Original Article

Effect of Sustained Release Polymers on Drug Release Profile of Aceclofenac Tablets- Physicochemical Properties, Analysis of Kinetics and Fit Factor

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ABSTRACT

Aim: The sustained release tablets of Aceclofenac were prepared and evaluated for the sustained release drug profile with an aim to reduce dosing frequency and provide patient compliance. **Materials and Method:** The tablets were prepared by using different percentages of Kollidon SR, Carbopol 934P and Eudragit L100 and their combination thereof by wet granulation method. The tablets were analyzed for post compression studies including thickness, diameter, mechanical strength and uniformity of content. The *in vitro* dissolution studies were carried out in pH 1.2 for first 2 h and in pH 6.8 buffer for total of 12 h. **Results:** The tablets exhibited acceptable physicochemical characteristics as per USP limits. The formulation containing Eudragit L100 failed to give the desired sustained release effect where as a slow drug release was observed in formulations containing Carbopol 934P. Therefore, a combination of pH dependant polymer (Eudragit L100) and pH independent polymer (Carbopol 934P) combination was used. The formulations were also prepared by Carbopol 934P with plastic polymer (Kollidon SR). The desired sustained release effect was given by latter combination at 2:1 concentration. **Conclusion:** This formulation, U13, followed zero order kinetics with non-Fickian drug release mechanism. When compared to the marketed brand by fit factor, U13 gave the *f*2 value greater than 50 indicating closer proximity to the approved brand.

Key word: Aceclofenac, Fit factor, Kinetics, Carobopol, Kollidon, Eudragit L100.

INTRODUCTION

Aceclofenac is a Nonsteroidal Anti-inflammatory Drug (NSAID) which is considered as the first-line therapy in the symptomatic treatment of osteoarthritis and rheumatoid arthritis. Aceclofenac has short half-life of four hour and require frequent dosing. The successful treatment of arthritis depends in the maintenance of effective concentration of drug in the body by means of a sustained drug delivery system.[1,2] Among the different approaches to achieve sustained drug delivery system, matrix tablets prepared by wet granulation method still appears as most efficient method in terms of process development and economy.[3] Various polymers have been used to retard the release of drug from matrix system. These polymers may include hydrophilic matrices, hydrophobic moieties and plastic matrix system.

The hydrophilic polymer develops a highly viscous gel surface barrier when they are exposed to aqueous medium. This gelatinous barrier controls the liquid penetration into the center of the matrix system and in turn controls the drug release. The hydrophobic polymers are potentially erodible material and control the drug release by pore formation and erosion. On the other hand

Submission Date: 12-06-2018;
Revision Date: 24-10-2018;
Accepted Date: 18-01-2019

DOI: 10.5530/ijper.53.2s.49

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the plastic system forms insoluble matrices and liquid penetration into the matrix is the rate limiting step in such systems unless channeling agents are employed in the matrix system.[4]

The objective of the present study was to evaluate the efficiency of above mentioned polymers to sustain the release rate of aceclofenac and to reduce the dosing frequency to improve patient compliance. Carbopol 934P (hydrophilic polymer), Kollidon SR (plastic matrix) and Eudragit L100 (hydrophobic polymer) were evaluated for their physicochemical properties and potential sustain release effect at different concentration independently and in possible combination with each other. The formulations were also evaluated with the marketed product of aceclofenac sustained release product (hereby denoted as Brand-A) by means of model independent approach (fit factor) as approved by the FDA.[5]

MATERIALS AND METHOD

Materials

Aceclofenac (donated by Medisearch Pharma, Lahore, Pakistan); Carbopol 934P (Corel Pharma Chem., India); Kollidon SR (BASF, Germany); Eudragit L100 (Merck, Germany); lactose (FDA foremost, USA); polyvinylpyrrolidone (Saad traders, Lahore); isopropyl alcohol (City corporation, Lahore); magnesium stearate (Wilfrid Smith Ltd, UK); potassium dihydrogen phosphate (Fluka, Germany); potassium hydroxide (Aldrich Chemicals Co. Ltd.); HCl (BDH, England); R.O water

Method

Preparation of matrix sustained tablet of aceclofenac

For the development of matrix tablet of aceclofenac by wet granulation method accurately weighed amount of diluent (lactose) and binder (PVP K-30) were added in the mortar followed by matrix forming polymer (Carbopol 934P, Kollidon SR and/or Eudragit L100) after passing them through 40 mesh screen (Table 1). Then drug was added and material was triturated slowly with Isopropyl alcohol (IPA) as solvent to form a dough mass. The wet mass was passed through sieve number 20. The granules were dried in hot air oven at 40°C for 60 min. Magnesium stearate was added as a lubricant to the dried granules and blended in a closed polyethylene bag. The tablets were compressed by single punch machine with a punch diameter of 10.8 mm.[6,7]

Physicochemical properties of sustained release tablets of aceclofenac Thickness and mechanical strength

The thickness of ten randomly selected tablets were taken from each formulation and measured with digital vernier caliper. Average and standard deviation was calculated by SPSS software.[8]

The mechanical strength of tablet can be determined by hardness and friability. For hardness test, ten tablets were randomly selected from each formulation. The hardness was measured with Monsanto hardness tester. The average was calculated by SPSS software.[7]

For friability test, ten tablets were randomly selected from each formulation and tumbled in a Roche friabilator at 25 rpm for 4 min. Percentage friability was calculated by:[8]

$$\text{Percentage friability} = (W_1\text{-}W_2)/W_1 \times 100$$

Where, W_1: weight of tablets before test; W_2: weight of tablets after test

Uniformity of mass and uniformity of content

It can be determined by weight variation and content uniformity. According to USP-NF, twenty tablets were weighed individually on a digital weighing balance. The percent deviation was calculated by the following equation.[9]

$$\text{Percentage deviation} = (\text{Average weight} - \text{individual weight}/\text{average weight}) \times 100$$

For content uniformity, the tablets were crushed in mortar and powder equivalent to 100 mg drug was dissolved in 5ml of methanol (70%). The volume was made up to 100 ml with phosphate buffer pH 6.8.The sample was mixed thoroughly and filtered through whatman filter paper. The solution was suitably diluted and analyzed spectrophotometrically by UV spectrophotometer at 276 nm.[1]

In vitro dissolution study

The dissolution study was carried out in USP apparatus II using pH 1.2 for 2 h and phosphate buffer 6.8 for 2nd to 12th h as dissolution medium (900 ml). The medium was maintained at 37 ± 0.5°C and paddle was operated at 50 rpm. Samples were withdrawn after suitable interval of time over a period of 12 h and filtered through whatman filter paper before analysis on UV spectrophotometer at 273 nm.[1]

Release rate kinetic

In vitro dissolution study was analyzed by model dependent approach by fitting the data in following models.[10]

Zero order equation: $Q_t = Q_0 + K_0 t$

First order equation: $\log Q_t = \log Q_0 + K_1 t / 2.303$

Higuchi equation: $M_t / M_\infty = k2 \sqrt{t}$

Korsmeyer-Peppas equation: $M_t / M_\infty = k_3 t^n$

Where, Q_t: amount of drug dissolved in time t; Q_0: initial amount of drug in the solution; K_0: zero order release constant; K_1: first order release constant; M_t: cumulative amount of drug released at time t; M_∞: absolute cumulative amount of drug released at infinite time; k_2: constant reflecting the design variable of the system; k_3: constant incorporating structural and geometric characteristics of the device; *n*: release exponent indicative of the mechanism of drug release.

Fit factors (f_1 and f_2)

The optimized formulation was compared with the commercially available Alkeris-SR (200 mg by Sami Pharmaceuticals, Pakistan) sustained release tablet of aceclofenac referred here as Brand-A. The factor, f_1, is the average percentage difference over time points in the amount of test batch dissolved as compared to the reference product. The f_1 is also known as the dissimilarity factor. As the value approaches 0 it signifies that the test and the reference profiles are identical and increases proportionally with the dissimilarity between the two dissolution profiles. It is calculated by the following equation:[9]

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100$$

The value of factor f_2 lies between 0 and 100. The f_2 is 100 when the test and the reference profiles are identical and it approaches 0 as the dissimilarity increases. The f_2 is also known as the similarity factor and is calculated by the following equation:[5]

$$f_2 = 50 \log \left[\frac{100}{\sqrt{1 + \left(\sum_{i=0}^{n} (R_t - T_t)^2 \right) / n}} \right]$$

RESULT AND DISCUSSION

Thickness and mechanical strength

The thickness and diameter of tablet is given in Table 2. The low value of S.D. in thickness indicated that the process was reproducible. Tablet thickness is consistent if the tablet granulation is adequately constant in particle size and distribution, punch tooling is of consistent length and tablet press is clean and in good working condition. As the average diameter of all formulations was less than 12.5 mm thus percentage deviation allowed was ±5.[11] The diameter of all formulation falls in this limit.

The hardness of the tablets should be between 4 to 6 kg but for some sustained release tablets the hardness may be between 10 to 20 kg.[12] Therefore, all the formulations were within the range of acceptable criteria (Table 2). Tablets formulated with Carbopol 934P had increased hardness as compared to Kollidon SR and Eudragit L100 formulations.[13] Although hardness is an unofficial test yet it can affect the disintegration rate of tablet; if the tablet is too hard it may not disintegrate in the required period of time where as if the tablet is too soft it will not be able to withstand handling during subsequent processing such as packaging. Therefore compliance of hardness is an important criterion for tablets. All the formulations complied with the USP limit i.e. friability was less than 1%.[11]

Uniformity of mass and uniformity of content

The result of weight variation and content uniformity are given in Table 2. According to USP; for tablets with total weight of 250 mg or more, the percentage deviation allowed is ±5%. As the percentage deviation was -2.76% to 1.40% range thus all formulation complied with the official criteria. The density of the material and physical dimensions of the tablet determine the weight of the tablet. It is determined to ensure that tablet contain proper amount of drug. The content uniformity of tablets should be in 85% to 115% range thus all the formulations complied with the specifications. Weight variation and uniformity of content were used to ensure that tablet contains intended amount of drug substance with little variations.[1,14-15]

Dissolution studies of aceclofenac sustained release tablet

Dissolution profile of formulations containing Kollidon SR as polymer

The cumulative percentage drug release profile of sustain release tablets of aceclofenac containing Kollidon SR as polymer is given in Figure 1. It depicts that increasing the concentration of Kollidon SR decreased the initial release of drug in 1st hour of dissolution. The $t_{50\%}$ and $t_{90\%}$ (Table 3) increased for these formulations as the polymer percentage increased. The variable release profile of Kollidon SR was due to composition of polymer; it contains 80% polyvinyl actete (PVAc) and 19% povidone that are capable of forming insoluble matrix of PVAc. The water soluble povidone gets dissolved from matrix and forms pores for drug diffusion and dissolution.[12] Kollidon SR was used for the development of pH independent sustain release matrix tablet.[16,17]

The drug release profile was fitted in different kinetic models like zero order, first order and Higuchi model and is given in Table 4. The formulations U1, U2 and

Table 1: Formulation of Aceclofenac sustained release matrix tablet using different polymers

Formulation	Drug (%)	Carbopol 934P (%)	Kollidon SR (%)	Eudragit L 100 (%)	Lactose (%)	PVP (%)	Magnesium stearate (%)	Total weight (mg)
U1	40		20		36	2	2	500
U2	40		25		31	2	2	500
U3	40		30		26	2	2	500
U4	40	20			36	2	2	500
U5	40	25			31	2	2	500
U6	40	30			26	2	2	500
U7	40			20	36	2	2	500
U8	40			25	31	2	2	500
U9	40			30	26	2	2	500
U10	40		10	20	26	2	2	500
U11	40		15	15	26	2	2	500
U12	40		20	10	26	2	2	500
U13	40	20	10		26	2	2	500
U14	40	15	15		26	2	2	500
U15	40	10	20		26	2	2	500

Table 2: Post-compression studies of compressed tablets of Aceclofenac

Formulation	Thickness (mm)	Hardness (kg)	Friability (%)	Weight (mg)	Weight variation (%)	Content uniformity (%)
U1	7.3±0.05	10.40±0.42	0.15	485.0	-3.00	98.82±0.04
U2	7.5±0.07	12.80±0.85	0.12	486.2	-2.76	103.85±0.02
U3	6.0±0.09	14.00±0.52	0.082	504.4	0.88	99.12±0.08
U4	5.6±0.11	19.50±0.74	0.02	485.0	-3.00	102.25±0.06
U5	5.7±0.08	18.50±0.21	0.05	497.1	-0.58	100.98±0.05
U6	5.8±0.04	18.00±0.15	0.035	507.0	1.40	98.58±0.09
U7	6.0±0.10	14.50±0.74	0.07	502.0	0.40	99.83±0.04
U8	6.0±0.05	15.50±0.15	0.09	493.4	-1.32	99.25±0.08
U9	6.0±0.08	12.90±0.25	0.08	493.26	1.34	101.08±0.06

Table 3: $t_{50\%}$ and $t_{90\%}$, similarity factor and dissimilarity factor of sustained release formulation of Aceclofenac

Formulation	U1	U2	U3	U4	U5	U6	U7	U8	U9	U10	U11	U12	U13	U14	U15	Brand-A
$t_{50\%}$ (hr)	4.93	5.18	5.36	5.09	5.23	5.63	5.10	4.87	4.73	4.85	5.15	5.82	5.79	5.04	4.75	4.77
$t_{90\%}$ (hr)	8.87	9.32	9.65	9.16	9.42	10.14	9.17	8.77	8.52	8.72	9.27	10.48	10.42	9.07	8.55	10.5
f_2	24	28	31	26	29	27	11	4	5	13	16	13	77	29	10	--
f_1	26	22	19	24	21	16	47	63	62	42	37	28	2	21	51	--

U3 followed Higuchi model. This signified that the main drug release mechanism from the polymeric matrix was diffusion as proportionality between percentage drug release and square root of time is regarded as an indicator

Table 4: Release kinetics of *in vitro* dissolution of sustained release tablets of Aceclofenac

Formulation	Zero Order		1st Order		Higuchi Model		Korsmeyer's Peppas	
	R^2	K_1	R^2	K_2	R^2	K_3	R^2	n
U1	0.9501	10.141	0.8977	0.249	0.9804	29.283	0.9818	0.54
U2	0.9521	9.660	0.8975	0.217	0.9623	27.667	0.9721	0.59
U3	0.9417	9.329	0.8948	0.195	0.9513	26.497	0.9741	0.63
U4	0.9512	9.831	0.8906	0.239	0.9932	28.547	0.9925	0.50
U5	0.9531	9.553	0.8937	0.222	0.9909	27.668	0.9909	0.52
U6	0.9657	8.876	0.8894	0.184	0.9913	25.532	0.9961	0.55
U7	0.8684	9.811	0.9198	0.186	0.8436	26.886	0.9428	0.85
U8	0.8579	10.259	0.9328	0.212	0.8715	28.498	0.9372	0.77
U9	0.8452	10.568	0.9340	0.232	0.8783	29.599	0.9243	0.72
U10	0.9213	10.317	0.9806	0.265	0.9380	29.833	0.9351	0.54
U11	0.9386	9.712	0.9475	0.224	0.9869	27.887	0.9521	0.58
U12	0.9581	8.588	0.9209	0.168	0.9592	24.428	0.9689	0.63
U13	0.9966	8.635	0.9487	0.148	0.8897	23.734	0.9926	0.86
U14	0.9731	9.928	0.9530	0.222	0.9805	28.362	0.9929	0.59
U15	0.9295	10.530	0.9321	0.305	0.9804	30.945	0.9853	0.45
Brand-A	0.985	8.4588	0.9116	0.1682	0.9148	29.629	0.9707	0.98

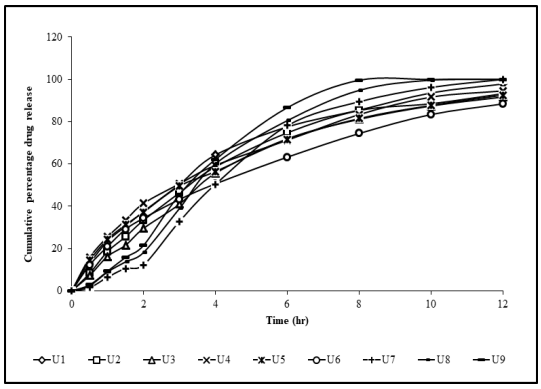

Figure 1: *In vitro* dissolution of sustained release Aceclofenac tablets of individual polymers

of diffusion controlled drug release. The 'n' value of Korsmeyer-Peppas equation signified that mechanism of drug release was non-Fickian or anomalous favoring both diffusion and erosion as the values were greater than 0.5.[18,19]

Dissolution profile of formulations containing Carbopol 934P as polymer

As the concentration of Carbopol 934P was increased, a decreased release rate effect was seen from U4 to U6 (Figure 1). The time required for 90% of the drug to be released from U6 at 30% w/w concentration of Carbopol 934P was beyond 10 h (Table 3). From Figure 1 it can be observed that drug release was inversely proportional to the level of rate retarding polymer in matrix system i.e. the rate and extent of drug release increases with decrease in total polymer content. During the initial phase of dissolution profile the increase in polymeric content lead to quicker hydration which decreased the rate of drug release from matrix system.[4] It was due to the formation of gel barrier around the tablet which became stronger with increased concentration of Carbopol 934P. Carbopol 934P polymers are highly effective at low concentration, typically 3-30%. Due to the anionic nature of the polymer, drug release may be media dependent. As the pH of the media increases it causes ionization of the –COOH group which results in maximum swelling and smaller regions of microcavities. This rapid gel formation acts as a barrier and prolongs the drug release. Carbopol 934P polymer has a good matrix forming property and enhances release of poorly soluble drugs in neutral or basic buffers.[9] Aceclofenac is a water insoluble drug but its solubility is enhanced in phosphate buffer pH 6.8 (1538.7 ± 1.215 mcg/ml) thus the dissolution medium favored both the drug release and sustained effect due to polymer.[20] The R^2 values of different kinetic models

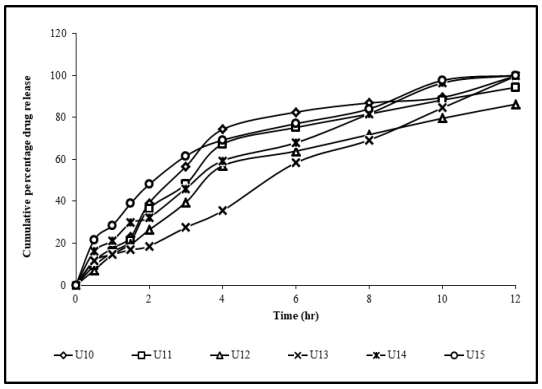

Figure 2: *In vitro* dissolution of sustained release Aceclofenac tablets with combination of polymers

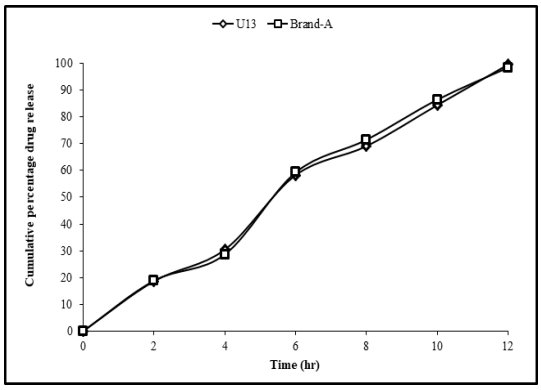

Figure 3: Comparison of U13 with commercially available brand of Aceclofenac sustained release tablet

(Table 4) showed that U4, U5 and U6 followed Higuchi model and the drug release mechanism was non-Fickian.[21]

Dissolution profile of formulations containing Eudragit L100 as polymer

The cumulative percentage drug release profile of formulations containing Eudragit L100 is shown in Figure 1. The time required for 50% of the drug release was achieved in less than 2 h in all formulations containing Eudragit L100 (Table 3). As the concentration of Eudragit L100 was increased it further increased the rapid release of drug from the matrix system. Eudragit L100 is a hydrophobic polymer but the solubility of polymer increases as the pH increases thus it depicts pH dependent profile. It has been established that Eudragit L100 dissolves at pH ≥6.0 upon deprotonation of –COOH group at alkaline pH.[22] As the amount of Eudragit L100 increases, it causes formation of more pores thus creating channels for the dissolution media to penetrate into the matrix system which results in faster dissolution of the drug.[23] The release behavior from these matrix systems was first order kinetics probably due to irregular erosion process from the matrix. Matrix tablets were thus prepared by using combination of pH dependent Eudragit with a pH independent Kollidon SR polymer in different ratios with the aim of attaining more regular and reproducible release profile.[24]

Dissolution profile of formulations containing combination of Kollidon SR and Eudragit L100

The cumulative percentage drug release of formulations containing combination of Kollidon SR and Eudragit L100 is shown in Figure 2 that depicts that as the concentration of Kollidon SR was increased the retarding effect of Kollidon SR also increased. The time required for 50% and 90% of the drug to release from the matrix system increased from U10 to U12 (Table 3). Kollidon SR contains no ionic groups and was inert to the drug and dissolution medium thus imparting sustaining effect whereas Eudragit L100 was soluble in basic pH dissolution medium leading to formation of pore which causes leaching of drug from the matrix. Hence increasing the amount of Eudragit L100 as compared to Kollidon SR lessens the retarding effect of Kollidon SR in sustained release tablets.[25] The R^2 value of different kinetic models shown in Table 4 indicated that formulation U10 followed first order kinetics. U11 and U12 followed Higuchi model with diffusion controlled drug release. The formulations had non-Fickian diffusion drug release mechanism as the '*n*' value was more than 0.5 and less than 1.0 as shown in Table 4.[10]

Dissolution profile of formulations containing different combination of Kollidon SR and Carbopol 934P

As the formulations containing Carbopol 934P alone had a slow drug release ($t_{90\%}$>12 h), the tablets were formulated containing a combination of hydrophilic (Carbopol 934P) and plastic polymer (Kollidon SR). The cumulative percentage drug release profile of formulations containing combination of Kollidon SR and Carbopol 934P is given in Table 3. As the concentration of Kollidon SR was increased the release rate of drug from the matrix system was faster. This faster release rate was because of lower gel strength, less entanglement and smaller diffusion path length as compared to formulation containing more concentration of Carbopol 934P which has better swelling property in contrast to Kollidon SR.[26] The $t_{50\%}$ and $t_{90\%}$ decreased by decreasing the Carbopol 934P concentration in matrix system with Kollidon SR (Table 3). When fitted in various kinetic models, U13 followed zero order whereas U14 and U15 followed Higuchi model as shown in Table 4. The zero order kinetics signified that the drug release from matrix was independent of concentration whereas Higuchi kinetics signified that the release rate was diffusion

controlled. The formulations U13 and U14 had anomalous drug release mechanism whereas U15 had Fickian diffusion mechanism.[10]

Fit Factor

The similarity in the release profile of aceclofenac formulations and marketed tablet, Brand-A, was compared by using model independent approach. The fit factor can be expressed by two approaches i.e. the difference factor (f_1) and the similarity factor (f_2). The f_1 is proportional to the average difference between the two profiles whereas f_2 is inversely proportional to the average squared difference between the two profiles.[5] The dissolution profiles are considered similar if f_1 is between 0 and 15 whereas f_2 is between 50 and 100.[2] In this study the fit factor signified the similarity of the dissolution profile of only U13 with Brand-A with f_2 >50 and f_1 < 15 (Table 3 and Figure 3). The formulation U13 containing Carbopol 934P and Kollidon SR (2:1) had similar zero order kinetic profile and non-Fickian drug release mechanism as Brand-A. The least similarity with the reference was observed in formulations containing Eudragit L100.

CONCLUSION

The formulations made of Kollidon SR, Carbopol 934P, Eudragit L100 and their combination thereof were suitable as matrix forming agents and allowed preparation of sustained release tablets of aceclofenac by wet granulation. The drug release behavior was influenced by the kind and concentration of polymer used and relative w/w ratio of mixtures. Even though the formulations have passed the USP (2012) specifications, most of the formulations were not interchangeable with the marketed product. The present study demonstrated that Carbopol 934P and Kollidon SR, at 20% and 10% concentration respectively, provide sustained release matrix system for the formulation of BCS II class drug aceclofenac. This formulation (U13) followed zero order release kinetics with anomalous drug release mechanism.

ACKNOWLEDGEMENT

Authors would like to thank Faculty of Pharmacy, University of Lahore for providing research facilities.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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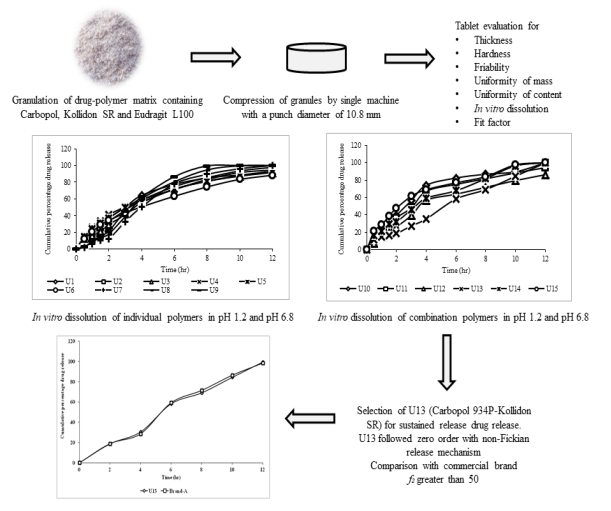
PICTORIAL ABSTRACT



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SUMMARY

- The Aceclofenac tablets were prepared for sustained release drug profile using different percentages of Kollidon SR, Carbopol 934P and Eudragit L100 and their combination thereof. The tablets were analyzed for micromeritic properties and post compression studies including thickness, diameter, mechanical strength, uniformity of content. The *in vitro* dissolution studies were carried out in pH 1.2 (initial 2 h) and pH 6.8 for 12 hrs. The tablets exhibited acceptable micromeritic properties and physical characteristics but tablets containing independent polymers had undesirable sustained release effects. Therefore, a combination of pH dependent polymer (Eudragit L100) with pH independent polymer (Carbopol 934P) and Carbopol 934P with plastic polymer (Kollidon SR) was used. The desired sustained release effect was given by latter combination at 2:1 concentration. This formulation, U13, followed zero order kinetics with non-Fickian drug release mechanism and had closer proximity to the marketed brand based on fit factor.

Cite this article: Nagra U, Adnan S, Shafqat S, Shabbir M, Ali S, Zafar A. Effect of Sustained Release Polymers on Drug Release Profile of Aceclofenac Tablets- Physicochemical Properties, Analysis of Kinetics and Fit Factor. Indian J of Pharmaceutical Education and Research. 2019;53(2S):s58-s65.