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DIFFERENT POLYMERS UESD TO DESIGN AND EVALUATION OF CONROLLED RELEASE MATRIX TABLETS OF ACECLOFENAC

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ABSTRACT
Aceclofenac is a Non-steroidal anti inflammatory drug (NSAID) used to the anti-inflammatory effects of aceclofenac have been shown in both acute and chronic inflammation. Controlled release matrix tablets of Aceclofenac were prepared by using three polymers, one of the hydrophilic polymer hydroxy propyl methyl cellulose K15M (HPMCK15M), carbapol-934 and Xanthan gum with four concentrations (drug: polymer ratios-1:1, 1:2, 1:3, 1:4), by wet granulation method. The granules were evaluated for bulk density, tapered density, bulkiness, angle of repose, Hausners ratio and compressibility index. In vitro release studies revealed that Aceclofenac formulation with high proportion of HPMCK15M (1:1) was able to control the drug release for 12 hours (85.4±1.26). The in-vitro drug release data, curve-fitting kinetic analysis[9] and all the formulations followed the mechanism of erosion and diffusion.[19] All the formulations were subjected to stability analysis for stored at 45° ±2°C, 75±5%RH up to 45 days.

KEYWORDS: Controlled release, HPMC K15M, carbapol-934, Xanthan gum, wet granulation, Hydrophilic polymer, NSAID.

INTRODUCTION
CR formulations of Aceclofenac can overcome some of these problems. Most of the matrix tablets can be prepared by wet granulation method.[7] Among many polymers (hydrophilic, lipophilic, natural gums, Hydrogels and Mucoadhesive[4] polymers) in the formulation of matrix based controlled release drug delivery systems. Their flexibility to obtain a desirable drug release profile, broad regulatory acceptance and cost effectiveness are advantages of hydrophilic polymer matrix systems.[11] The benefits providing hydroxypropyl methylcellulose (HPMCK15M) for formulation of hydrophilic matrix system like nonionic nature, Robust mechanism, consistent reproducible release profile[15] choice of viscosity grades, effectiveness of cost, and utilization of conventional methods and equipments. The following factors like drug dissolution, water penetration, polymer swelling, drug diffusion and matrix erosion are controlled by the hydration of HPMC, due to forms the gel barrier through which the drug diffuses.[1]

MATERIALS AND METHODS
Materials
Aceclofenac was kind gift sample from Trinity labs private limited, Mumbai India. HPMCK15M, Talc and Magnesium stearate were procured from KP labs, Hyderabad, India. Lactose, Xanthan gum Isopropyl alcohol, carbapol-934 were procured from S.d fine chemicals Pvt Ltd; Mumbai, India. All other chemicals and reagents were used of analytical grade.

Preparation of Aceclofenac controlled release tablets
Twelve formulations of controlled release tablets of Aceclofenac using HPMCK15M, Carbapol-934 and Xanthan gum each with four formulations (1:1, 1:2 and 1:3, 1:4) were prepared by wet granulation method. The details of each formulation and with composition are shown to table-1.

Carbapol-934l (drug) and polymers HPMCK15M, Xanthan gum, carbapol-934 were mixed separately. Lactose and cross caramellose sodium were added to the polymer-drug mixture and blended thoroughly for 5-6 minutes. A coherent mass is formed to dissolve the in sufficient quantity of isopropyl alcohol (IPA) and finally added to drug mixture.[5] Then the coherent mass was passed through sieve number-16 to form granules and the collected granules were dried at $40°C \pm 2°c$ for 2 hours. The dried granules were passed through the sieve

number-22. The granules retained on sieve number-22 were evaluated for tapped density, bulk density, bulkiness, compressibility index, Hausners index and angle of repose(Table-IIA,IIB,IIC). Then the granules were mixed with talc, magnesium stearate and finally compressed in to tablets.[3] The same procedure was followed to prepare Aceclofenac tablets without polymers.

Table 1: Composition of matrix tablet formulation of Aceclofenac.

Ingredients	Drug : Polymers												n
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	
Aceclofenac	10	10	10	10	10	10	10	10	10	10	10	10	10
HPMC K15M	10	20	30	40									
PVPK-300					10	20	30	40					
Karayagum									10	20	30	40	
Lactose monohydrate	65	55	45	35	65	55	45	35	65	55	45	35	75
Talc	6	6	6	6	6	6	6	6	6	6	6	6	6
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4	4	4
Cross caramellose sodium	5	5	5	5	5	5	5	5	5	5	5	5	5
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total	100	100	100	100	100	100	100	100	100	100	100	100	100

IR spectral analysis

The drug (Aceclofenac) and polymers like (HPMC K15M, carbapol-934 and xanthangum) must be compatible with one another to produce a stable product.[13] FTIR (Shimadzu, Japan, model-8400s) using studied by interaction between drug and polymer as per the method described by Sharma. IR spectral analysis of pure aceclofenac, aceclofenac with HPMC K15M and aceclofenac with Xanthan gum carried out. The peaks and patterns produced by the pure drug were compared with combination of polymers and pure drug.[10]

Evaluation of tablets

Hardness

The tablets to be tested by Monsanto hardness test apparatus.[8] The test was performed by the tablet are held between a fixed and moving jaw of apparatus and the reading of the indicator is adjusted to zero (0). The screw knob was moved forward until the tablet breaks and noted the reading, force required to break the tablet.

Friability test

The Roche friabilator is used to performance of friability test.[10] The weighing ten (10) tablets and placed in the friabilator, which was then operated for 25 revolutions per minute (RPM). After 100 revolutions the tablets were dusted and reweighed. The formula used to determine the percentage of friability was

Percentage friability = Initialweight-Finalweight/Initial weight$\times$100

Weight variation

For weight variation test, twenty (20) tablets were randomly selected and weighed individually. The individual weights were compared with average weight for determination of weight variation.[18]

Dissolution test studies

In-vitro dissolution release studies were performed using USP apparatus type-II at 50 rpm. The dissolution medium was 900 ml of phosphate buffer at PH7.4. The temperature was maintained at 37$\pm$0.5°C. The drug release rate was evaluated by taking 10 ml sample, which was replaced with fresh medium every one one-hour interval up to 12 hours and suitable diluted with phosphate buffer (PH 7.4) and absorbance was measured at 341.5 nm using UV spectrophotometer.[20]

Drug content

Ten tablets (10) were weighed and powdered. The powder equivalent to 100 mg of aceclofenac was dissolved in 10 ml of 0.1 M Hcl, then make up to 100ml of phosphate buffer PH 7.4 in 100 ml standard flask. From this 10$\mu g/ml$, equivalent solution was prepared and analyzed at 341.5 nm using UV spectrophotometer.

Kinetic analysis

The mechanism of drug release rate kinetics of all the formulations to analyze the results of in-vitro release profiles were fitted in to zero order kinetic model, first order kinetic model, Higuchi model and korsmeyer Peppas model.[6] The results of in-vitro release profiles were plotted in models of data treatment as follows

Zero order kinetic models – Log cumulative percent drug released versus time

First order kinetic model – Log cumulative percent drug remaining versus time

Higuchi model – Cumulative percent drug release versus squire root of time

Korsmeyer model - Log cumulative percent drug released versus log time

Stability studies

Stability studies were analyzed to assess the stability of all controlled release formulations of aceclofenac tablets. The prepared CR tablets were kept at 45°C $\pm$ 2°C, 75$\pm$ 5%RH for 45 days. At 15 days intervals the tablets were evaluated for all physical parameters. The perentage of

aceclofenac content and in-vitro drug release studies were also determined.

RESULTS AND DISCUSSION

Evaluation of aceclofenac granules and tablets

The prepared granules for compression of matrix tablets were evaluated for their flow properties. The bulk density ranged between0.40 to 0.45gm/cm3. Tapped density was within the range of 0.40 to 0.46 gm/cm3. Bulkiness was found to be the range of 2.02 to 2.46 gm/cm^3. Compressibility index was found to be the range of 10.02 to 12.66. Angle of repose was within the range of 20.23 to 24.11 and Hausners ratio ranged from 0.950 to 1.051. These above values indicate that the prepared granules were exhibited good flow properties.

Table II: (A) Evaluation of aceclofenac granules.

Parameters	Ratio of drug and polymer (aceclofenac: HPMCK15M)			
	F1	F2	F3	F4
Bulk density(gm/cm3)*	0.43±0.11	0.40±0.10	042±0.50	0.45±0.76
Tapped density(gm/cm3)*	0.44±0.91	0.41±0.21	0.46±0.11	0.40±0.32
Bulkiness(gm/cm3)*	2.13±0.16	2.17±0.71	2.22±0.11	2.02±0.95
Angle of repose *	21.23±0.94	24.11±0.82	23.9±0.25	22.7±0.12
Compressibility index (%)*	10.50±0.26	11.24±0.22	12.65±0.91	10.21±0.51
Hausners ratio*	1.005	1.027	1.018	0.976

Table II: (B) Evaluation of aceclofenac granules.

Parameters	Ratio of drug and polymer (aceclofenac:carbopol-934)			
	F5	F6	F7	F8
Bulk density(gm/cm3)*	0.42±0.11	0.41±0.10	044±0.50	0.40±0.76
Tapped density(gm/cm3)*	0.42±0.91	0.44±0.21	0.43±0.11	0.45±0.32
Bulkiness(gm/cm3)*	2.17±0.16	2.42±0.71	2.32±0.11	2.30±0.95
Angle of repose *	21.23±0.94	24.11±0.82	22.3±0.25	23.7±0.12
Compressibility index (%)*	11.50±0.26	12.40 ± 0.22	10.11±0.91	11.76±0.51
Hausners ratio*	1.023	1.006	1.051	0.950

Table II: (C) Evaluation of aceclofenac granules.

Parameters	Ratio of drug and polymer (Aceclofenac: Xanthan gum)				Control
	F9	F10	F11	F12	F13
Bulk density(gm/cm3)*	0.41±0.11	0.44±0.10	045±0.50	0.43±0.76	0.44±0.16
Tapped density(gm/cm3)*	0.44±0.91	0.40±0.21	0.42±0.11	0.41±0.32	0.43±0.31
Bulkiness(gm/cm3)*	2.27±0.16	2.32±0.71	2.12±0.11	2.38±0.95	2.43±0.95
Angle of repose *	22.23±0.94	21.11±0.82	22.90 ± 0.25	20.27±0.12	20.49±0.25
Compressibility index (%)*	10.29±0.26	12.66±0.22	11.57±0.91	10.82±0.51	11.06±0.26
Hausners ratio*	1.021	0.956	1.042	1.002	0.966

Table III: (A) Evaluation of Aceclofenac tablets.

Parameters	Ratio of drug and polymer (Aceclofenac : HPMCK15M)			
	F1	F2	F3	F4
Hardness (kg/cm2)	4.84±0.12	4.90±0.07	4.94±0.15	4.98±0.14
Friability (%)	0.34±0.04	0.40±0.01	0.29±0.04	0.31±0.07
Weight variation(mg)	98.6±4.7	99.5±4.4	99.4±2.5	98.2±3.2
Content uniformity (%)	99.16±0.33	98.6±1.10	98.8±0.60	98.4±0.20
Thickness(mm)	3.42±0.02	3.21±0.12	3.29±0.04	3.16±0.14
Diameter(mm)	7.22±0.31	7.60±0.15	7.38±0.08	7.44±0.02

Table III: (B) Evaluation of Aceclofenac tablets.

Parameters	Ratio of drug and polymer (Aceclofenac : Carbapol-934)			
	F5	F6	F7	F8
Hardness (kg/cm2)	4.57±0.12	4.81±0.07	4.82±0.15	4.69±0.14
Friability(%)	0.58±0.04	0.55±0.01	0.49±0.04	0.45±0.07
Weight variation(mg)	99.4±4.7	99.1±4.4	99.2±2.5	99.0±1.2
Content uniformity (%)	99.63±0.33	98.53±1.1	98.8±0.6	97.8±0.20
Thickness(mm)	3.42±0.02	3.36±0.12	3.40±0.04	3.16±0.12
Diameter(mm)	7.22±0.31	7.46±0.15	7.28±0.08	7.49±0.02

Table III: (C) Evaluation of Aceclofenac tablets.

Parameters	Ratio of drug and polymer (Aceclofenac: Xanthan gum)				Control
	F9	F10	F11	F12	F13
Hardness (kg/cm2)	4.84±0.12	4.96±0.07	4.48±0.15	4.72±0.14	4.83±0.12
Friability (%)	0.40±0.04	0.44±0.01	0.34±0.04	0.44±0.07	0.35±0.03
Weight variation(mg)	99.9±4.7	98.5±4.4	99.1±2.5	98.2±3.2	99.5±3.2
Content uniformity (%)	99.66±0.22	98.61 ± 1.10	98.2±0.60	99.4±0.20	98.4±0.42
Thickness(mm)	3.12±0.02	3.24±0.12	3.56±0.04	3.16±0.14	3.42±0.02
Diameter(mm)	7.12±0.31	7.16±0.15	7.24±0.08	7.08±0.02	7.10±0.06

All the prepared tablets show good elegance and appearance. All formulated tablets the hardness range was found to be 4.57 to 4.98 kg/cm2, indicating good mechanical strength. In the friabilty test the particle loss was below 1% for all the formulations, which is an indication of satisfactory or good mechanical resistance of the tablets. The weight variation was within the range of ± 7.5% complying with Pharmacopoeial standards. The percentage of aceclofenac in all formulations was ranging from 97.4 to 99.46% indicating content uniformity was within the limits (10%). The range of thickness and diameter of aceclofenac tablets was found to be 3.12 to 3.56mm and 7.08 to 7.60mm respectively which showed uniform diameter and thickness.

IR spectral analysis

The IR spectral studies of pure aceclofenac and combinations of aceclofenac with HPMC K15M (1:1) were carried out to study the interaction between the drug and polymers (HPMC K15M, Xanthan gum used. C-H stretching, C-H deformation, N-H stretching of primary amine and N-H out of plain bending of pure Aceclofenac and Aceclofenac with polymers were almost in the same wave number region ranging from 524 cm^{-} to 2868 cm^{-}. It showed there was no significant interaction between the polymers and drug and they are compatible with each other.

Dissolution studies

In- vitro dissolution release studies were performed to determine the percentage of drug released from Aceclofenac matrix tablet formulations with polymer, marketed tablet and Aceclofenac tablet formulation without polymer (control formulation). Results of the in-vitro dissolution release studies of Aceclofenac matrix tablet formulation with polymer are show in table-IV.

The percentage drug release of all formulations after 12 hours using HPMC K15M as polymer was found to be 91.2% (F1), 89.2% (F2), 88.1 (F3) and 86.4(F4). It was found that the cumulative percentage drug release in the formulationF1 was more thanF2, F3 and F4. The cumulative percentage of drug release in the formulation F4 showed controlled release than F1, F2 and F3. A major role played in drug release was the polymer concentration. At higher polymer concentration, the drug release was prolonged than the lower concentration of the polymer. The graphical presentation data of the Aceclofenac matrix tablet formulations with polymer is shown in (Figure – I).

The percentage drug release of all formulations after 12 hours using carbapol-934 as polymer was found to be 91.2% (F5), 90.2% (F6), 87.7 (F7) and 86.7(F8). It was found that the cumulative percentage drug release in the formulationF5 was more than F6, F7 and F8. The cumulative percentage of drug release in the formulation F8 showed controlled release than F5, F6 and F7.

The percentage drug release of all formulations after 12 hours using xanthangum as polymer was found to be 93.8% (F9), 92.1% (F10),91.0 (F11) and 89.9(F12). It was found that the cumulative percentage drug release in the formulationF9 was more than F10, F11 and F12. The cumulative percentage of drug release in the formulation F12 showed controlled release than F9, F10 and F11.

In overall twelve formulations Carbapol-934 as polymer was found to be 85.7% (F4).). It was found that the

cumulative percentage of drug release was very low compare to overall twelve formulations in different polymers, because of best formulation in controlled release.

In-vitro dissolution of Aceclofenac from the tablet formulation without polymer (control) was found to be 96.3% where as the Aceclofenac release from marketed matrix tablet was 96.1% in 30 minutes.

Table IV: Percentage drug release of Aceclofenac Matrix Tablet Formulations.

Time (hrs)	Cumulative percentage drug release *											
	Aceclofenac:HPMC K15M				Aceclofenac : carbapol-934				Aceclofenac : xanthangum			
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	16.6	14.1	12.9	11.4	17.1	15.4	13.4	12.2	21.2	20.6	20.0	19.7
2	22.1	21.0	20.2	19.4	23.0	21.7	21.2	20.8	25.6	24.7	23.5	22.8
3	30.7	28.6	27.1	25.9	30.9	30.2	28.0	26.8	33.8	32.1	31.4	31.0
4	38.2	36.3	35.0	34.2	39.2	37.9	36.1	35.6	44.6	43.0	42.1	41.4
5	43.6	42.7	40.9	40.0	44.1	43.0	41.2	40.8	47.6	46.4	45.6	45.1
6	49.9	47.9	44.6	42.1	50.4	48.6	46.6	44.0	53.8	52.6	51.7	50.2
7	57.1	55.4	54.3	52.6	58.7	56.4	55.8	53.9	62.1	61.0	60.4	59.4
8	63.6	62.6	60.2	59.6	65.0	63.8	61.2	60.2	68.5	66.7	65.8	64.5
9	69.9	68.3	67.0	65.6	70.8	68.9	67.4	66.0	71.4	70.8	69.0	68.7
10	77.6	75.1	74.3	73.5	78.6	76.8	74.9	74.3	80.6	79.2	77.8	76.7
11	85.9	84.6	82.1	81.4	86.2	85.4	83.4	82.2	87.9	86.5	85.4	85.1
12	91.4	89.2	88.1	86.4	92.1	90.2	87.7	85.7	93.8	92.1	91.0	89.9

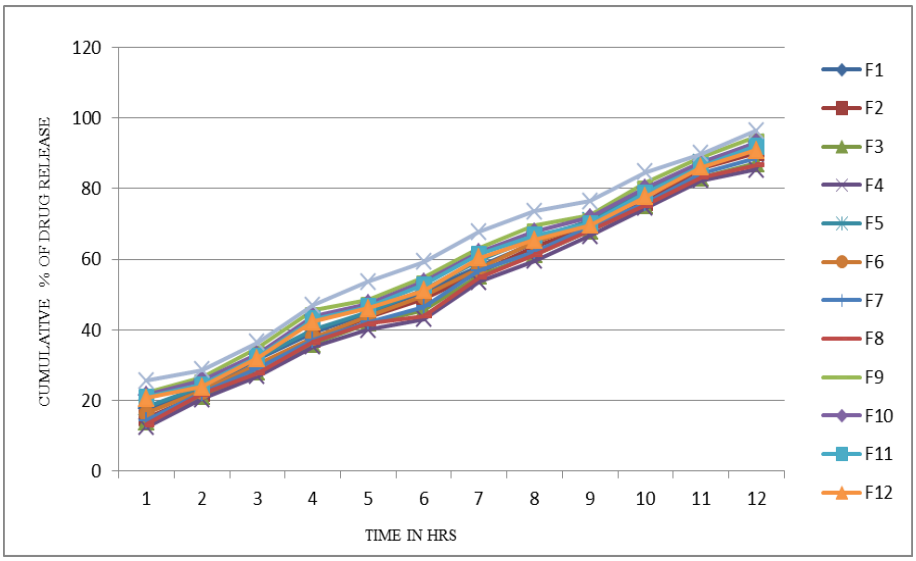

Figure I: Percentage drug release of Aceclofenac matrix tablet formulations.

Kinetic Analysis

The kinetic data for release rate of all formulations were shown in table-V. When the data were plotted according to zero order kinetics, the matrix formulations showed to a high linearity, with regression co-efficient (R2) values between 0.9824 to 0.9985. Huguchi's model explained by diffusion is related to transport of drug from the dosage form in to the in-vitro study, fluid depending on the concentration. In all the formulations the drug release profiles[2] could be expressed by Higuchi's equations[23] as the plot showed high linearity with high regression co-efficient values between 0.9464 to 0.9688. By using korsmeyer Peppas model, if n value less than 0.45 it is fickian diffusion, if n value is 0.45 to 0.89 values between 0.686 to 0.838. It showed that all the formulations follow Non-Fickian transport mechanism[22] and also follow the mechanism of both erosion and diffusion.

Table V: Curve fitting analysis for Aceclofenac formulations.

Formulation code	Regression co-efficient (R2)			Korsmeyer plot	
	Zero order plot	First order plot	Higuchi's plot	R2	Slope
F1	0.9824	0.9575	0.9660	0.6986	0.686
F2	0.9936	0.9585	0.9554	0.7165	0.734
F3	0.9942	0.9646	0.9576	0.7272	0.798
F4	0.9985	0.9682	0.9526	0.7486	0.838
F5	0.9864	0.9584	0.9688	0.6898	0.698
F6	0.9884	0.9588	0.9555	0.7096	0.724
F7	0.9934	09666	0.9586	0.7174	0.734
F8	0.9974	0.9684	0.9518	0.7378	0.772
F9	0.9874	0.9586	0.9636	0.7026	0.728
F10	0.9889	0.9639	0.9688	0.7131	0.734
F11	0.9923	0.9656	0.9554	0.7222	0.748
F12	0.9962	0.9696	0.9543	0.7254	0.756

Stability analysis

All the formulations of Aceclofenac matrix tablets were stored at 45° ± 2°C, 75±5% RH up to 45 days. The evaluation tests of tablets were carried out at every 15 days intervals. Physically stable[12] at all formulations. There were no deviations found in the evaluation tests and all formulations are within the limits. There were no significant change in in-vitro drug release profiles and drug content.[21] It observed that all the formulations are chemically stable.

CONCLUSION

The results of experimental studies of Aceclofenac matrix tablets proved that the granules of Aceclofenac showed good flow properties, evaluation tests of tablets are within the acceptable limits, Infra Red (IR) spectral analysis[16] proved that there was no polymer- drug interaction, all the formulations of kinetic studies were followed zero order drug release and stability analysis revealed that all formulations were found to be stable after storing at 45° ± 2°C, 75±5% RH up to 45 days. The main drawbacks of the conventional dosage forms of Aceclofenac can be minimized by Aceclofenac controlled release (CR) tablets. Thus the results of the above study clearly indicated that Aceclofenac may be formulated as CR tablets using HPMC K15M as polymer by wet granulation method[17] which will be provide continuous release of drug at a predetermined rate and time.

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Abbreviations

HPMC = Hydroxy Propyl Methyl Cellulose, CR = Controlled Release, RH = Relative Humidity, UV = Ultra Violet.

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