Global Journal of Pharmacology 9 (3): 282-288, 2015
ISSN 1992-0075

DOI: 10.5829/idosi.gjp.2015.9.3.95281

Effect of Calcium Chloride and Barium Chloride on Release Behavior of Babul (*Acacia nilotica*) Gum Microspheres

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Abstract: The aim of this study was to prepare Diclofenac sodium microspheres using natural polymer, i.e. Babul (*Acacia nilotica*) gum and show the effect of calcium chloride and barium chloride on release behavior of microspheres. The microspheres of Diclofenac sodium were successfully developed by ionic gelation technique in which calcium chloride and barium chloride were used as cross-linking agents. Ten formulations were successfully prepared i.e. F1 to F10. All the formulations were evaluated for micromeritic properties, particle size analysis, percentage yield, drug content, percent moisture loss, swelling index and *in vitro* dissolution studies, etc. The percentage yield of microspheres ranged from 88.23 ± 0.19% to 98.86 ± 0.21%. Batch F8 showed maximum percentage yield as compare to the other formulations. The bulk density and tapped density of babul gum loaded microspheres were in ranged from 0.68 ± 0.004 g/cm^3 to 1.29 ± 0.001 g/cm^3 and 0.80 ± 0.004 g/cm^3 to 1.68 ± 0.051 g/cm^3 respectively. The angle of repose was <25^o showed excellent flow property of the prepared microspheres. Microspheres which were prepared from Barium chloride shows maximum drug concentration as compared to microspheres prepared from Calcium chloride. Batch F1 of calcium chloride and F6 of Barium chloride shows highest drug release for 6hrs. But batch F10 shows controlled release of drug because it shows 79.91% release after 6 hrs. So we concluded that as the concentration of the polymer is increases, the rate of drug release is decreases. Therefore from the above data, we concluded that the prepared microspheres can be used for the controlled delivery of the drug for a prolonged period of time.

Key words: Microspheres · *Acacia nilotica* · Diclofenac Sodium · Ionic Gelation Technique · *In-Vitro* Drug Release

INTRODUCTION

Oral route is one of the best routes since decade for administration of drug. The delivery of drug through oral route is the most common and widely acceptable route through all over world. Due to their inability to restrain and localize at gastro-intestinal tract, oral administration of the drugs in conventional dosage forms have short-term limitations [1]. Some time it also leads to decrease the patient compliance. In order to overcome these problems various types of controlled release formulations have been formulated [2]. Micro-particulate drug delivery systems are considered as one of the system to deliver the drug to the effective biological site with specificity, to maintain the desired concentration, without any effects. It is one of the methods to provide controlled and sustained delivery of drug for prolonged period of time [3]. Carrier technology may provide many approaches for the delivery of drug by coupling the drug to a carrier particle such as Microspheres, nanoparticles and liposomes, which modulate the release and absorption characteristics of the drug [4].

Microspheres play important role in noval drug delivery system. The short residence time at the absorption site is the only limitation for the success of these microspheres [5].

Microspheres are the spherically small particles having diameter 1-1000µm. Microspheres are sometimes referred to as micro particles. Microspheres vary widely in quality, sphericity, uniformity of particle and particle size

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distribution [6]. Microspheres are characteristically free flowing particles and can be manufactured from various synthetic and natural materials [7]. Microspheres are the multi-particulate delivery system and are prepared to control the release of drug from the dosage form which helps to improve the bioavailability, reduces the adverse effect and prolong the action of drug. It also reduce the absorption difference in patients, reduce the dosing frequency and adverse effects during prolong treatment. For reaching to the effective biological site rapidly, it is needed to formulate long acting dosage form [8]. Microspheres based drug delivery system has received a wide appreciation due to its flexibility, cost effectiveness and broad regulatory acceptance. Microspheres provide constant and prolonged therapeutic effect, reduced the GI toxic effects and dosing frequency and thereby improve the patient compliance [9].

Advantage of Microsphere [10-11]:

- The frequency of drug administration is reduced.
- Patient compliance can be improved.
- Drug administration can be made more convenient.
- The blood level oscillation characteristics of multiple dosing of conventional dosage form is reduced, because a more even blood level can be maintained.
- Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.
- Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumor.
- Reliable means of site specific drug targeting by maintaining the desired concentration at the site of interest without any untoward effect.

Disadvantages of Microsphere [12]:

- Administration of sustained release medication does not permit prompt termination of therapy.
- Flexibility in adjustment in dosage regimen is limited.
- Controlled release forms are designed for normal population i.e., on the basis of average drug biological half-lives.
- Economy factors may also be assessed, since most costly process and equipment are involved in manufacturing so many controlled release dosage forms.

Diclofenac Sodium:

Diclofenac Sodium or Sodium 2-[(2, 6-dichlorophenyl) amino] phenyl acetate, is a broadly used non-steroidal anti-inflammatory drug for the treatment of inflammatory conditions such as rheumatoid arthritis, osteoarthritis and ankylosing spondilytis [13].

Babul Gum: *Acacia nilotica*, commonly known as Babul, is indigenous to India and is one of the most useful medicinal plants in India. Its gum, bark, pods, leaves and flowers have medicinal value [14].

MATERIALS AND METHODS

Material: Diclofenac Sodium was received as a gift sample from Aegis Pharmaceuticals Pvt. Ltd., Roorkee. *Acacia nilotica* gum was purchased from Ghaziabad and purification was done in the laboratory. All other excipients were used of analytical grade method.

Purification of *Acacia nilotica* Gum: As described by the author elsewhere, the crude plant material was soaked in warm water for 4 h, boiled for 2 h and kept aside for 2 h for release of gum in water. After that the material was squeezed in a muslin bag to remove the mark from the filtrate. For isolation of gum, equal volume of ethyl alcohol was added in the filtrate to separate the gum. After separation, gum was dried in the oven at 45°C, powdered and passed through sieve #80. The powdered gum was stored in desiccator until further use [15].

Method: The microspheres of diclofenac sodium were prepared by Ionic gelation method. Sodium alginate was dissolved in sufficient amount of water by maintaining the temperature between 40-50°C. Then required amount of polymer was added into it. When the polymer dissolved, drug was added into it and dispersed in the polymeric solution. A 5% Calcium chloride solution and 5% Barium chloride solution were prepared as cross-linking agents and placed on the magnetic stirrer separately. The drug and polymers solution were filled into the syringe and drop wise added into the solutions by using needle size 24#. The prepared microspheres were allowed to stand for 2 hrs for curing in both solutions. After that the prepared microspheres were filtered by using Whatman filter paper and dried using hot air oven at 50°C temperature and stored carefully. Composition of the prepared microspheres is represented in Table 1 [16].

Table 1: Different Concentration of Drug and Polymer

Batch No.	Diclofenac Sodium (mg)	Sodium Alginate (% w/w)	*Acacia nilotica* (% w/w)	Calcium chloride (%w/w)	Barium chloride (%w/w)
F1	200	2.5	2.5	5	-
F2	200	2.5	3.5	5	-
F3	200	2.5	4.5	5	-
F4	200	2.5	5.5	5	-
F5	200	2.5	6.5	5	-
F6	200	2.5	2.5	-	5
F7	200	2.5	3.5	-	5
F8	200	2.5	4.5	-	5
F9	200	2.5	5.5	-	5
F10	200	2.5	6.5	-	5

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Evaluation of Microspheres

Micromeritic Properties: The prepared microspheres were evaluated for their flow properties by determining various parameters like the Bulk density, Tapped density, Angle of repose, Carr's Index, Hausner's ratio. These parameters were calculated by using the following formula [17]:

$$\text{Bulk density} = \frac{\text{Weight of Powder}}{\text{Bulk Volume}} \quad (1)$$

$$\text{Tapped density} = \frac{\text{Weight of Powder}}{\text{Tapped Volume}} \quad (2)$$

$$\text{Carr's ratio} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100 \quad (3)$$

$$\text{Hausner's ratio} = \frac{\text{Bulk density}}{\text{Tapped density}} \quad (4)$$

$$\text{Angle of repose, } \tan ? = h/r \quad (5)$$

Particle Size Determination: Particle size analysis of drug-loaded microspheres was performed by optical microscopy using a compound microscope. A small amount of dry microspheres was suspended in n-hexane (10 ml). A small drop of the suspension thus obtained was placed on a clean glass slide. The slide containing microspheres was mounted on the stage of the microscope and 50 particles were measured using a calibrated ocular micrometer. The average particle size was determined by using equation 6 [18].

$$\text{Particle size Determination} = \frac{\text{Stage reading}}{(\textit{Occular reading})} \times 0.01 \quad (6)$$

Percentage Yield: The percentage yield of each batch was calculated on basis of weight with respect to the weight of starting material. All experiments were carried out in triplicate. The percent yield of prepared microsphere was calculated by using equation7 [19].

$$\%\text{Yield} = \frac{\text{Weight of dried microsphere recovered}}{\text{Weight of drug} + \text{Weight of polymer}} \times 100 \quad (7)$$

Swelling Index: Swelling index helps to examine the ability of the microspheres swell at the absorbing surface by absorbing fluids available at the site of absorption. Microspheres (100mg) were weighed and placed in a Petri-dish containing 100 ml of phosphate buffer pH 6.8 and kept aside and swelling was allowed at 37°C and readings were taken at different time intervals and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically after soaking with filter paper. The swelling index of the microsphere is calculated by using the equation 8 [20].

$$\text{Swelling index} = \frac{\text{Mass of swollen microspheres} - \text{Mass of dry microspheres}}{\text{Mass of dry microspheres}} \times 100 \quad (8)$$

Drug Content Estimation: As described elsewhere, the drug content of the prepared microspheres was determined by the method of extraction of drug present in microspheres. Drug loaded microspheres (100mg) were powdered and extracted in 100 ml Phosphate buffer 6.8 pH for 24 hrs. Then the resultant dispersion of microspheres was sonicated for 30 minutes for complete mixing and filtered through a Whatman filter paper. The concentration of drug present in filtrate was determined spectrophotometrically at 276 nm using 6.8 PH phosphate buffer as blank. Each determination was made in triplicate. The drug content of prepared microsphere was calculated by using equation10 [19].

$$\text{DrugContent} = \frac{\text{Drug content}}{\text{Total amount of microspheres}} \times 100 \quad (9)$$

Percent of Moisture Loss: As describe elsewhere, the Diclofenac Sodium loaded microspheres of different polymers were evaluated for percentage moisture loss which gives idea about its hydrophilic nature. The microspheres were weighed initially and kept in desiccators containing calcium chloride at 37^{0}C for 24 hrs. The final weight was noted when there was no further change in the weight of sample. The percent of moisture loss was calculated by using equation10 [21].

$$\%\text{Moisture loss} = \frac{\text{Initialweight-Finalweight}}{\text{Initialweight}} \times 100 \quad (10)$$

***In vitro* Drug Release Study:** *In vitro* release of Diclofenac Sodium from the microspheres was examined in Phosphate buffer at pH 6.8 using USP (XXI) one stage dissolution rate test apparatus. Microspheres equivalent to 100 mg of drug were taken and packed in capsule suspended in dissolution medium at 50 rpm and 37 ± 0.5°C. An aliquot of 5 ml was withdrawn periodically at different intervals for next 6hrs. Same volume of fresh medium is replaced. The samples were filtered through Whatman filter paper and analyzed at 276 nm for amount of drug released [22].

RESULT AND DISSCUSSION

The Diclofenac sodium microspheres were prepared by ionic gelation technique by using Sodium alginate and babul gum as natural polymers. Ten formulations were prepared, i.e. F1 to F10. First five batches, F1-F5 were prepared by using Calcium chloride as a cross-linking agent whereas remaining five batches, F6-F10 with Barium chloride as cross-linking agent.

The result of the micromeritic properties of Babul gum loaded microspheres prepared with calcium chloride and barium chloride, used as cross-linking agent were shown in table 2 and table 3 respectively. The bulk density and tapped density of babul gum loaded microspheres were in ranged from 0.68 ± 0.004 g/cm^3 to 1.29 ± 0.001 g/cm^3 and 0.80 ± 0.004 g/cm^3 to 1.68 ± 0.051 g/cm^3 respectively. The angle of repose was <25^o showed excellent flow property of the prepared microspheres.

The Carr's index of all batches was in the ranged of 12.50% ± 0.11 to 19.19% ± 0.011, which indicate good packability of microspheres, whereas the Hausner's ratio of the maximum batches was less than 1.25 indicate good flow.

The particle size, percentage yield, swelling index, entrapment efficiency, drug content and moisture loss of formulated microsphers were determined and results are shown in table 4. The particle size of prepared microspheres in radius ranged from 14.55 ± 0.29µm to 21.03 ± 0.13µm. It was observed that the microspheres prepared from babul gum have small particle size. They have moderate size range and shows spherical, oval and irregular shape of microspheres at different batches. It was also observed that the microspheres which were prepared by using Barium chloride shows better spherical and oval shape as compare to that prepared using Calcium chloride.

Table 2: Micromeritic properties of microspheres prepared in Calcium chloride

	Formulation				
Parameter	F1	F2	F3	F4	F5
Bulk density (g/cm^3)	1.27±0.004	0.68±0.004	1.23±0.002	1.18±0.010	0.84±0.002
Tapped density(g/cm^3)	1.49±0.004	0.80±0.004	1.46±0.040	1.41±0.020	0.96±0.020
Angle of repose (^{o})	24.85±0.30	20.23±0.10	24.32±0.100	21.40±0.040	23.26±0.10
Carr's index (%)	14.76±0.30	15.00±0.015	15.75±0.016	16.31±0.005	12.50±0.11
Hausner's ratio	1.14±0.004	1.17±0.004	1.18±1.011	1.19±0.040	1.14±0.004

Table 3: Micromeritic properties of microspheres prepared in Barium chloride

	Formulations				
Parameter	F6	F7	F8	F9	F10
Bulk density (g/cm^3)	1.29±0.001	0.88±0.003	1.43±0.002	1.08±0.020	0.80±0.003
Tapped density(g/cm^3)	1.56±0.010	1.04±0.004	1.68±0.051	1.30±0.024	0.99±0.010
Angle of repose (^{o})	21.63±0.32	23.29±0.10	19.98±0.020	24.80±0.025	20.66±0.10
Carr's index (%)	17.30±0.30	15.38±0.015	14.88±0.016	16.92±0.005	19.19±0.11
Hausner's ratio	1.20±0.004	1.18±0.004	1.17±1.011	1.20±0.040	1.23±0.004

Table 4: Particle size analysis, percentage yield, swelling index, entrapment efficiency, drug content and moisture loss of babul gum loaded microspheres

Formulation code	Particle size (µm)	Percentage yield (%)	Swelling index (%)	Drug content (%)	Moisture Loss (%)
F1	19.46±0.45	89.27±1.16	0.79±0.02	86.31±0.24	2.95±0.01
F2	14.55±0.29	88.23±0.19	0.85±0.13	90.29±0.02	3.96±0.01
F3	16.89±0.12	95.70±0.02	0.88±0.03	87.38±0.01	2.37±0.01
F4	20.18±0.15	90.30±0.86	1.06±0.10	93.65±0.24	3.38±0.02
F5	17.98±0.21	88.56±0.38	1.40±0.06	89.67±0.04	2.88±0.01
F6	15.88±0.23	92.24±0.41	15.88±0.23	82.02±0.01	2.14±0.05
F7	14.98±0.22	92.70±0.12	14.98±0.22	91.28±0.02	2.89±0.02
F8	21.03±0.13	98.86±0.21	21.03±0.13	86.15±0.05	3.06±0.01
F9	18.67±0.01	96.50±0.31	18.67±0.01	93.28±0.12	2.73±0.06
F10	20.87±0.16	97.35±0.28	20.87±0.16	94.98±0.22	3.12±0.01

Table 4: *In vitro* drug release data of babul gum microsphere

	% drug release in phosphate buffer (pH 6.8)									
Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
15	10.26	9.86	11.61	8.99	10.62	11.23	10.68	10.52	9.13	10.95
30	23.64	22.54	21.14	24.32	20.96	22.84	24.11	22.36	21.89	20.56
45	35.82	34.57	36.38	39.13	35.11	36.60	37.31	34.98	35.42	33.99
60	47.18	49.31	46.15	71.73	49.26	49.12	48.69	49.33	43.99	44.65
120	69.32	65.28	59.90	64.35	59.01	66.99	69.35	65.82	56.96	58.25
180	76.19	74.23	70.60	68.17	65.43	79.20	77.90	78.36	69.29	67.10
240	81.48	79.79	78.14	73.22	68.71	86.29	85.26	82.56	75.10	73.84
300	87.35	83.98	81.26	79.43	72.13	90.31	89.01	86.31	80.64	76.38
360	91.35	90.42	84.74	86.38	78.48	93.43	90.52	89.12	86.98	79.91

The percentage yield of microspheres ranged from 88.23% ± 0.19 to 98.86% ± 0.21. The maximum percentage yield was found of F8 formulation and was noted to be 98.86% ± 0.21. It was found that average percentage yield was greater than 80% for all the batches. Thus it shows that ionic gelation technique was acceptable for the preparation of microspheres. It was also noticed that the percentage yield of babul gum loaded microspheres which was prepared in Barium chloride has the maximum yield as compared to microspheres prepared with Calcium chloride.

The swelling index of microspheres prepared from babul gum ranges from 0.75% ± 0.05 to 1.56% ± 0.03. Formulations F1 to F5 showed swelling index of microsphere prepared using Calcium chloride whereas formulation F6 to F10 showed for the microspheres prepared using Barium chloride. From the data we concluded that all formulations shows swelling index in respective order: F1<F2<F3<F4<F5 and F6<F7<F8<F9<F10 respectively. Hence we said that the formulation F5 of Calcium chloride and F10 of Barium chloride possess higher swelling index whereas F6 shows low swelling index. Swelling index studies showed that there was an increase in swelling with increase in polymer concentration.

The % drug content recovered from the babul gum loaded microspheres which were prepared from Calcium chloride ranged from 86.31% ± 0.24 to 93.65% ± 0.24 whereas microspheres prepared from Barium chloride ranged from 82.02% ± 0.01 to 94.98% ± 0.22. It was noticed that the babul gum loaded microspheres which were prepared from Barium chloride shows maximum drug concentration as compared to microspheres prepared from Calcium chloride.

The percent moisture loss of babul gum loaded microspheres which were prepared by using Calcium chloride as a cross-linking agent ranges from 2.37% ± 0.01 to 3.96% ± 0.01 and microspheres prepared using Barium chloride ranges from 2.14% ± 0.05 to 3.12% ± 0.01. It was noticed that the babul gum loaded microspheres prepared from Barium chloride show minimum percent moisture loss as compared to microspheres prepared from Calcium chloride.

The dissolution profile of Diclofenac sodium microsphere was obtained in phosphate buffer at pH 6.8. The *in vitro* dissolution testing was performed for 6 hrs. The *in vitro* drug release studies of babul gum containing microspheres ranged from 8.99% to 93.43%. The maximum in *vitro* drug release was found to be 93.43% at 6 hrs for the formulation F6 which is prepared by using Barium chloride. The drug releases of all formulations were shown in table 4.

The graph plotted between % drug release *vs* time of F1, F2 and F3 formulations are shown in figure 1. Batch F5 of calcium chloride and F10 of barium chloride released less amount of drug in comparison to other batches.

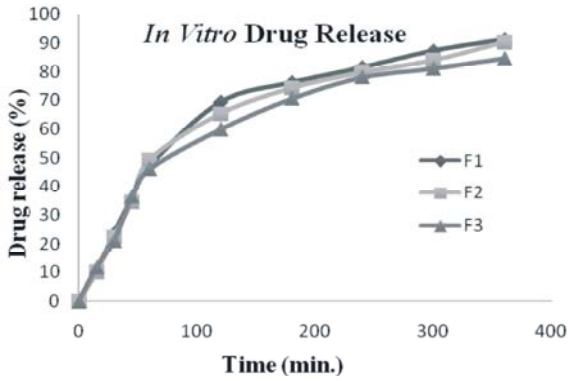

Fig. 1: % drug release of F1, F2 and F3 batches

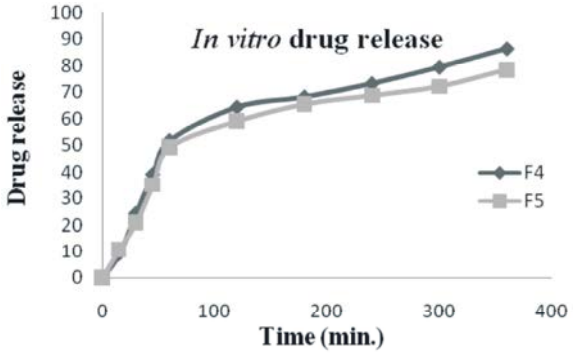

Fig. 2: % drug release of F4 and F5 batches

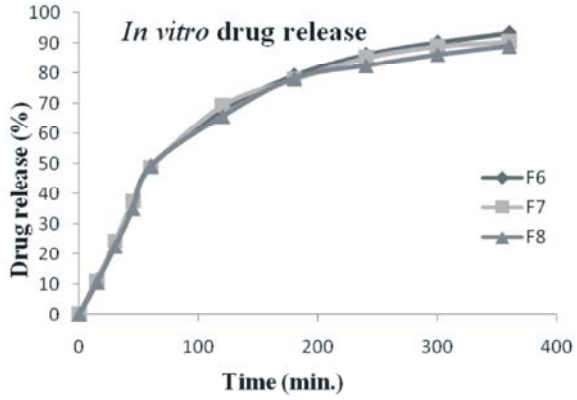

Fig. 3: % drug release of F6, F7 and F8 batches

The graph plotted between % drug release *vs* time of F4 and F5 formulations are shown in figure 2. The graph plotted between % drug release *vs* time of F6, F7 and F8 formulations which were prepared using barium chloride are shown in figure 3 where as graph of formulations F9 and F10 shown in figure 4.

From the *in vitro* release studies, it was concluded that the batch F5 and F10 shows better controlled release of the drug as compare to the other formulations. The graph between % drug release *vs* time of F5 and F10 batches are shown in figure5.

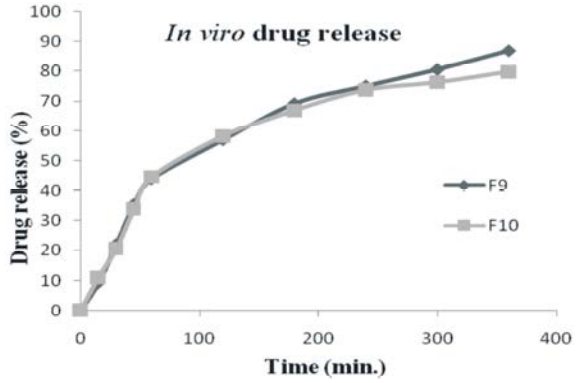

Fig. 4: *In vitro* drug release of F9 and F10 batches

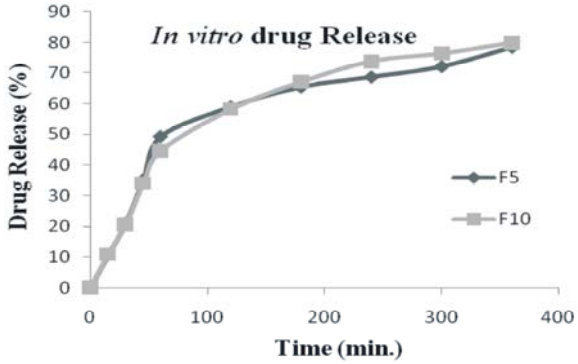

Fig. 5: *In vitro* drug release of F5 and F10 batches

CONCLUSION

The present study reports a novel attempt to prepare microspheres of Diclofenac sodium by using natural polymers like sodium alginate and *Acacia nilotica*. Microspheres of Diclofenac sodium were successfully prepared by ionic gelation method using babul gum and sodium alginate. The microspheres thus obtained were subjected to different tests such as drug content, particle size analysis, percent drug release, swelling index etc. From the experimental results it can be concluded that preformulation studies like solubility, melting point and UV analysis of Diclofenac sodium complied with specifications as per IP. It was also concluded that the batch F5 of calcium chloride and batch F10 of barium chloride shows better release of drug as compare to the other batches. Batch F1 of calcium chloride and F6 of Barium chloride shows highest drug release for 6hrs. It means these batches shows poor release of drug as compare to the other formulations. From the above result, it was also observed that all the formulations shows drug release in ranged 50-60% after 2 hours. But batch F10 shows controlled release of drug because it shows 79.91% release after 6 hrs. So we concluded that as the concentration of the polymer is increases, the rate of drug

release is decreases. Therefore from the above data, we concluded that the prepared microspheres can be used for the controlled delivery of the drug for a prolonged period of time.

ACKNOWLEDGEMENT

Authors would like to thanks Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University, Greater Noida.

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