

Research Article



DESIGN, DEVELOPMENT AND *IN VITRO* EVALUATION OF DICLOFENAC SODIUM MATRIX TABLET PREPARED BY DIRECT COMPRESSION USING METHOCEL K100LV CR POLYMER

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ABSTRACT

The objective of this work was to design, develop and assay of sustained release Diclofenac sodium matrix tablet using Methocel K100LV CR by direct compression. Tablets of five formulations were developed each containing different amount of the polymer. The compatibility of drug and polymer was tested by FTIR spectroscopy. Formulated tablets were evaluated on the basis of their percentage weight variation, hardness, thickness, friability and *in vitro* dissolution profile. Zero order, First order, Higuchi and Hixson-Crowell equations were used to analyze the drug release kinetics; and the Korsmeyer-Peppas equation was used to explain the drug release mechanism. The drug and polymer showed no incompatibility; and the physical parameters of the formulated tablets were quite on spot as well. The release kinetics showed that, with the increase of polymer content the drug release rate becomes more controlled and achieved USP specifications. Most of the formulations followed the Higuchi kinetics; and from the Korsmeyer-Peppas equation it can be concluded that the drug release mechanisms were ranging from Fickian to super case II transport.

Keywords: Diclofenac sodium, Drug release kinetics, Drug release mechanism, FTIR study, Methocel K100LV CR.

INTRODUCTION

Diclofenac sodium is one of the most popular non-steroidal anti-inflammatory drugs (NSAIDs). It supposedly inhibits any of the three enzymes: cyclooxygenase (COX), lipoxygenase and prostaglandin synthetase; or all of them to provide its therapeutic actions.^{1,2} Diclofenac sodium is indicated for relieving pain, inflammation and fever related to arthritis, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout arthritis, dysmenorrhoea, headache, cancer etc.³

The most common side effects this drug elicits are GIT disorders like diarrhea, indigestion, stomach discomfort, flatulence, loss of appetite.³ Moreover, the drug has a very short biological half-life of about 1-3 hours, therefore it requires multiple dosing to maintain therapeutic level of the drug.^{4,5} These problems can be resolved by incorporating the drug in matrix tablet, which is known as controlled release or sustained release dosage form.

The activity of matrix tablet depends on the key polymer in the formulation.⁶ Hydrophilic polymers are of particular interest in the field of controlled release as because they are non-ionic with high gelling capacity & due to their flexibility and reproducibility to obtain a desirable drug release profile.^{7,8} Methocel K100LV CR, a grade of hydroxypropyl methylcellulose (HPMC), is such a hydrophilic polymer that provides a robust mechanism for the controlled release of drug from matrix tablets, as it gets hydrated by the dissolution fluid, a viscous porous gel layer forms via which the fluid enters slowly to dissolve the drug, ensuring sustained release of the drug from the matrix. Moreover, Methocel K100LV CR can be

used to prepare tablets by applying direct compression method.⁹

Dissolution test is known as the most important test to determine the drug release pattern which includes drug release kinetics and drug release mechanisms of a tablet. It is a more controlled and reproducible way to assess the factors that influence bioavailability of a drug.¹⁰ Dissolution rate determination can therefore be a useful guide to comparative bioavailability. Since drug absorption and physiological availability depend on the availability of the drug substance in the dissolved state, suitable dissolution characteristics are important property for a satisfactory matrix tablet.¹¹ However, the drug dissolution and release from matrix tablet can be influenced by various formulation factors like polymer viscosity, drug to polymer ratio, polymer particle size, drug solubility, and compression force etc.^{12,13}

The objective of this study was to obtain a therapeutically desirable and pharmaceutically compatible formulation for Diclofenac sodium-Methocel K100LV CR matrix tablet prepared by direct compression.

MATERIALS AND METHODS

Pure Diclofenac sodium was obtained as a gift from Beximco Pharmaceuticals Ltd., Bangladesh. Methocel K100LV CR (Merck, Germany), Polyvinylpyrrolidone (PVP) 40 (Carl Roth, Germany), Microcrystalline cellulose (Merck, Germany), Avicel i.e. Colloidal silicon dioxide (Senyang, China) and Lactose monohydrate (Merck, India) were used to prepare the matrix tablets of Diclofenac sodium. All other solvents and chemicals used were of reagent grade.



Characterization of drug polymer interactions

Fourier transformation infrared (FTIR) spectroscopy (Shimadzu, Japan) study was carried out on the drug-polymer dry mixture and their hydrated granules to determine the interactions between the drug and polymer in presence or in absence of water. The IR spectra were recorded at 4000 - 400 cm⁻¹.

Preparation of matrix tablets

Required amount of Diclofenac sodium, Methocel, Lactose, PVP and Microcrystalline cellulose were weighed and sieved (mesh size 24) for three times for uniform mixing of the powders. After that colloidal silicone dioxide was added to the mixture and sieved again for three times. Then magnesium stearate was added and mixed thoroughly. Finally, 385 mg of powder was weighed from the formulation mixture for 20 tablets, and were pressed using the locally fabricated single punch tablet compression machine to make each tablet. Same procedure was followed for all the five formulations and the formulations were coded as F1 to F5 shown in table 1.

Table 1: Composition of matrix tablets with five different compositions

Ingredients (mg)	Formulation code				
	F1	F2	F3	F4	F5
Diclofenac sodium	50	50	50	50	50
Methocel K100LV CR	50	100	150	200	250
Lactose	250	200	150	100	50
Microcrystalline cellulose	15	15	15	15	15
Polyvinylpyrrolidone	10	10	10	10	10
Magnesium stearate	5	5	5	5	5
Colloidal silicon dioxide	5	5	5	5	5
Total (mg)	385	385	385	385	385
Polymer % (w/w)	12.99	25.97	38.96	51.95	64.94

Physical characterization of matrix tablets

The percentage weight variations of the formulated tablets were carried out with electronic balance (Shimadzu, Japan) on five tablets from each formulation. Friability, hardness and thickness tests were carried out with Friability tester (Veego, India), Monsanto hardness tester (Intech, Korea), and Vernier callipers (Tricle Brand, China) respectively, on five tablets (i.e. n = 5) from each formulation.

In vitro dissolution study of matrix tablets

The dissolution study for three Diclofenac sodium-Methocel K100LV CR matrix tablets from five formulations were conducted using a six station USP type 1 dissolution tester (Vanguard Pharmaceutical Machinery, Inc, USA). 900 ml of demineralized water of pH 7 at temperature 37°C (±5°C) was used as dissolution medium and the rotation speed was 50 rpm. The drug released from the matrix tablets were determined at each interval using UV-VIS spectrophotometer (Hach, USA), which was set at 277nm. As a media demineralized water was used in place of conventional phosphate buffer for the

dissolution of Diclofenac sodium- Methocel K100LV CR matrix tablets. This is because Diclofenac sodium is a practically insoluble in acidic solution (pKa=4.0), but dissolves in intestinal fluid and water. Moreover, it has been found that, water decreases the release of active ingredient from some preparations and therefore good dissolution of a preparation in water indicates that it will release even better *in vivo*.¹⁴ The amount of drug dissolved was checked at the intervals of 20, 40, 60, 120, 180, 240, 300, 360, 420 and 480 minutes.

Characterization of drug release kinetics for matrix tablet

The drug release rate of given controlled release dosage forms can follow either of the mathematical models, which are zero-order kinetic model (Equation 1), first-order kinetic model (Equation 2), Hixson-Crowell kinetic model (Equation 3) and the Higuchi kinetic model (Equation 4).

$$C = k_0 t \quad \text{Equation 1}$$

In Equation 1, C is the concentration of the drug, k_0 is the zero order rate constant expressed as concentration/time and t is the time in hour.¹⁴ Moreover, according to the USP specification a desirable the matrix tablet should have the following drug release percentages: 3-15%, 60 ± 15% and 90 ± 15%, in the first hour, fourth hour and in the eighth hour respectively.^{16,17} The zero-order plot could clearly demonstrate which formulation was following the USP specification closely.

$$\text{Log} C = \text{Log} C_0 - \frac{k_1 t}{2.303} \quad \text{Equation 2}$$

In Equation 2, C is the amount of undissolved drug at time t , C_0 is drug concentration at $t = 0$ and k_1 is the release rate constant. It is plotted as log cumulative percentage of drug remaining versus time.¹⁵

$$Q_0^{\frac{1}{3}} - Q_t^{\frac{1}{3}} = k_{HC} t \quad \text{Equation 3}$$

In Equation 3, Q_0 is the initial amount of the drug in the tablets; Q_t is the amount of drug release in time t , and k_{HC} is the rate constant for this model. This law represents the concept about the evaluation of drug release pattern changes with the surface area and diameter of particles or tablets.^{15,18}

$$Q = k_H \sqrt{t} \quad \text{Equation 4}$$

In Equation 4, Q is equal to the amount of drug dissolved at time t , k_H is the constant that represents the drug release rate and \sqrt{t} is the square root of time. This process usually follows Fickian diffusion mechanism.¹⁵

Drugs can be released from any hydrated matrix by diffusion, erosion followed by diffusion & swelling followed by erosion and diffusion or by combination of one or more of any of these mechanisms. Korsmeyer-Peppas is mathematical model (Equation 5) that is most extensively used to determine drug release mechanism.¹³



$$\frac{M_t}{M_\infty} = kt^n \quad \text{Equation 5}$$

In Equation 5, M_t is the amount of drug release at time t , M_∞ is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the dosage form, n is the diffusional exponent indicative of the mechanism of drug release.¹⁹

When $n \leq 0.5$, the release mechanism is Fickian diffusion, which normally represents Higuchi drug release kinetics; and when $0.5 < n < 1$, the release is anomalous or non-Fickian diffusion, where drug is released by diffusion coupled with erosion. Then when $n = 1$ the release mechanism is case II transport and it normally follows zero order kinetics, but if $n > 1$, then the release mechanism is super case II transport, and in this transport the release mechanism is unknown or more than one release phenomena is present in the preparation.²⁰

Statistical analysis

Statistical comparisons were performed with Student's ' t ' tests using Microsoft Excel 2007. A p value of 0.05 or less was considered to be significant. Mean values \pm S.D. were calculated for the parameters where applicable.

RESULTS

FTIR study

From the FTIR spectroscopy it has been found that the IR spectra of physical mixture of Diclofenac sodium and polymer (figure 1) were almost similar to IR spectra of the granules.

Both the spectra had peaks at the region $1600 - 600 \text{ cm}^{-1}$, which were similar to the peaks seen in the same region of the IR spectra of Diclofenac sodium. This implies that in both cases the intensity of the peaks of functional groups Diclofenac sodium were stronger than the peaks of the functional groups of Methocel. Another similarity in both the spectra was that the N-H stretching vibration and sp^2 C-H peaks of Diclofenac sodium had overlapped with the -OH peaks of the Methocel. The difference in the two spectra was that the peaks in the Diclofenac sodium and Methocel K100LV CR physical mixture IR spectrum were broader and blunter than the granules IR spectrum.

Physical parameters of the designed matrix tablets

The percentage weight variation of five tablets from each of the five formulations and their hardness, thickness and friability test results are shown in table 2. The percentage weight variation ranged from -0.026% to 2.935%, the hardness, thickness and friability of the formulated tablets ranged from 21.281N to 37.760N, 3.60mm to 4.50mm and 0.264% to 0.620% respectively.

Table 2: Results of physical characterization of matrix tablets ($n=5$).

Formulation Code	% Weight Variation	Hardness N \pm SD	Thickness mm \pm SD	Friability (%)
F1	1.008	21.281 \pm 8.46	3.60 \pm 0.54	0.264
F2	0.312	21.304 \pm 4.16	4.50 \pm 0.00	0.560
F3	2.935	26.479 \pm 0.27	3.74 \pm 0.04	0.620
F4	-0.026	27.170 \pm 1.75	4.08 \pm 0.05	0.618
F5	0.208	37.760 \pm 2.80	4.10 \pm 0.00	0.401

Table 3: The kinetic parameters of the drug release kinetic studies.

Formulation code	Zero-order		First-order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas
	R^2	k_0	R^2	k_1	R^2	k_H	R^2	k_{HC}	n
F1	0.5356	0.0777	0.5813	-0.0008	0.6856	2.351	0.5717	-0.0022	0.2989
F2	0.6836	0.1309	0.7454	-0.0015	0.8266	3.851	0.7285	-0.0037	0.5249
F3	0.8280	0.1567	0.9352	-0.0017	0.9278	4.439	0.9062	-0.0044	0.6650
F4	0.8790	0.1656	0.9526	-0.0015	0.9476	4.599	0.9312	-0.0041	0.7936
F5	0.8897	0.1808	0.9372	-0.0016	0.9544	5.010	0.9260	-0.0045	1.0724

k_0 , k_1 , k_H and k_{HC} rate constants for the corresponding kinetic models.

Drug release kinetic parameters of the designed matrix tablets

The drug dissolution test was carried out for eight hours. The data obtained were fitted into the drug release kinetic equations and curves were plotted. The data were analyzed by the regression coefficient method, and regression coefficient values. The kinetic parameters obtained from these equations were shown in table 3; also the percentage drug releases at the 1h, 4h and 8h were shown in the table 4. The F1, F2 and F5 followed the Higuchi kinetic model, whereas the F3 and F4 followed the first-order kinetics, thus none of them followed the

Hixson-Crowell or Zero-order kinetics, according to their respective highest R^2 values.

Table 4: The % drug release in 1h, 4h and 8h

% drug release in	Formulation Code				
	F1	F2	F3	F4	F5
1h	57.98	38.76	27.68	13.69	11.61
4h	68.59	76.19	71.1	68.26	65.78
8h	72.94	78.78	87.39	80.63	80.92



Since the drug release kinetic models do not clearly define the drug release mechanism of the individual formulations, the Korsmeyer-Peppas release kinetics was used to determine their actual drug release mechanism, through the diffusional exponent, n value.

DISCUSSION

FTIR study

The difference in the FTIR-spectra of physical mixture & granules of the drug and the polymer (figure 1) could be the result of higher interaction of the drug and polymer in the physical mixture than the granules. In the physical mixture there was very small or no water was present, so the reactive functional groups of both the substances might have created weak vander Waals force of attraction or hydrogen bonds, which ultimately reduced the intensity of each other's peaks. Whereas, in the granules water was used and that water had possibly made a larger number of hydrogen bonds with the electronegative oxygen of $-OH$ and ether groups of Methocel, thus leaving the Diclofenac sodium uninterrupted. Therefore in the spectrum of the granules intensified and sharper peaks were obtained. The $-OH$ peaks also appeared sharper might be due to increased number of hydrogen bonds.

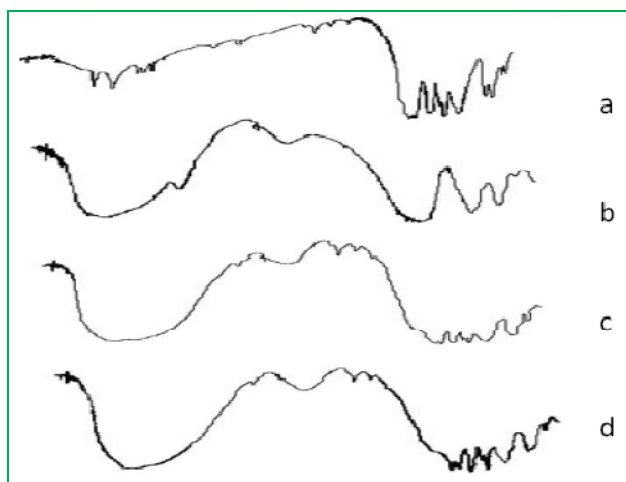


Figure 1: FT-IR spectra showing drug-polymer compatibility ($4000-1200\text{cm}^{-1}$). Spectrum of Diclofenac sodium (a); Methocel K100LV CR (b); physical mixture of drug and polymer (c); granule of drug and polymer (d).

The polymer had a very less interaction with the drug as in both the spectra the peaks for the drug were prominent; and from the spectrum of the granules it could be assumed that the polymer had more affinity for water than the drug, which means that the polymer would only retard the drug release from the matrix tablet but not its action. Finally, it could be concluded that, Methocel K100LV CR is a compatible polymer for developing Diclofenac sodium matrix tablet.

The physical studies of the matrix tablets

The theoretical average weight of five tablets from each formulation was supposed to be 0.385 g. According to USP, tablets with average weight more than 0.324g

should have percentage weight variation within the range of $\pm 5\%$.²¹ The results in table 2 showed that percentage weight variations of the formulated tablets were within the specified range. Moreover, according to USP tablet hardness should range from 39.228 N to 98.07 N.^{21,22} However, the average hardness of the tablets from each formulation did not quite meet the specification as their values varied largely from the specification. But the hardness of the tablets was increased with the increase of the percentage of the polymer (table 1) in the formulations (figure 2) and the hardness of the tablets of F5 were significantly ($p < 0.05$) higher compared to other formulations.

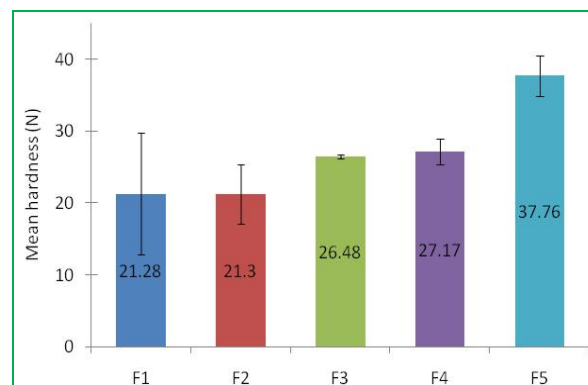


Figure 2: Changes in hardness with the increase of percentage of polymer in the formulations.

The thicknesses of the tablets from each formulation however were quite uniform, shown by their small standard deviation value. Finally, the tablets from each formulation had clearly passed the friability test, since their percentage weight losses were below 1% as specified by the USP (table 2).²³

In vitro drug release studies of the matrix tablets

The *in vitro* drug release study of F1 showed that (table 3), it had the highest R^2 value in case of Higuchi kinetic model (figure 4), which was 0.686, and it had a diffusional exponent, n value of 0.299. This meant that the drug release mechanism for this formulation was Fickian diffusion (figure 3), thus quite naturally it followed Higuchi release kinetics (figure 4).¹⁵

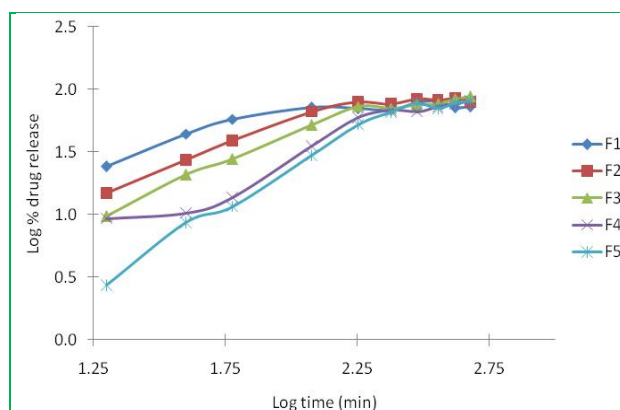


Figure 3: Release profile of Diclofenac sodium from Methocel K100LV CR matrix tablets: Korsmeyer-Peppas plot.

However, from the Zero-order plot (figure 5) and (table 4), it was seen that the percentage drug release from F1 in 1h was 57.98%, which was much higher than the USP specified limit, so it did not exactly elicit the effect of a desirable sustained release dosage form according to the USP.

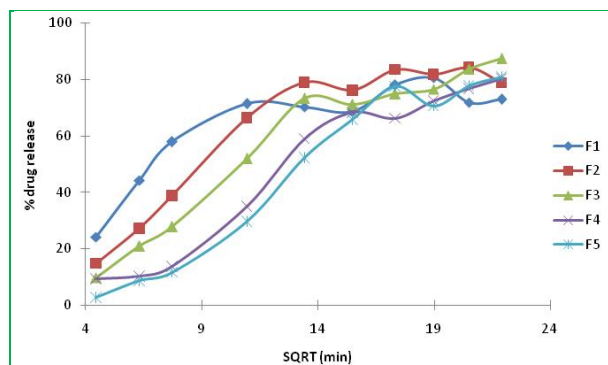


Figure 4: Release profile of Diclofenac sodium from Methocel K100LV CR matrix tablets: Higuchi plot.

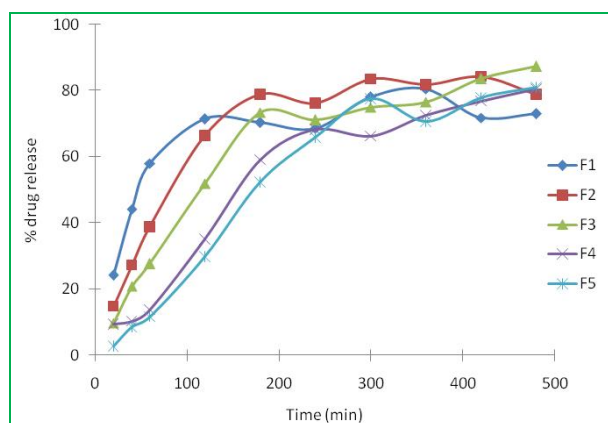


Figure 5: Release profile of Diclofenac sodium from Methocel K100LV CR matrix tablets: Zero order plot.

Like F1, F2 also followed the Higuchi kinetic model (figure 4), as it had the highest ($R^2 = 0.8266$) from this model; but the drug was released from the matrix through anomalous or non-Fickian diffusion, since it had $n=0.5249$ (table 3). However, its Zero-order kinetics (figure 5 and table 4) revealed that it had undesirable percentage drug release from the matrix in the 1st and 4th hour. The percentages of drug release in these hours greatly exceeded the USP specified limits. Most of the drugs were released from the matrix within the first four hours. This kind of release pattern observed in F1 and F2 may be due to the presence of lesser amount of Methocel K100LV CR polymer and higher amount of Lactose. Therefore, both the F1 and F2 failed to meet the criteria of suitable sustained release dosage form.

However, when the percentages of drug release from the tablets were compared from table 4, it has been found that the percentage drug release of F3 in the 1st hour was 27.68%, which was well above the USP specified value, whereas the percentage drug release of F4 in the 1st hour was 13.69%, which was within the USP specified limit. The percentages of drug release of F4 at the 4th and 8th hours were also within the USP specified. Moreover, it has been

found that drug release rate of F3 was faster than that of F4, but the drug release rate of F4 was fairly steadier than F3 (figure 6) and it also had higher R^2 value than the F3. Therefore it was a better formulation than F3. Both the formula followed the first order release kinetic which indicates that the drug release is dependent on concentration gradient between the static liquid layer next to the solid surface and the dissolution media.²⁴

The *in vitro* drug release study of F5 revealed that it had the highest R^2 value of 0.9544 in case of Higuchi kinetic model, which meant it followed this release kinetic model. However it had the n value of 1.072, which indicated that F5 followed super case II transport mechanism as its drug release mechanism; since when $n > 1$, then the release mechanism is super case II transport (figure 3). When the data on table 4 were analyzed it has found that F5 like F4 closely followed the USP specification for desirable sustained release dosage form. Apart from the fact that F5 did not follow Fickian drug release mechanism, from the physical parameters (table 2) and *in vitro* drug release studies indicated that it has sustained release property closest to the specifications.

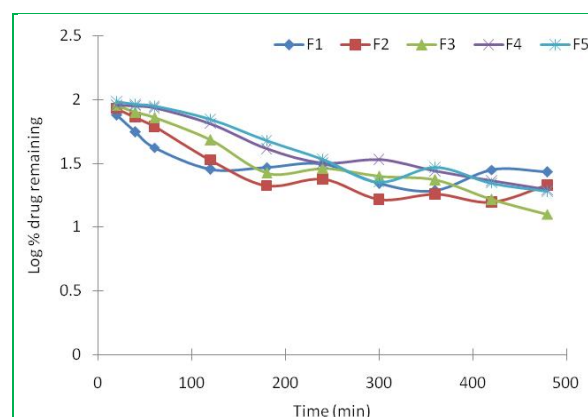


Figure 6: Release profile of Diclofenac sodium from Methocel K100LV CR matrix tablets: First order plot.

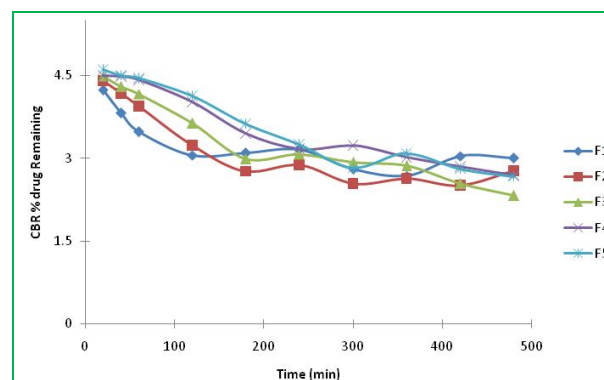


Figure 7: Release profile of Diclofenac sodium from Methocel K100LV CR matrix tablets: Hixson-Crowell plot.

None of the formulations, however, followed the Hixson-Crowell drug release kinetics (figure 7), which was indicated by the fact that none of the formulations had their highest R^2 values from this kinetic model, and thus none of the tablets released their drugs through the

changes of the surface area and diameter of particles or the tablets.^{15,18}

The overall drug release pattern showed that the increasing polymer content slowed the drug release rate, and gradually provided a steady and desirable release rate, as it was seen in case of F4 and F5. Whereas, the formulations with low polymer content (F1 and F2) had an undesirable high release rate initially, however, at the end moment they could not even release 80% of the drugs. Also, the drug release mechanism varied with the increase of the polymer content. F1 which had the lowest polymer content, 12.99%, only showed Fickian diffusion mechanism and also followed Higuchi model as expected.^{15,18} The F2 and F5, which had higher polymer content than F1, even though followed Higuchi model. Both the formula showed that their drug release mechanism involved other release mechanism like swelling & erosion and that they were not solely dependent on diffusion mechanism. F3 and F4 also showed non-Fickian or anomalous drug transport which also contained higher polymer ratio than the F1.

CONCLUSION

The study revealed that sustained release dosage form of Diclofenac sodium and Methocel K100LV CR can be successfully manufactured by direct compression method & the drug and particular grade of HPMC is compatible with each other. The *in vitro* dissolution study revealed that with the increase in polymer proportions in the formulation the drug release rate becomes more controlled and complies greatly with the USP specifications for sustained release dosage form. However, the increased polymer content could contribute to more than one drug release mechanism in a single formulation.

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