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Research Article

Design and Optimizations of Aceclofenac Bioadhesive Extended Release Microspheres

G. Prasad [1*], K. Devika [2], P. Varshith [2], B. Shravani [2], E. Pavithra [2] and Ch. Swathi [2]

[1] M. Pharm., Ph. D, Associate Professor, Department of Pharmaceutics, Unity College of Pharmacy, Telangana, India.

[2] B. Pharm, Unity College of Pharmacy, Telangana, India.

***Corresponding Author:** G. Prasad M. Pharm., Ph. D, Associate Professor, Department of Pharmaceutics, Unity College of Pharmacy, Telangana, India.

Received date: October 27, 2021; Accepted date: November 02, 2021; Published date: November 13, 2021

Citation: G. Prasad, K. Devika, P. Varshith, B. Shravani, E. Pavithra and Ch. Swathi (2021) Design and Optimizations of Aceclofenac Bioadhesive Extended Release Microspheres Development; *J. Pharmaceutics and Pharmacology Research* 4(4) DOI: 10.31579/2693-7247/055

Abstract

The oral route for drug delivery is the most popular, desirable, and most preferred method for administrating therapeutically agents for systemic effects because it is a natural, convenient, and cost effective to manufacturing process. Oral route is the most commonly used route for drug administration. Although different route of administration are used for the delivery of drugs, oral route remain the preferred mode. Even for sustained release systems the oral route of administration has been investigated the most because of flexibility in designing dosage forms.

Present controlled release drug delivery systems are for a maximum of 12 hours clinical effectiveness. Such systems are primarily used for the drugs with short elimination half life.

Keywords: microspheres; zaltoprofen; aceclofenac

1. Introduction

For many decades, medication of an acute disease or a chronic disease has been accomplished by delivering drugs to the patients via various pharmaceutical dosage forms like tablets, capsules, pills, creams, ointments, liquids, aerosols, injectable and suppositories as carriers [1]. To achieve and then to maintain the concentration of drug administered within the therapeutically effective range needed for medication, it is often necessary to take this type of drug delivery systems several times in a day. This results in a fluctuated drug level and consequently undesirable toxicity and poor efficiency. This factor as well as other factors such as repetitive dosing and unpredictable absorption leads to the concept of controlled drug delivery systems [2, 3]. The word new or novel in the relation to drug delivery system is a search for something out of necessity. An appropriately designed sustained or controlled release drug delivery system can be major advance toward solving the problem associated with the existing drug delivery system.

The objective of controlled release drug delivery includes two important aspects namely spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue.

Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is be filled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable motility and relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose.

The objective in designing a controlled release system is to deliver the drug at a rate necessary to achieve and maintain a constant drug blood level. This rate should be similar to that achieved by continuous intravenous infusion where a drug is provided to the patient at a rate just equal to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time, i.e., release from the dosage form should follow zero-order kinetics.

2. Aim and Objective

- Aim of the study is to formulate Aceclofenac bioadhesive extended release microspheres using different polymers.

- To formulate the Aceclofenac bioadhesive extended release microspheres using different polymers like sodium alginate, Guar Gum, Locust Bean Gum, Xanthan Gum.
- To choose the better formulation among the prepared formulations which shows better release and bioadhesion.

Preformulation Studies

Spectroscopic Studies
Preparation of 0.1N HCl (pH 1.2)
Take 8ml of HCl in a 1000ml volumetric flask and make up the volume with distilled water

Determination of λMax:

Stock solution (1000µg/ml) of Aceclofenac was prepared in methanol. This solution was appropriately diluted with 0.1N HCl(pH 1.2) and 6.8 pH phosphate buffer to obtain a concentration of 10µg/ ml. The resultant solution was scanned in the range of 200nm to 400nm on UV-Visible spectrophotometer. The drug exhibited a λmax at 252nm and 254nm.

Preparation of Standard Calibration Curve of Aceclofenac:

- 10 mg of Aceclofenac was accurately weighed and dissolved in 10ml of methanol (Stock Solution–I) to get a concentration of 1000 µg/ml.
- From the stock solution- I,1ml of aliquots was taken and suitably diluted with 0.1N HCl (Stock Solution-II) to get concentrations of 100µg/ml.
- From the stock solution- II,aliquots were taken and suitably diluted with 0.1N HCl (pH 1.2) to get concentrations in the range of 2 to 10µg/ml.The absorbance of these samples were analyzed by using UV-Visible Spectrophotometer at 252nm against reference solution 0.1N HCl (pH 1.2).The same procedure is repeated with 6.8pH phosphate buffer also

The Linear Regression Analysis:

The linear regression analysis was done on Absorance points. The standard calibration curve obtained had a Correlation Coefficient of 0.998 with of slope of 0.028 and intercept of 0.004.

Compatibility Studies

A proper design and formulation of a dosage form requires considerations of the physical, chemical and biological characteristics of both drug and excipients used in fabrication of the product. Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product. If the excipient(s) are new and if no previous literature regarding the use of that particular excipient with an active ingredient is available, then compatibility studies are of paramount importance. Hence, before producing the actual formulation, compatibility of Aceclofenac with different polymers and other excipients was tested using the Fourier Transform Infrared Spectroscopy (FT-IR) technique.

Fourier Transform Infrared Spectroscopy (Ft-Ir):

In order to check the integrity (Compatibility) of drug in the formulation,FT-IR spectra of the formulations along with the drug and other excipients were obtained and compared using Shimadzu FT-IR 8400 spectrophotometer. In the present study, Potassium bromide(KBr) pellet method was employed. The samples were thoroughly blended with dry powdered potassium bromide crystals. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded.The FT-IR spectra of the formulations were compared with the FT-IR spectra of the pure drug and the polymers.

3. Method of Preparation

Ionotropic Gelation Method:

Batches of microcapsules were prepared by ionotropic gelation method which involved reaction between sodium alginate and polycationic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate and the mucoadhesive polymer were dispersed in purified water (10 ml) to form a homogeneous polymer mixture. The API, Aceclofenac (100 mg) were added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added through a 22G needle into calcium chloride (4% w/v) solution. The addition was done with continuous stirring at 200rpm. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce rigid spherical microcapsules. The microcapsules were collected by decantation, and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microcapsules and then air-dried.

S. No.	Formulation Code	Drug:Polymer Ratio	Polymer Ratio
1	**T_1**	**1:2.5**	Na alginate : Guar Gum(1.5:0.5)
2	**T_2**	**1:3**	Na alginate : Guar Gum(2:1)
3	**T_3**	**1:3.5**	Na alginate : Guar Gum(2.5:1)
4	**T_4**	**1:4**	Na alginate : Guar Gum(3:1)
5	**T_5**	**1:2.5**	Na alginate: Locust Bean Gum(1.5:0.5)
6	**T_6**	**1:3**	Na alginate: Locust Bean Gum(2:1)
7	**T_7**	**1:3.5**	Na alginate: Locust Bean Gum(2.5:1)
8	**T_8**	**1:4**	Na alginate: Locust Bean Gum(3:1)
9	**T_9**	**1:2.5**	Na alginate: Xanthan gum (1.5:0.5)
10	**T_{10}**	**1:3**	Na alginate: Xanthan gum (2:1)
11	**T_{11}**	**1:3.5**	Na alginate: Xanthan gum (2.5:1)
12	**T_{12}**	**1:4**	Na alginate: Xanthan gum (3:1)

Table 1: *Prepared formulation of Bioadhesive Microcapsules*

Figure 1. *Photograph of prepared microcapsule*

Characterization of Microcapsules:

Percentage yield

The percentage of production yield was calculated from the weight of dried microsphe-res recovered from each batch and the sum of the initial weight of starting materials. The percentage yield was calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Practical mass (Microcapsules)}}{\text{Theoretical mass (Polymer + Drug)}} \times 100$$

Drug entrapment efficiency:

Microcapsules equivalent to 100 mg of the drug Aceclofenac were taken for evaluation. The amount of drug entrapped was estimated by crushing the microcapsules. The powder was transferred to a 100 ml volumetric flask and dissolved in 10ml of methanol and the volume was made up using simulated gastric fluid pH 1.2. After 24 hours the solution was filtered through Whatmann filter paper and the absorbance was measured after suitable dilution spectrophotometrically at 252 nm. The amount of drug entrapped in the microcapsules was calculated by the following formula,

$$\% \text{ Drug Entrapment Efficiency} = \frac{\text{Experimental Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Particle size analysis:

Samples of the microparticles were analyzed for particle size by optical microscope. The instrument was calibrated and found that 1unit of eyepiece micrometer was equal to 12.5µm. Nearly about 100 Microparticles sizes were calculated under 45x magnification. The average particle size was determined by using the Edmondson's equation:

$$D_{mean} = \frac{nd}{n}$$

Where,

n – Number of microcapsules observed

D – Mean size range

Swelling study:

Swelling ratio of different dried microcapsules were determined gravimetrically in simulated gastric fluid pH 1.2 .The microcapsules were removed periodically from the solution, blotted to remove excess surface liquid and weighed on balance. Swelling ratio (% w/v) was determined from the following relationship:

$$\text{Swelling ratio} = \frac{(Wt - W0)}{(W0)} \times 100$$

Where W0 & Wt are initial weight and Final weight of microcapsules respectively.

Evaluation of mucoadhesive property:

The mucoadhesive property of microcapsules was evaluated by an in vitro adhesion testing method known as wash-off method. Freshly excised pieces of goat stomach mucous were mounted on to glass slides with cotton thread. About 20 microcapsules were spread on to each prepared glass slide and immediately thereafter the slides were hung to USP II tablet disintegration test, when the test apparatus was operated, the sample is subjected to slow up and down movement in simulated gastric fluid pH 1.2 at 37^0C contained in a 1-litre vessel of the apparatus. At an interval of 1 hour up to 8 hours the machine is stopped and number of microcapsules still adhering to mucosal surface was counted.

$$\% \text{ Mucoadhesion} = \frac{\text{Number of microcapsules adhered}}{\text{Number of microcapsules applied}} \times 100$$

In vitro drug release study:

The dissolution studies were performed in a fully calibrated eight station dissolution test apparatus (37 ± 0.5^0C, 50 rpm) using the USP type – I rotating basket method in simulated gastric fluid pH 1.2 (900ml). A quantity of accurately weighed microcapsules equivalent to 100mg Aceclofenac each formulation was employed in all dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 252nm. At the same time the volume withdrawn at each time intervals were replenished immediately with the same volume of fresh pre-warmed

simulated gastric fluid pH 1.2 maintaining sink conditions throughout the experiment.

4. Results and Discussion

4.1. Preformulation Studies

4.1.1. Spectroscopic Studies

Determination of λmax

A solution of 10µg/ml of Aceclofenac was scanned in the range of 200 to 400nm. The drug exhibited a λmax at 252nm in simulated gastric fluid pH 1.2 and had good reproducibility. Correlation between the concentration and absorbance was found to be near to 0.998, with a slope of 0.028 and intercept of 0.004.

Calibration curve of Aceclofenac in simulated gastric fluid pH 1.2

Concentration (µg /ml)	Absorbance
2	0.051
4	0.110
6	0.163
8	0.221
10	0.290

Table 4.1 *shows the calibration curve data of Aceclofenac in simulated gastric fluid pH 1.2 at 252nm and 254nm in 6.8pH phosphate buffer.*

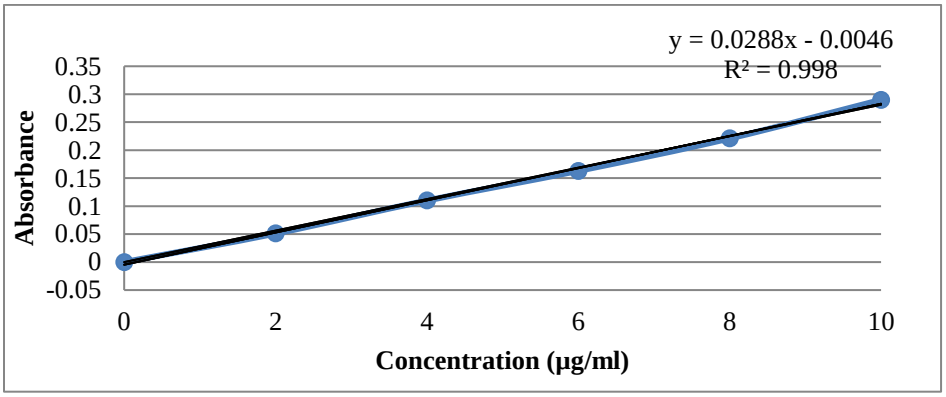

Figure 4.1(a): *Standard graph of Aceclofenac in simulated gastric fluid pH 1.2*

S. No.	Concentration (µg/ml)	Absorbance*
1	2	0.193
2	4	0.34
3	6	0.461
4	8	0.579
5	10	0.709
Correlation Coefficient = 0.9985 y = 0.0636x + 0.0751		

Table 4.1 (b): *Calibration curve data for Aceclofenac in 6.8pH phosphate buffer*

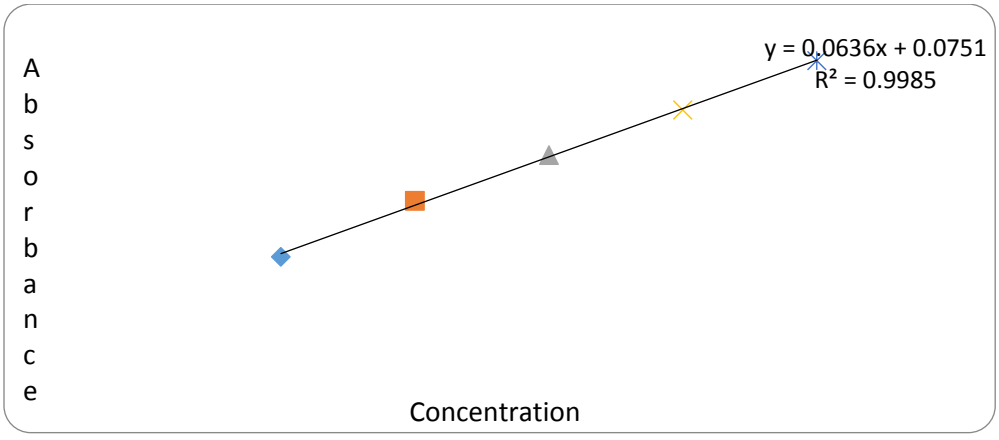

Figure 4.1(b): *Standard graph of Aceclofenac in 6.8pH phosphate buffer*

Compatibility Studies

Drug polymer compatibility studies were carried out using Fourier Transform Infra-Red spectroscopy to establish any possible interaction of Drug with the polymers used in the formulation. The FT-IR spectra of the formulation were compared with the FTIR spectra of the pure drug.

Evaluation and Characterisation of Microspheres

Percentage Yield

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug-polymer solution, adhesion of polymer solution to the magnetic bead and microspheres lost during the washing process. The percentage yield was found to be in the range of 80 to 88% for microspheres containing sodium alginate along with GUAR GUMas copolymer, 62.22 to 87% for microspheres containing sodium alginate along with LOCUST BEAN GUM as copolymer and 80 to 87.5% for microspheres containing sodium alginate along with XANTHAN GUMas copolymer. The percentage yield of the prepared microspheres is recorded in Table 6.2 and displayed in Figures 6.4 to 6.6.

Drug Entrapment Efficiency

Percentage Drug entrapment efficiency of Aceclofenac ranged from 82.66 to 88.66% for microspheres containing sodium alginate along with GUAR GUMas copolymer, 53.2 to 76.66% for microspheres containing sodium alginate along with Locust Bean Gum as copolymer and 66.73 to 79.2% for microspheres containing sodium alginate along with Xanthan Gum as copolymer. The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency. The % drug entrapment efficiency of the prepared microspheres is displayed in Table 6.3, and displayed in Figures.

S.No.	Formulation code	% yield	Drug Content (mg)	% Drug entrapment efficiency
1	T_1	80	12.40	82.66
2	T_2	83.33	12.66	84.4
3	T_3	85	12.70	84.66
4	T_4	88	13.29	88.66
5	T_5	62.22	8.07	53.2
6	T_6	80	8.25	55
7	T_7	80	10.33	68.86
8	T_8	87	11.5	76.66
9	T_9	80	10.01	66.73
10	T_{10}	86	10.5	70
11	T_{11}	86.66	11.25	75
12	T_{12}	87.5	11.88	79.2

Table 4.2: *Percentage yield and percentage drug entrapment efficiency of the prepared microspheres*

Particle Size Analysis

The mean size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to an increased droplet size and finally a higher microspheres size. Microspheres containing sodium alginate along with Guar gum as copolymer had a size range of 512µm to 826µm, microspheres containing sodium alginate along with Locust Bean Gum as copolymer exhibited a size range between 517µm to 834µm and microspheres containing sodium alginate along with XANTHAN GUM as copolymer had a size range of 664µm to 903µm. The particle size data is presented in Tables 6.3 to 6.13 and displayed in Figures. The effect of drug to polymer ratio on particle size is displayed in Figure. The particle size as well as % drug entrapment efficiency of the microspheres increased with increase in the polymer concentration.

Particle Size Range (µm)	Midpoint Size Range (d)	Frequency (n)	Average Particle Size (µm)
200-300	250	9	512 µm
300-400	350	13	
400-500	450	17	
500-600	550	29	
600-700	650	32	
		$\sum n=100$	

Table 4.3: *Particle size data of T_1*

Particle Size Range (µm)	Midpoint Size Range (d)	Frequency (n)	Average Particle Size (µm)
300-400	350	15	617 µm
400-500	450	13	
500-600	550	18	
600-700	650	12	
700-800	750	28	
800-900	850	14	

		∑n=100	

Table 4.4: *Particle size data of T_2*

Particle Size Range (µm)	Midpoint Size Range (d)	Frequency (n)	Average Particle Size (µm)
400-500	450	10	711 µm
500-600	550	12	
600-700	650	18	
700-800	750	27	
800-900	850	33	
		∑n=100	

Table 4.5: *Particle size data of T_3*

Particle Size Range (µm)	Midpoint Size Range (d)	Frequency (n)	Average Particle Size (µm)
500-600	550	6	826 µm
600-700	650	12	
700-800	750	16	
800-900	850	32	
900-1000	950	34	
		∑n=100	

Table 4.6: *Particle size data of T_4*

Particle Size Range (µm)	Midpoint Size Range (d)	Frequency (n)	Average Particle Size (µm)
200-300	250	8	517 µm
300-400	350	12	
400-500	450	18	
500-600	550	29	
600-700	650	33	
		∑n=100	

Table 4.7: *Particle size data of 5*

Particle Size Range (µm)	Midpoint Size Range (d)	Frequency (n)	Average Particle Size (µm)
300-400	350	12	642 µm
400-500	450	11	
500-600	550	15	
600-700	650	14	
700-800	750	31	
800-900	850	17	
		∑n=100	

Table 4.8: *Particle size data of T_6*

Particle Size Range (µm)	Midpoint Size Range (d)	Frequency (n)	Average Particle Size (µm)
400-500	450	6	792 µm
500-600	550	10	
600-700	650	8	
700-800	750	19	
800-900	850	26	
900-1000	950	31	
		∑n=100	

Table 4.9: *Particle size data of T_7*

Particle Size Range (µm)	Midpoint Size Range (d)	Frequency (n)	Average Particle Size (µm)
500-600	550	6	
600-700	650	11	
700-800	750	13	

800-900	850	33	834µm
900-1000	950	37	
		∑n=100	

Table 4.10: *Particle size data of T_8*

Particle Size Range (µm)	Midpoint Size Range (d)	Frequency (n)	Average Particle Size (µm)
400-500	450	18	664µm
500-600	550	19	
600-700	650	18	
700-800	750	21	
800-900	850	24	
		∑n=100	

Table 4.11: *Particle size data of T_9*

Particle Size Range (µm)	Midpoint Size Range (d)	Frequency (n)	Average Particle Size (µm)
400-500	450	8	774µm
500-600	550	12	
600-700	650	10	
700-800	750	17	
800-900	850	24	
900-1000	950	29	
		∑n=100	

Table 4.12: *Particle size data of T_{10}*

Particle Size Range (µm)	Midpoint Size Range (d)	Frequency (n)	Average Particle Size (µm)
500-600	550	8	814µm
600-700	650	14	
700-800	750	17	
800-900	850	28	
900-1000	950	33	
		∑n=100	

Table 4.13: *Particle size data of T_{11}*

Particle Size Range (µm)	Midpoint Size Range (d)	Frequency (n)	Average Particle SIZE (µm)
600-700	650	2	903 µm
700-800	750	3	
800-900	850	35	
900-1000	950	60	
		∑n=100	

Table 4.14: *Particle size data of T_{12}*

The swelling ratio is expressed as the percentage of water in the hydrogel at any instant during swelling. Swell ability is an important characteristic as it affects mucoadhesion as well as drug release profiles of polymeric drug delivery systems. Swell ability is an indicative parameter for rapid availability of drug solution for diffusion with greater flux. Swell ability data revealed that amount of polymer plays an important role in solvent transfer. It can be concluded from the data shown in Table 6.14 that with an increase in polymer concentration, the percentage of swelling also increases. Thus we can say that amount of polymer directly affects the swelling ratio. As the polymer to drug ratio increased, the percentage of swelling increased from 28 to 85% for microspheres containing sodium alginate along with GUAR Gum as copolymer, 24 to 64% for microspheres containing sodium alginate along with Locust Bean Gum as copolymer and 31 to 85 for microspheres containing sodium alginate along with Xanthan Gum as copolymer. The percentage of swelling of the prepared microspheres is displayed in Figures. The effect of drug to polymer ratio on percentage swelling is displayed in Figure.

S.NO.	Formulation Code	Initial (Wt)	Final (Wt)	Percentage Swelling
1	T_1	10	12.8	28
2	T_2	10	14.2	42
3	T_3	10	16.2	62
4	T_4	10	18.5	85
5	T_5	10	12.4	24

6	T_6	10	13.9	39
7	T_7	10	15.5	55
8	T_8	10	16.4	64
9	T_9	10	13.1	31
10	T_{10}	10	15.3	53
11	T_{11}	10	16.7	67
12	T_{12}	10	18.5	85

Table 4.15: *Percentage swelling of the prepared microspheres*

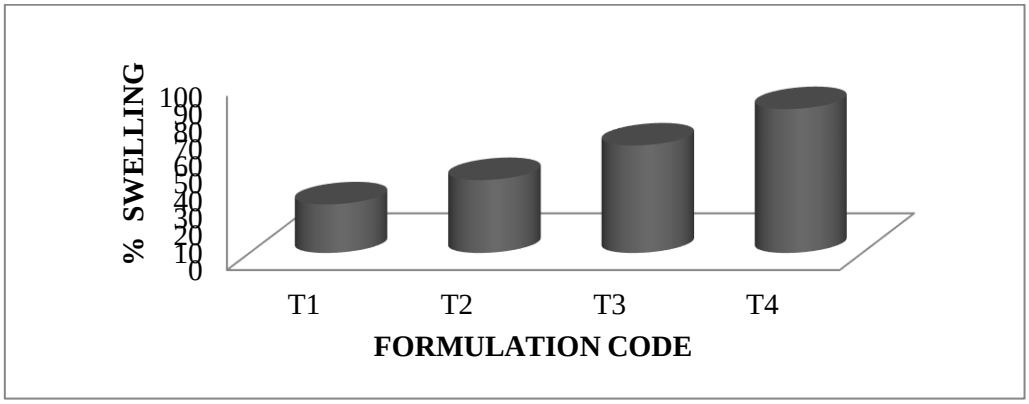

Figure 4.2: *Percentage swelling of microspheres containing sodium alginate along with Guar Gumas copolymer*

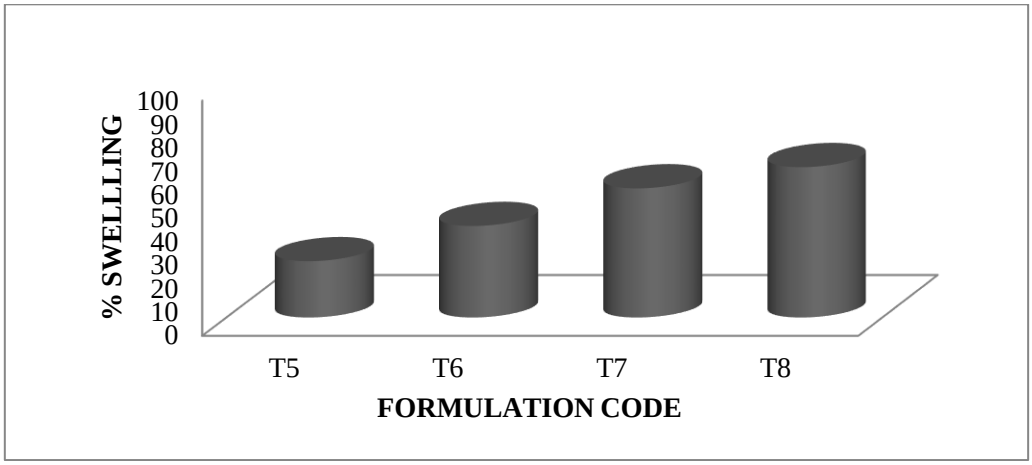

Figure 4.3: *Percentage swelling of microspheres containing sodium alginate along with Locust Bean Gum as copolymer*

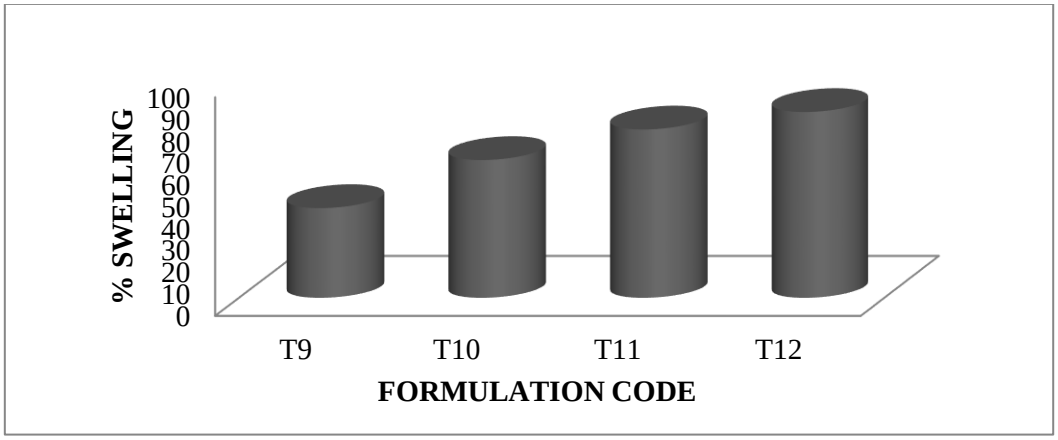

Figure 4.4: *Percentage swelling of microspheres containing sodium alginate along with XANTHAN Gumas copolymer*

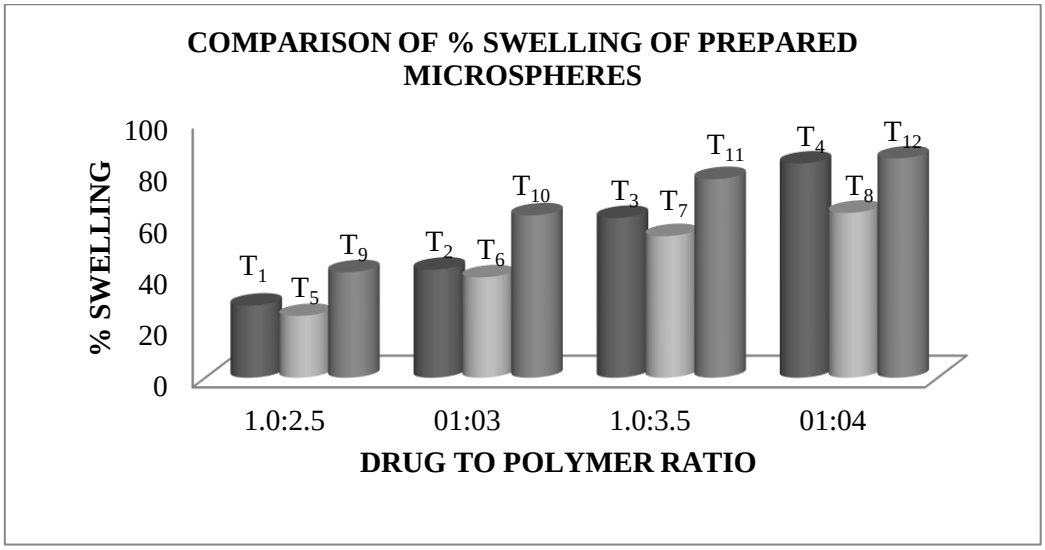

Figure 4.5: *Comparison of percentage swelling of prepared microspheres*

In-Vitro Mucoadhesion Test

As the polymer to drug ratio increased, microspheres containing sodium alginate along with Guar Gum as copolymer exhibited % mucoadhesion ranging from 65 to 85%, microspheres containing sodium alginate along with Locust Bean Gum as copolymer exhibited % mucoadhesion ranging from 60 to 75% and microspheres containing sodium alginate along with Xanthan Gum as copolymer exhibited % mucoadhesion ranging from 60 to 80%.

The rank of order of mucoadhesion is Guar Gum> Xanthan Gum > Locust Bean Gum. The results of in-vitro mucoadhesion test are compiled in Table 6.15. Effect of polymer proportion on % mucoadhesion is depicted in Figures 6.14 to 6.16 and comparative depiction of % mucoadhesion is depicted in Figure 6.17.

S.NO.	Formulation Code	No. of Microspheres		Percentage Mucoadhesion
		Initial	Final	
1	T_1	20	13	65
2	T_2	20	14	70
3	T_3	20	15	75
4	T_4	20	17	85
5	T_5	20	12	60
6	T_6	20	13	65
7	T_7	20	14	70
8	T_8	20	15	75
9	T_9	20	12	60
10	T_{10}	20	14	70
11	T_{11}	20	15	75
12	T_{12}	20	16	80

Table 4.16: *Percentage mucoadhesion of the prepared microspheres*

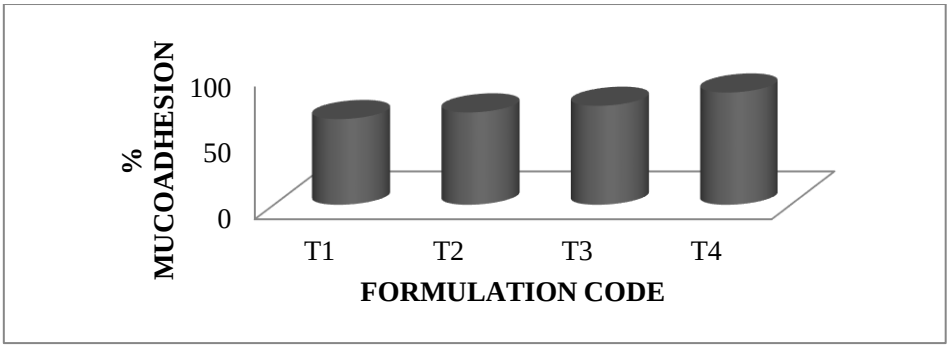

Figure 4.6: *Percentage mucoadhesion of microspheres containing sodium alginate along with Guar Gumas copolymer*

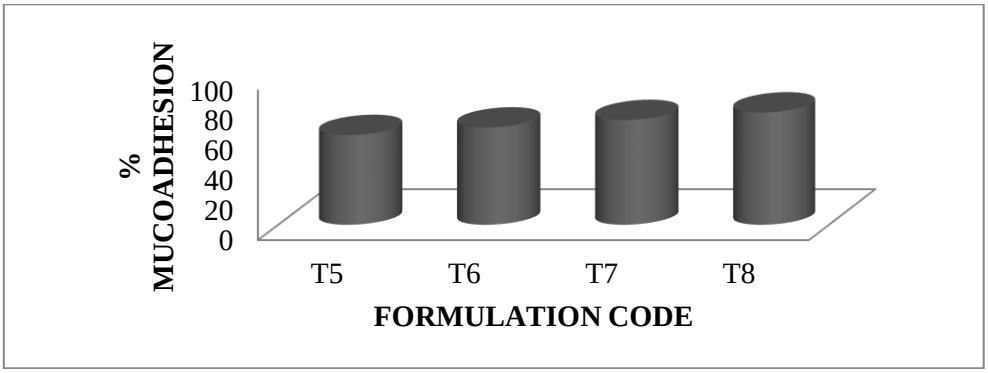

Figure 4.7: *Percentage mucoadhesion of microspheres containing sodium alginate along with Locust Bean Gum as copolymer*

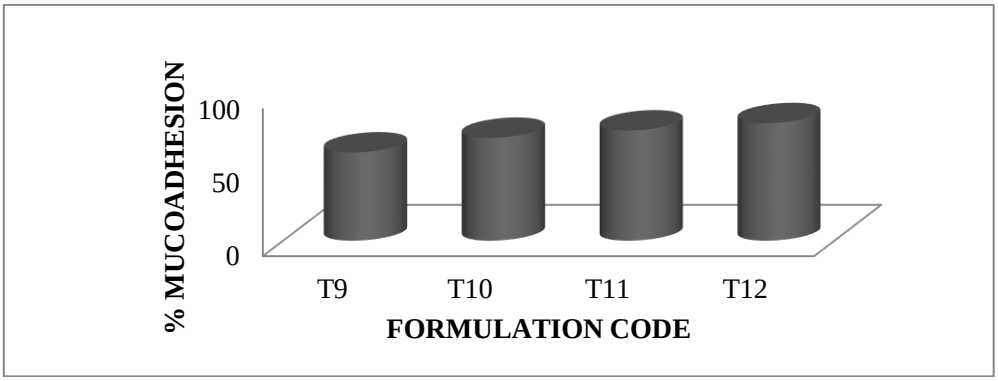

Figure 4.8: *Percentage mucoadhesion of microspheres containing sodium alginate along with Xanthan Gumas copolymer*

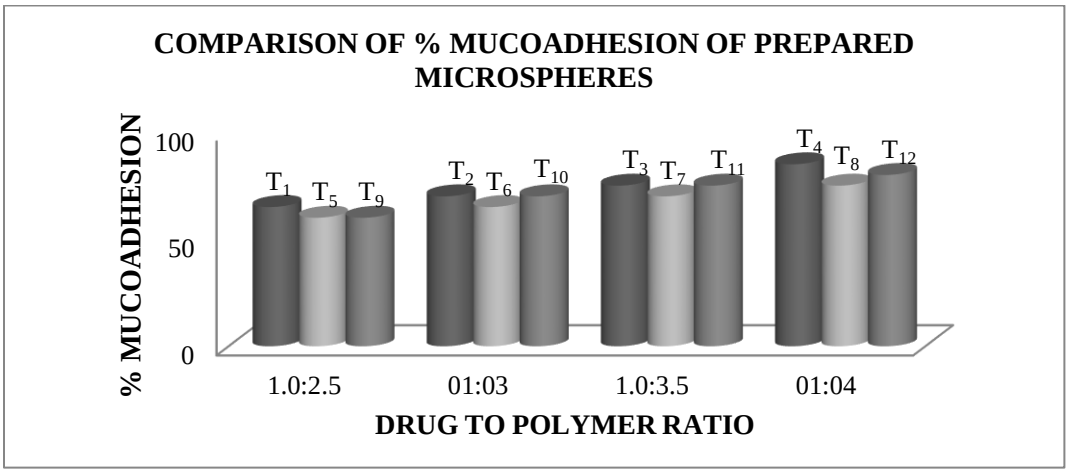

Figure 4.9: *Comparison of percentage mucoadhesion of prepared microspheres*

In-Vitro Drug Release Studies

Dissolution studies of all the formulations were carried out using dissolution apparatus USP type I. The dissolution studies were conducted by using dissolution media, pH 1.2.for fisrt 2hr and then it was eplaced with 6.8ph phosphate buffer The results of the in-vitro dissolution studies of formulations T1 to T4, T5 to T8 and T9 to T12 are shown in table. The plots of Cumulative percentage drug release Vs Time. Figure shows the comparison of % CDR for formulations T1 to T4, figure for formulations T5 to T8 and figure 6.26 for formulations T9 to T12. Korsmeyer-Peppas plots of Aceclofenac microspheres formulations T1 to T12 are displayed in figures.

The formulations T1, T2, T3 and T4 containing Sodium alginate along with GUAR GUMas copolymer showed a maximum release of 92.66% after 9 hours, 90.66% after 10 hours, 90.6% after 11 hours and 94.66% after 12 hours respectively.

The formulations T5, T6, T7 and T8 containing Sodium alginate along with Locust Bean Gum as copolymer showed a maximum release of 92.22% after 9 hours, 91.33% after 10 hours, 89.55% after 11 hours and 90.66% after 12 hours respectively.

The formulations T9, T10, T11 and T12 containing Sodium alginate along with Xanthan Gumas copolymer showed a maximum release of 92.6% after 9 hours, 91.3% after 10 hours, 90% after 11 hours and 92.44% after 12 hours respectively.

This shows that more sustained release was observed with the increase in percentage of polymers. As the polymer to drug ratio was increased the

extent of drug release decreased. A significant decrease in the rate and extent of drug release is attributed to the increase in density of polymer matrix that results in increased diffusion path length which the drug molecules have to traverse. The releaseof the drug has been controlled by swelling control release mechanism. Additionally, the larger particle size at higher polymer concentration also restricted the total surface area resulting in slower release.

TIME (h)	CUMULATIVE PRECENT OF DRUG RELEASED			
	T_1	T_2	T_3	T_4
0	0	0	0	0
1	24.88	21.11	18.66	15.88
2	31.55	31.55	25.11	24.22
3	42.44	39.77	35.44	32.66
4	53.55	47.77	40.66	39.33
5	62	56.66	52	47.55
6	74.66	62.44	57.33	55.77
7	83.55	69.55	63.11	61.77
8	89.33	75.33	69.11	69.55
9	92.66	84.66	75.33	77.55
10	85.55	90.66	82.66	85.55
11	80.22	84.22	90.66	90.66
12	78.88	80.88	89.55	94.66

Table 4.17: *In-Vitro drug release data of Aceclofenac microspheres containing sodium alginate along with Guar Gum as copolymer*

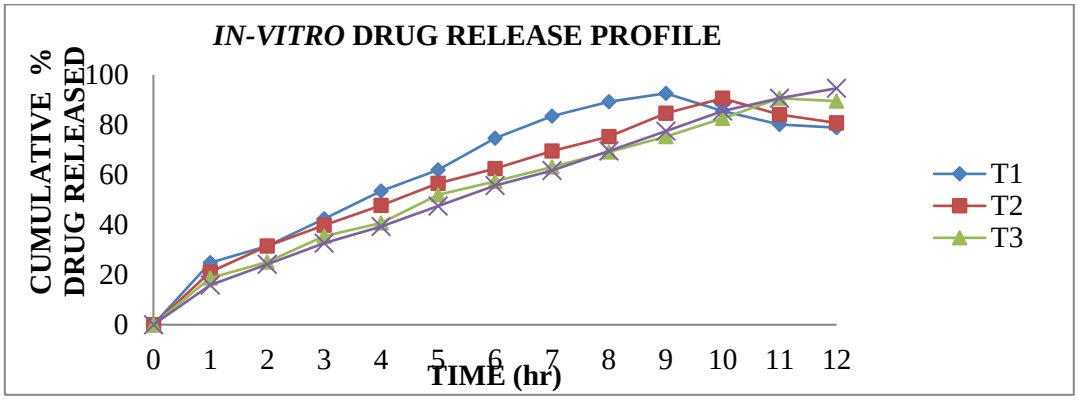

Figure 4.10: *Comparison of In-Vitro drug release profile of Aceclofenac microspheres containing sodium alginate along with Guar Gum as copolymer*

TIME (h)	CUMULATIVE PRECENT OF DRUG RELEASED			
	T_5	T_6	T_7	T_8
0	0	0	0	0
1	27.77	22.44	18.44	17.11
2	36.44	32.22	29.33	26.44
3	43.77	40.88	39.55	37.55
4	54.66	48.66	45.55	46.88
5	64.01	57.55	57.33	55.77
6	75.77	63.55	65.33	63.55
7	84.65	70.44	71.55	71.33
8	90	76.55	77.56	75.77
9	92.22	85.55	81.55	79.77
10	84.88	91.33	83.33	82.44
11	79.55	85.77	89.55	86.88
12	77.55	81.11	87.55	90.66

Table 4.18: *In-Vitro drug release data of Aceclofenac microspheres containing sodium alginate along with Locust Bean Gum as copolymer*

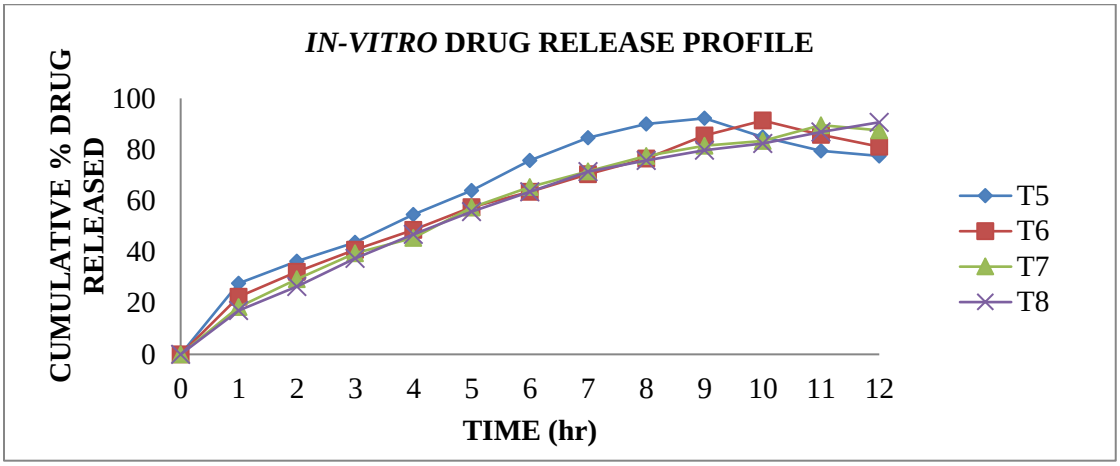

Figure 4.11 *Comparison of In-Vitro drug release profile of Aceclofenac microspheres containing sodium alginate along with Locust Bean Gum as copolymer*

Time (h)	Cumulative Percent of Drug Released			
	T_9	T_{10}	T_{11}	T_{12}
0	0	0	0	0
1	25.77	21.55	18.66	16.44
2	35.33	31.77	26.55	27.11
3	43.55	40.44	36.55	36.44
4	54	48.44	43.66	45.55
5	63.55	57.11	54.55	55.33
6	75.33	63.11	62.33	63.11
7	84	70.22	67.68	71.55
8	89.77	76	73.55	76.44
9	92.66	85.11	78.55	80.66
10	85.11	91.33	83	85.55
11	80.66	85.33	90	89.55
12	78	81.11	87.55	92.44

Table 4.19: *In-Vitro drug release data of Aceclofenac microspheres containing sodium alginate along with Xanthan Gum as copolymer*

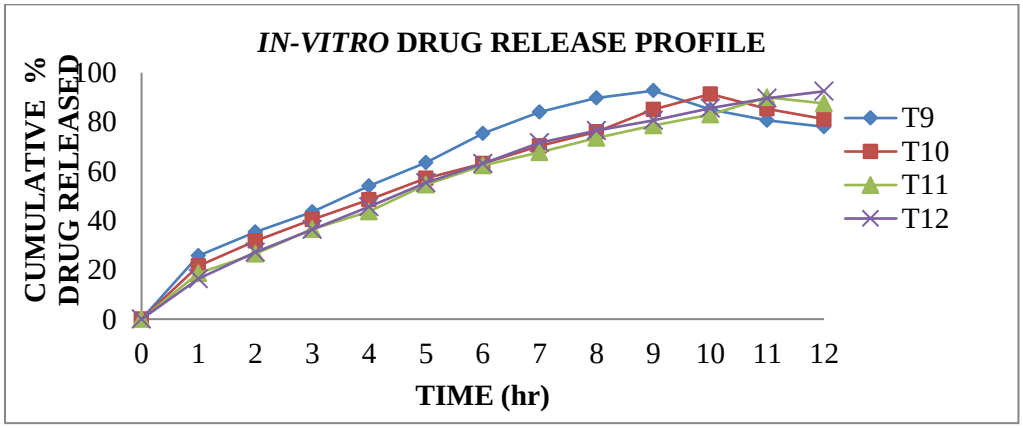

Figure 4.12: *Comparison of In-Vitro drug release profile of Aceclofenac microspheres containing sodium alginate along with XANTHAN GUM as copolymer*

In-Vitro Drug Release Kinetics

For understanding the mechanism of drug release and release rate kineti cs of the drug from dosage form, the in-vitro drug dissolution data obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix, and Krosmeyer-Peppas model. The values are compiled in Table 6.21. The coefficient of determination (R^2) was used as an indicator of the best fitting for each of the models considered. The kinetic data analysis of all the formulations reached higher coefficient of determination with the Korsmeyer-Peppas model (R^2 = 0.914 to 0.996) whereas release exponent value (n) ranged from 0.498 to 0.743. From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows Korsmeyer-Peppas model along with non-Fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion.

Formulation code	Release model								
	Zero order		First order		Higuchi matrix		Koresmeyer-peppas		
	K	R^2	K	R^2	K	R^2	n	K	R^2
T_1	21.6	0.797	1.923	0.720	-0.313	0.912	0.556	1.388	0.925
T_2	16.39	0.908	1.991	0.890	-3.945	0.970	0.595	1.326	0.983
T_3	10.45	0.976	2.062	0.945	-8.966	0.975	0.673	1.233	0.991
T_4	7.434	0.990	2.118	0.914	-12.25	0.962	0.743	1.171	0.996
T_5	24.34	0.768	1.897	0.689	2.624	0.903	0.498	1.442	0.914
T_6	17.19	0.904	1.990	0.885	-3.333	0.971	0.579	1.346	0.981
T_7	14.53	0.936	2.018	0.985	-6.239	0.983	0.655	1.278	0.990
T_8	13.06	0.948	2.032	0.991	-7.587	0.984	0.690	1.241	0.991
T_9	23.20	0.783	1.909	0.704	1.336	0.909	0.526	1.418	0.925
T_{10}	16.73	0.906	1.992	0.885	-3.771	0.970	0.591	1.334	0.982
T_{11}	12.50	0.957	2.036	0.974	-7.640	0.982	0.667	1.253	0.993
T_{12}	11.94	0.959	2.061	0.982	-8.986	0.981	0.712	1.226	0.995

Table 7: *Release Kinetics Studies of the Prepared Formulations*

5. Conclusion

In the present work, bioadhesive controlled release microspheresof Zaltoprofen using Sodium alginate along with HPMC K100M, HPMC K15M, XANTHAN GUMas copolymers were formulated to deliver Zaltoprofen via oral route.

Details regarding the preparation and evaluation of the formulations have been discussed in the previous chapter. From the study following conclusions could be drawn:-

- The results of this investigation indicate that ionic cross linking technique Ionotropic gelation method can be successfully employed to fabricate Zaltoprofen microspheres. The technique provides characteristic advantage over conventional microsphere method, which involves an "all-aqueous" system, avoids residual solvents in microspheres. Other methods utilize larger volume of organic solvents, which are costly and hazardous because of the possible explosion, air pollution, toxicity and difficult to remove traces of organic solvent completely.
- FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymers used.
- Micromeritic studies revealed that the mean particle size of the prepared microspheres was in the size range of 512-903µm and are suitable for bioadhesive controlled release microspheresfor oral administration.
- Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size, % swelling and % Mucoadhesion.
- The *in-vitro* mucoadhesive study demonstrated that microspheres of Zaltoprofen using sodium alginate along with HPMC K100M as copolymer adhered to the mucus to a greater extent than the microspheres of Zaltoprofen using sodium alginate along with HPMC K15M and XANTHAN GUM as copolymers.

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