International Journal of Research In Pharmaceutical sciences and Technology

Formulation and invitro evaluation of oral extended release microspheres of aceclofenac using various natural polymers

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ABSTRACT

In the present work, bioadhesive microspheres of Aceclofenac using Sodium alginate along with Carbopol 934, Carbopol 971, HPMC K4M as copolymers were formulated to deliver Aceclofenac via oral route. The results of this investigation indicate that ionic cross-linking technique Ionotropic gelation method can be successfully employed to fabricate Aceclofenac microspheres. The technique provides characteristic advantage over conventional microsphere method, which involves an "all-aqueous" system, avoids residual solvents in microspheres. 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 microspheres for oral administration. The in-vitro mucoadhesive study demonstrated that microspheres of Aceclofenac using sodium alginate along with Carbopol934 as copolymer adhered to the mucus to a greater extent than the microspheres of Aceclofenac using sodium alginate along with Carbopol 971 and HPMC K4M as copolymers. The invitro drug release decreased with increase in the polymer and copolymer concentration. Analysis of drug release mechanism showed that the drug release from the formulations followed non-Fickian diffusion and the best fit model was found to be Korsmeyer-Peppas. Based on the results of evaluation tests formulation coded T4 was concluded as best formulation.

Keywords: Aceclofenac; Carbopol 934; Carbopol 971; HPMC K4M and Microspheres.

ISSN: 2581-9143
Research Article

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Article Info

Received on: 14-03-2019
Revised on: 21-04-2019
Accepted on: 29-04-2019

DOI: https://doi.org/10.33974/ijrpst.v1i2.69

INTRODUCTION

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

The treatment of acute diseases or chronic illnesses has been achieved by delivery of drugs to the patients for many years. These drug delivery systems include tablets, indictables, suspensions, creams, ointments, liquids and aerosols. Today these conventional drug delivery systems are widely used. The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body. Conventional drug therapy require periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability.

For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems.

In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels. To overcome these problems, controlled drug delivery systems were introduced three decades ago. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity, and improved patient convenience. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies.

Advantages of controlled drug delivery system

- Improved patient convenience and compliance due to less frequent drug administration.
- Reduction in fluctuation in study state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization drug enabling reduction in total amount of dose administered.
- Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction personal time to dispense, administer and monitor patients.

Disadvantages of controlled drug delivery syste m

- Decreased systemic availability in comparison to immediate release conventional dosage forms; this may be due to incomplete release, increased first- pass metabolism, increased in stability, in sufficient residence time for complete release, site specific absorption, pH dependent solubility etc.
- Poor *in vitro- in vivo* correlation.
- Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patients and thus, increased risk of toxicity.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
- Higher cost of formulation.

Colon targeted drug delivery has the potential to deliver bioactive agents for the treatment of a variety of colonic diseases and to deliver proteins and peptides to the colon for their systemic absorption. Various strategies, currently available to target release of drugs to colon, include formation of pro drug, coating of pH-sensitive - polymers, use of colon-specific biodegradable polymers , timed released systems , osmotic systems , and pressure controlled drug delivery systems. Polysaccharides are bacterial enzymes that are available in sufficient quantity to be exploited in colon targeting of drugs.

Aceclofenac is a nonsteroidal anti-inflammatory, analgesic and antipyretic drug used in the treatment of rheumatoid arthritis, post-traumatic pain, masculoskeletal and joint disorders. It is a newer derivative of diclofenac with low gastrointestinal complications. The biological half-life [3-4hr] and dosing frequency more than one per day [2]. It is completely absorbed after oral administration. Aceclofenac is partially insoluble for poorly soluble oral administrated drugs, the rate of absorption is often controlled by the rate of dissolution.

METHODS AND MATERIALS

Fourier transform infrared spectroscopy (FTIR)

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.

Method of preparation

Ionotropic gelation method: Batches of microspheres 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 microspheres. The microspheres 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 microspheres and then air-dried.

Determination of λmax

10mg of drug was accurately weighed and dissolved in 10ml of 0.1N HCl, 7.4 PH, and 6.8 PH in 10 ml volumetric flask, to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 µg/ml) standard stock solution (2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 2, 4,6, 8, 10, 12, 14, 16, 18 ,and 20µg/ml with 0.1N HCl, 7.4 pH, and 6.8 pH. The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 269nm. Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis.

The calibration curve data of Aceclofenac in simulated gastric fluid pH 1.2 at 269nm. Fig. 6.2 shows the standard calibration curve with a regression value of 0.998, slope of 0.028 and intercept of 0.004 in simulated gastric fluid pH 1.2. The curve was found to be linear in the concentration range of 2-10µg/ml.

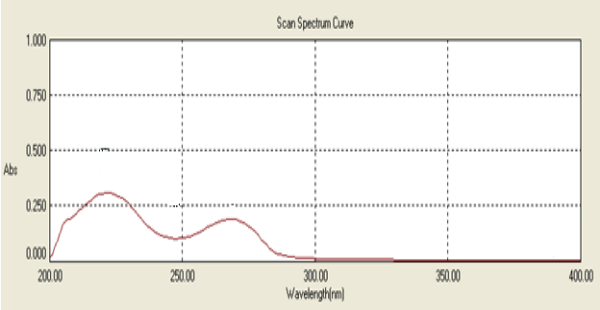

Figure 1: UV of Aceclofenac in simulated gastric fluid pH 1.2

Table 1: calibration curve Aceclofenac in simulated gastric fluid in different pH

Concentration (µg/ml)	Absorbance pH 1.2	Concentration (µg/ml)	Absorbance pH 6.8
0	0	0	0
2	0.051	0.5	0.153
4	0.110	1	0.312
6	0.163	1.5	0.445
8	0.221	2	0.634
10	0.290	2.5	0.814

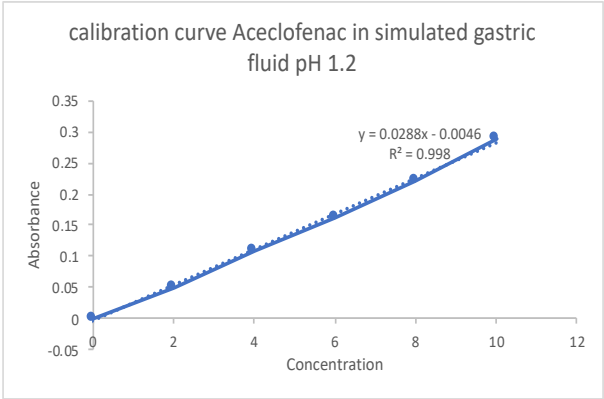

Figure 2: calibration curve Aceclofenac in simulated gastric fluid pH 1.2

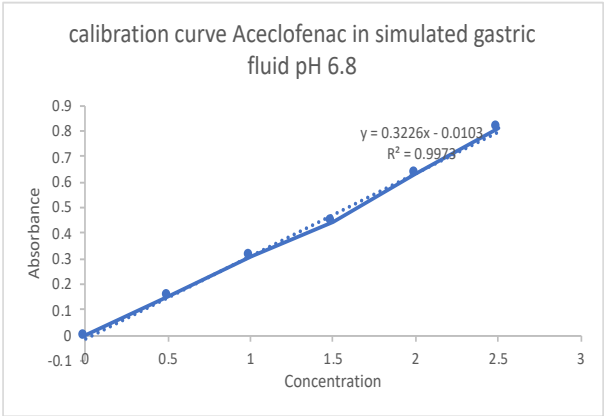

Figure 3: calibration curve Aceclofenac in simulated gastric fluid pH 6.8

Compatibility studies

Drug polymer compatibility studies were carried out using Fourier Transform InfraRed spectroscopy to establish any possible interaction of Aceclofenac with the polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FTIR spectra of the pure drug. The results indicated that the characteristic absorption peaks due to pure Aceclofenac have appeared in the formulated microspheres, without any significant change in their position after successful encapsulation, indicating no chemical interaction between Aceclofenac and Polymers.

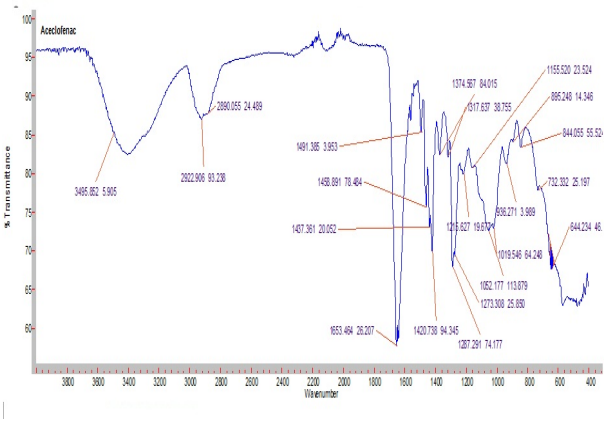

Figure 4: FTIR of Aceclofenac

Table 2: Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

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 3: In-Vitro drug release data of Aceclofenac microspheres

Time	Cumulative percent of drug released											
	sodium alginate+carbopol 934				sodium alginate+carbopol 971				sodium alginate+HPMC K 4 M			
	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	24.88	21.11	18.66	15.88	27.77	22.44	18.44	17.11	25.77	21.55	18.66	16.44
2	31.55	31.55	25.11	24.22	36.44	32.22	29.33	26.44	35.33	31.77	26.55	27.11
3	42.44	39.77	35.44	32.66	43.77	40.88	39.55	37.55	43.55	40.44	36.55	36.44
4	53.55	47.77	40.66	39.33	54.66	48.66	45.55	46.88	54	48.44	43.66	45.55
5	62	56.66	52	47.55	64.01	57.55	57.33	55.77	63.55	57.11	54.55	55.33
6	74.66	62.44	57.33	55.77	75.77	63.55	65.33	63.55	75.33	63.11	62.33	63.11
7	83.55	69.55	63.11	61.77	84.65	70.44	71.55	71.33	84	70.22	67.68	71.55
8	89.33	75.33	69.11	69.55	90	76.55	77.56	75.77	89.77	76	73.55	76.44
9	92.66	84.66	75.33	77.55	92.22	85.55	81.55	79.77	92.66	85.11	78.55	80.66
10	85.55	90.66	82.66	85.55	84.88	91.33	83.33	82.44	85.11	91.33	83	85.55
11	80.22	84.22	90.66	90.66	79.55	85.77	89.55	86.88	80.66	85.33	90	89.55
12	78.88	80.88	89.55	94.66	77.55	81.11	87.55	90.66	78	81.11	87.55	92.44

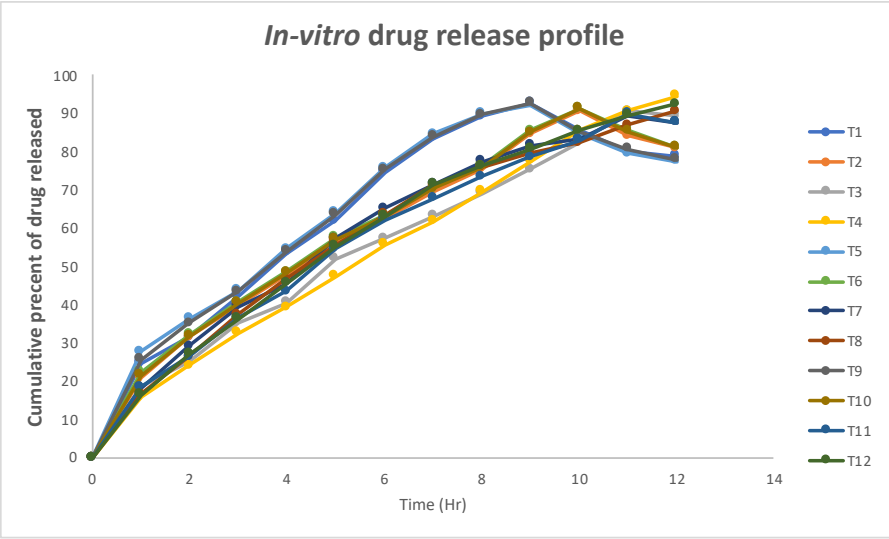

Figure 5: In-Vitro drug release data of Aceclofenac microspheres

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 carbopol 934 as copolymer, 62.22 to 87% for microspheres containing sodium alginate along with carbopol 971 as copolymer and 80 to 87.5% for microspheres containing sodium alginate along with HPMC K 4 M as copolymer. The percentage yield of the prepared microspheres is recorded in

Table 4: Prepared formulation of Biooadhesive Microspheres

S.no.	Formulation code	Drug : polymer ratio	Polymer ratio
1	T_1	1:2.5	Na alginate: Carbopol 934 (1.5:0.5)
2	T_2	1:3	Na alginate: Carbopol 934 (2:1)
3	T_3	1:3.5	Na alginate: Carbopol 934 (2.5:1)
4	T_4	1:4	Na alginate: Carbopol 934 (3:1)
5	T_5	1:2.5	Na alginate: Carbopol 971 (1.5:0.5)
6	T_6	1:3	Na alginate: Carbopol 971 (2:1)
7	T_7	1:3.5	Na alginate: Carbopol 971 (2.5:1)
8	T_8	1:4	Na alginate: Carbopol 971 (3:1)
9	T_9	1:2.5	Na alginate: HPMC K 4M (1.5:0.5)
10	T_{10}	1:3	Na alginate: HPMC K 4 M (2:1)
11	T_{11}	1:3.5	Na alginate: HPMC K 4 M (2.5:1)
12	T_{12}	1:4	Na alginate: HPMC K 4 M (3:1)

Table 5: Release kinetics studies of the prepared formulations

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	0.72	-0.313	0.912	0.556	1.388	0.925
T_2	16.39	0.908	1.991	0.89	-3.945	0.97	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	0.99	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	1.99	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	0.99
T_8	13.06	0.948	2.032	0.991	-7.587	0.984	0.69	1.241	0.991
T_9	23.2	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	0.97	0.591	1.334	0.982
T_{11}	12.5	0.957	2.036	0.974	-7.64	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 2 and displayed in Figures 6 to 8.

Drug entrapment efficiency: Percentage Drug entrapment efficiency of Aceclofenac ranged from 82.66 to 88.66% for microspheres containing sodium alginate along with carbopol 934 as copolymer, 53.2 to 76.66% for microspheres containing sodium alginate along with carbopol 971 as copolymer and 66.73 to 79.2% for microspheres containing sodium alginate along with HPMC K4M as copolymer.

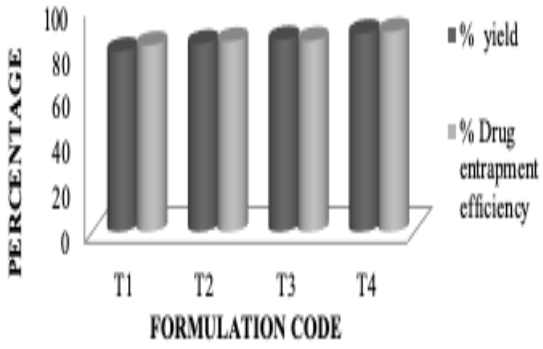

Figure 6: Comparison of % Yield and % drug entrapment efficiency microspheres containing sodium alginate along with carbopol 934 as copolymer

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 2.

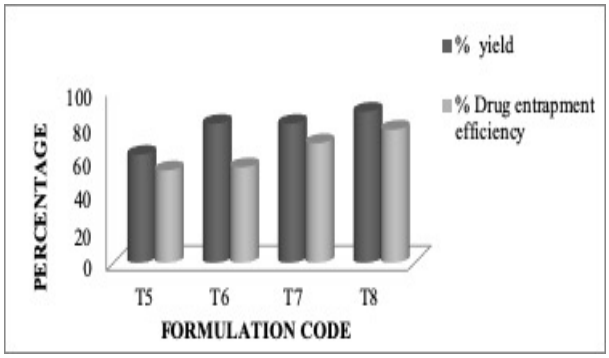

Figure 7: Comparison of % Yield and % drug entrapment efficiency microspheres containing sodium alginate along with carbopol 971 as copolymer

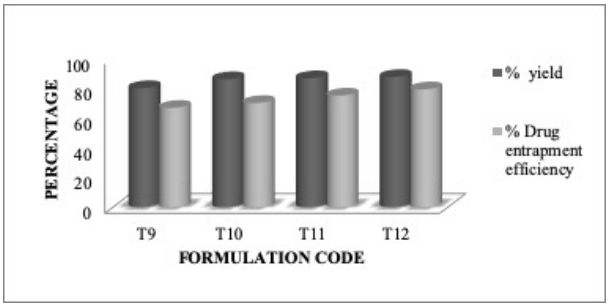

Figure 8: Comparison of % Yield and % drug entrapment efficiency microspheres containing sodium alginate along with HPMC K 4 M as copolymer

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 carbopol 934 as copolymer had a size range of 512µm to 826µm, microspheres containing sodium alginate along with carbopol 971 as copolymer exhibited a size range between 517µm to 834µm and microspheres containing sodium alginate along with HPMCK4M as copolymer had a size range of 664µm to 903µm. The particle size data is presented in Tables 6.4 to 6.15 and displayed in Figure 6.10 to 6.12. The effect of drug to polymer ratio on particle size is displayed in Figure 10. The particle size as well as % drug entrapment efficiency of the microspheres increased with increase in the polymer concentration.

The swelling ratio is expressed as the percentage of water in the hydrogel at any instant during swelling. Swellability is an important characteristic as it affects mucoadhesion as well as drug release profiles of polymeric drug delivery systems. Swellability is an indicative parameter for rapid availability of drug solution for diffusion with greater flux. Swellability data revealed that amount of polymer plays an important role in solvent transfer. It can be concluded from the data shown in Table 6 that with an increase in polymer concentration, the percentage of swelling also increases.

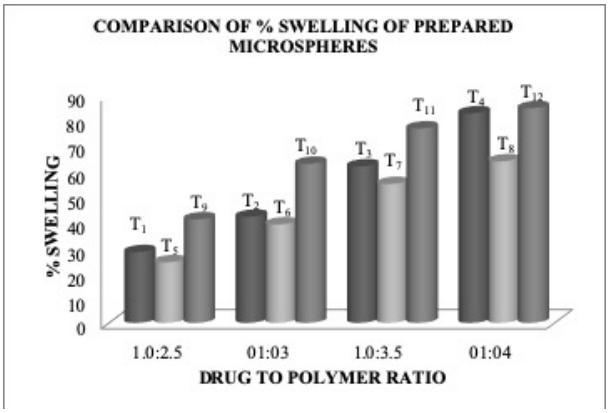

Figure 9: Comparison of percentage swelling of prepared microspheres

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 carbopol 934 as copolymer, 24 to 64% for microspheres containing sodium alginate along with carbopol 971 as copolymer and 31 to 85 for microspheres containing sodium alginate along with HPMC K 4 M as copolymer. The percentage of swelling of the prepared microspheres is displayed in Fig. 6.16 to 6.18. The effect of drug to polymer ratio on percentage swelling is displayed in Figure 9.

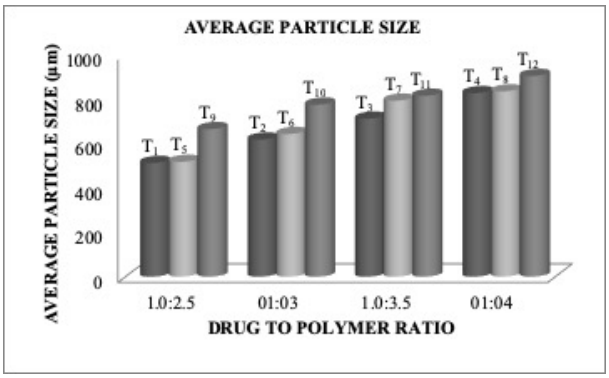

Figure 10: Comparison of average particle size of prepared microspheres

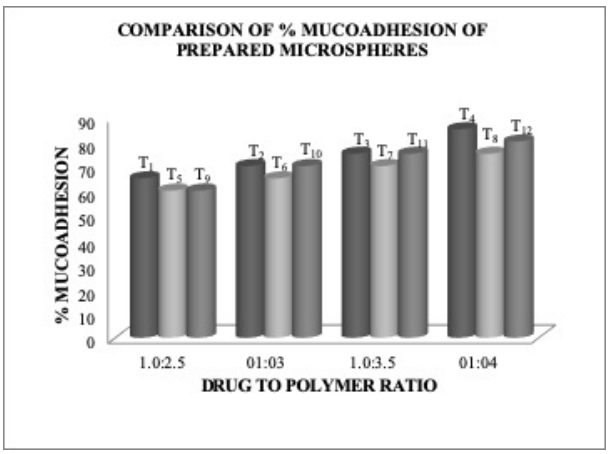

Figure 11: Comparison of percentage mucoadhesion of prepared microspheres

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. The results of the in-vitro dissolution studies of formulations T_1 to T_4, T_5 to T_8 and T_9 to T_{12} are shown in table. The plots of Cumulative percentage drug release Vs Time. Figure 6.24 shows the comparison of % CDR for formulations T1 to T4, figure 6.25 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 6.27 to 6.30.

The formulations T1, T2, T3 and T4 containing Sodium alginate along with Carbopol 934 as

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 Carbopol 971 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 T_9, T_{10}, T_{11} and T_{12} containing Sodium alginate along with HPMC K 4 M as 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 release of 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.

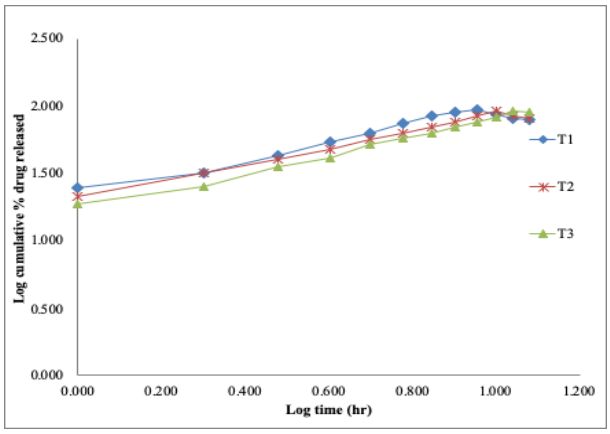

Figure 12: Korsmeyer-Peppas plots of Aceclofenac microspheres formulations T1, T2 and T3

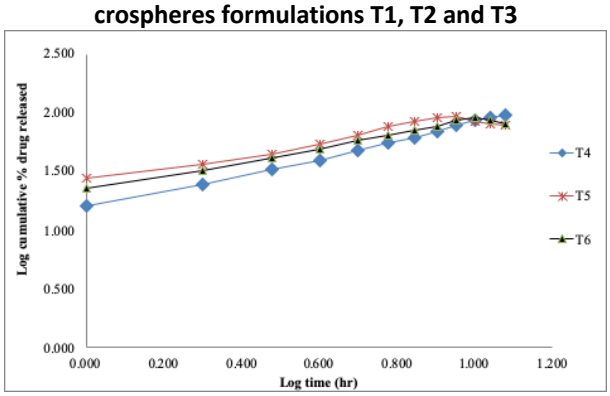

Figure 13: Korsmeyer-Peppas plots of Aceclofenac microspheres formulations T4, T5 and T6

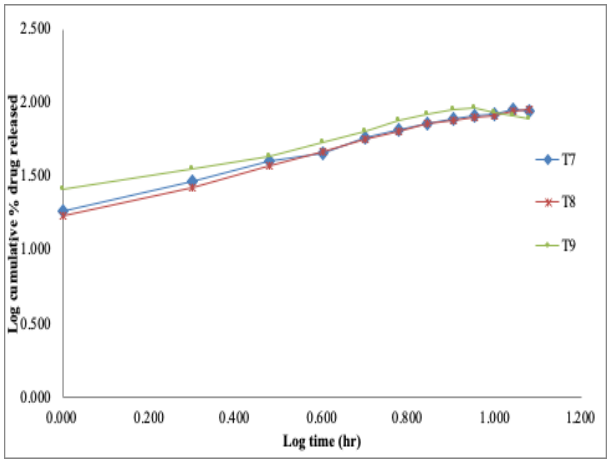

Figure 14: Korsmeyer-Peppas plots of Aceclofenac microspheres formulations T7, T8 and T9

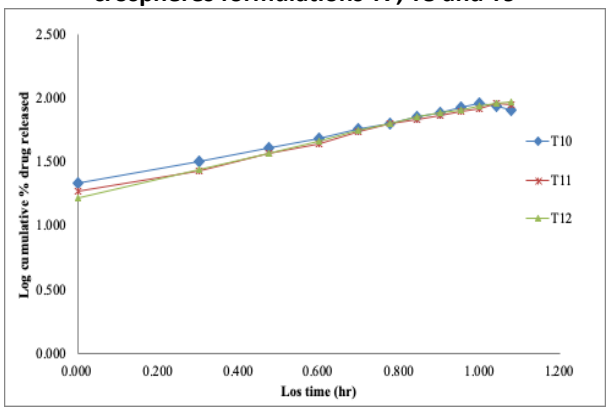

Figure 15: Korsmeyer-Peppas plots of Aceclofenac microspheres formulations T10, T11, T12

CONCLUSION

In the present work, bioadhesive microspheres of Aceclofenac using Sodium alginate along with Carbopol 934, Carbopol 971, HPMC K4M as copolymers were formulated to deliver Aceclofenac via oral route. Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size, % swelling and % Mucoadhesion. Analysis of drug release mechanism showed that the drug release from the formulations followed non-Fickian diffusion and the best fit model was found to be Korsmeyer-Peppas. Based on the results of evaluation tests formulation coded T4 was concluded as best formulation.

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