrounding the emulsified droplet during solvent evaporation [14].

3.2 CONTRACTION RATIO

The sizes (n=20) of Aceclofenac pellets were measured with a digital slide caliper (Fisher brand) and the contraction ratio of the bead was calculated by dividing the mean volume of dried gel (dried pellet) by that of the hydrogel (wet pellet) table 3. The contraction of particle increased with the increase of the polymer. This is also affects the release of polymer from Aceclofenac pellets which was showed in figure 7.

Fig. 6. Pellet Diameter Analysis

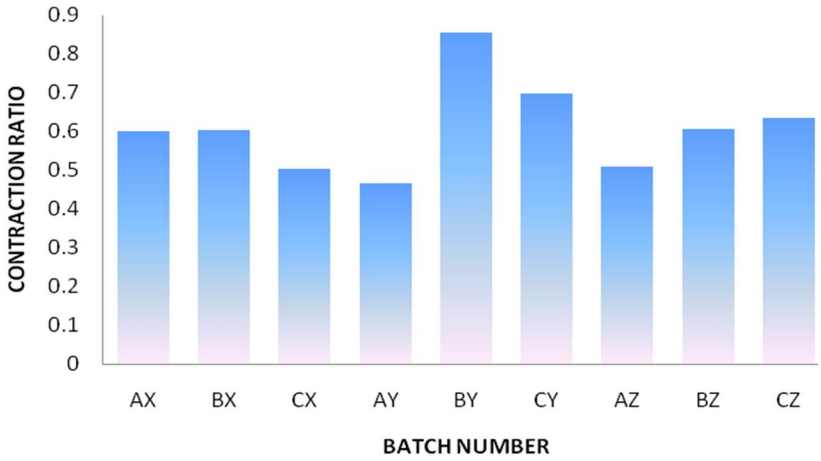

Fig. 7. Contraction ratio of Aceclofenac pellets

3.3 FRIABILITY TEST AND MOISTURE CONTENT OF PELLETS

Percent of loss of weight was minimum for designed batches. So the friability rate of the pellets of the prepared batches can be considered for stable formulation. Moisture content in percentage is shown in the following table 4. The residual moisture content was considerable for stable batches.

3.4 BUOYANCY OF PELLETS

When Alginate concentration was 1% and HPMC K4M & HPMC K100LV ratio was 2%, then, the Aceclofenac pellets were not floated for long time. When the concentration of Na-Alginate increased to 1.5%, 2%, then all pellets were floated in physiological saline, water or HCl solution for long time, even more than 8 hours. Pellets first sink & gradually released Aceclofenac and floated. When Alginate concentration was increased and HPMC concentration was varied like the table table 5 and figure 8 then the beads floated in physiological saline, HCl solution or the buffer solution (pH 1.2), all of which have specific gravity about 1.01. The Buoyancy time and floating time were calculated for each batch which are shown in the table.

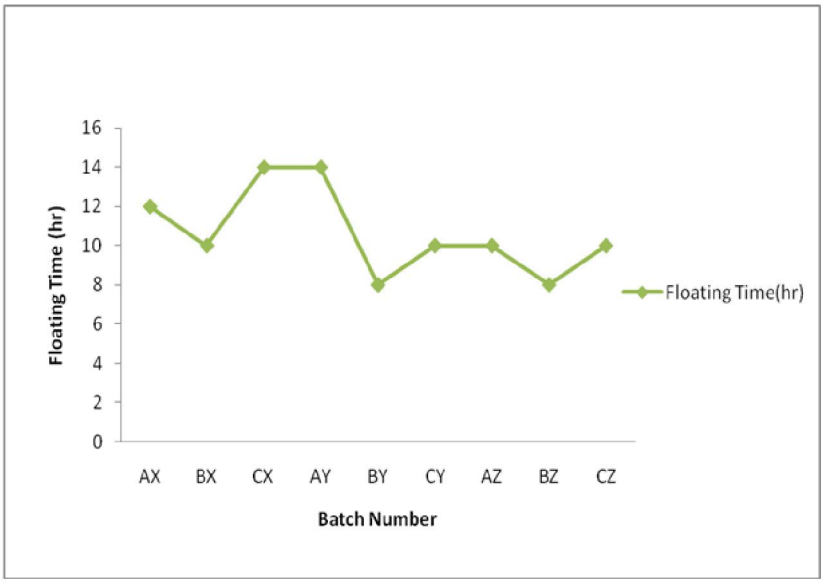

Fig. 8. Floating Time of Aceclofenac Pellets

3.5 SWELLING STUDY

In the formulation were prepared using different ratio of Sodium Alginate and HPMC (K4M & K100LV) polymer blend. Among the 9 batches CY, BZ, CZ contain 1.5 %, 2%, 2 % of Sodium Alginate table 6. These batches showed highest swelling of approximately 8%. BY and CY batches contain 1.5% Sodium Alginate and they showed lowest swelling of 2.9% at 4hrs. So from the result it was evident that with the increasing the polymer content the swelling index also increased figure 9.

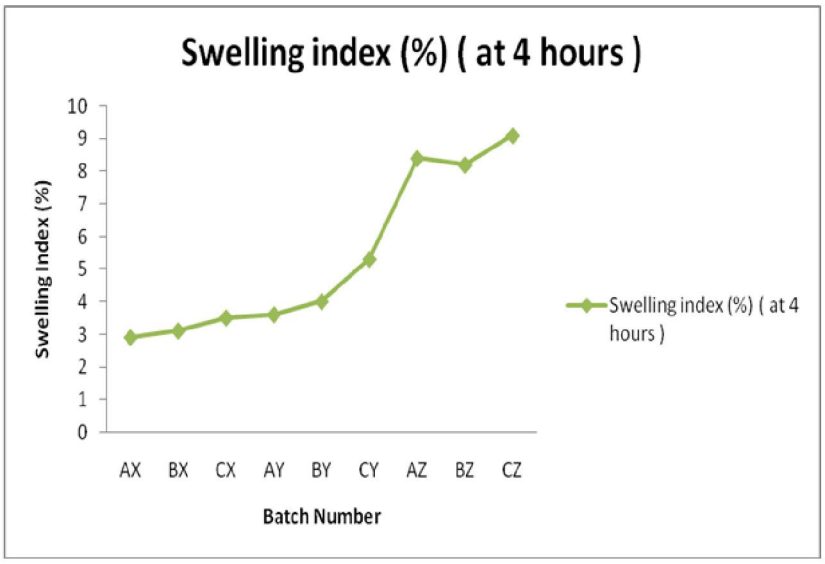

Fig. 9. Swelling time of Aceclofenac pellets

4 CONCLUSION

The Morphological Study and particle size by Scanning Electron Microscopy (SEM), contraction ratio, moisture content, friability Test, swelling study, buoyancy time and floating time of the pellets were investigated in this study. The scanning electron Microscopy gives us idea about the diameter, shape, surface and polymer network of the Aceclofenac floating pellet. The contraction of particle increased with the increase of the polymer. The floating time of Aceclofenac floating pellets increases with increasing drug and polymer concentration. The friability rate and moisture content was within the

acceptable limits. So, it can be concluded that the above parameter of Aceclofenac floating pellets is depend on the appropriate selection of drug polymer ratio. From results obtained, it was concluded that the formulation of Aceclofenac floating pellet containing a combination of both polymers (Sodium Alginate and HPMC (HPMC K4M & HPMC K100LV) was taken as formulation because, it fulfills all the requirement of sustained release dosage form. The further studies should be carried out determine the *in vitro* release kinetics of Aceclofenac floating pellets and to check the reproducibility of pellets by using *in- vitro- in -vivo* correlation .This will help to get information about the efficacy of Na- alginate and HPMC based floating pellets of Aceclofenac in *in- vivo* environment.

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