IJPPR (2021), Vol. 13, Issue 3 *Research Article*

INTERNATIONAL JOURNAL OF BIOPHARMACEUTICAL & TOXICOLOGICAL RESEARCH

IN VITRO RELEASE PROFILE OF EXTENDED RELEASE MATRIX TABLET OF DICLOFENAC SODIUM BASED ON HYDROPHOBIC MATRIX USING ETHYL CELLULOSE POLYMER

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Keywords:
Diclofenac Sodium, matrix tablet, COX, granulation, prostaglandin synthesis

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ABSTRACT:
The anti-inflammatory action effects of Diclofenac sodium are believed to be due to inhibition of both leukocyte migration and enzyme COX (COX-1&COX-2) leading to peripheral inhibition of prostaglandin synthesis. Formulation of Diclofenac sodium was formed by different techniques like direct compression and wet granulations having 100 mg strength. Batch M1 was formed by direct compression and batch M3 was formed by wet granulations. Four batches (M3, M4, M5 and M6) were formed to check the effect of different viscosity grade of ethyl cellulose. Four batches (M7, M8, M9 and M10) were formed to check the effect of different fine particle grade of ethyl cellulose. Batches M10 and M11 shows the comparisons on the basis of different concentrations of the binder (Microcrystalline cellulose). Batches M10 and M12 shows the comparisons on the basis of different concentrations of the ethyl cellulose. Batches M13 and M14 shows the comparisons on the basis of different concentrations of the diluents with their elastic and plastic properties. Batches M15 and M16 show the comparisons with batch M10 and M13 using different diluents in double concentrations.
The overall studies show that the formulation techniques were shown an effect on extended release dosage forms. The wet granulation technique is the best technique for extended release dosage forms. This technique gives the best evaluation parameters of the tablets. Another studies show that the concentration of binder plays an important role in the release of extended release. When the concentration of the binder is increased, the release of the dosage form will decrease which is necessary for extended release.

Introduction:
Diclofenac sodium exhibits anti-inflammatory, analgesic, and antipyretic activities. The anti-inflammatory action are believed to be due to inhibition of both leukocyte migration and enzyme COX (COX-1 & COX-2) leading to peripheral

inhibition of prostaglandin synthesis. Antipyretic effect may be due to action in hypothalamus, resulting in peripheral dilation, increased cutaneous blood flow and subsequent heat dissipation. It is a benzene acetic acid derivative, designated chemically as 2-[(2, 6-dichlorophenyl) amino] benzene acetic acid, monosodium salt. It is a white or off- white powder having melting point is 156-158oC. It is soluble in methanol, soluble in ethanol, sparingly soluble in water and practically insoluble in chloroform and in dilute acid. Diclofenac should not be stored above 30°C (86°F) and should be protected from moisture. The n-octanol/water partition coefficient is 13.4 at pH 7.4 and 15.45 at pH 5.2. Diclofenac sodium has a dissociation constant (pKa) of 4.0 ± 0.2 at 25°C in water. The structure of Diclofenac Sodium is given below (figure 1)

Figure 1: The structure of Diclofenac Sodium

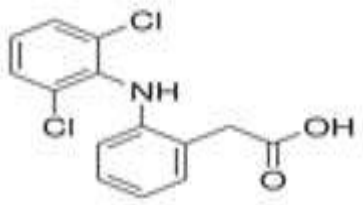


Table 1: Pharmacokinetics of Diclofenac Sodium

Bioavailability	40-45%
Plasma Half Life	2 hrs.
Plasma Protein Binding	99%
Peak Plasma Concentration (C_{max})	1- 4.5 hours
Excretion	Renal Excretion (65%) Metabolic Excretion (35%)

Material and methods

Diclofenac sodium was obtained from Amoli Orgenics; Ethylcellulose with different viscosity and particle size grades were received as a gift from Dow Chemical Company, USA; Microcrystalline cellulose was obtained from FMC Biopolymers; Lactose 200M was obtained from DMV fonsera excipients GmbltScokc, Germany; Polyvinylpyrrolidine from ISP technology; Dicalcium phosphate by Signet chemicals; Magnesium stearate from Mallinckrodt, USA; and Talc from Barrents, USA. Ethyl cellulose polymer is available in Standard Premium and Standard FP Premium grades, which are designed to meet the requirements of pharmaceutical applications.

Experimental methods

Two batches with different grades of Ethyl cellulose (Ethocel 20 cps & Ethocel 45 cps) were prepared using direct compression method.

Table 2: Formulation of Diclofenac sodium tablet with Ethylcellulose for 100mg strength

Batch no.	M 1	M 2
Grade	Ethocel 20cps	Ethocel 45cps
Hardness	5.0-6.0kp	5.0-6.0kp
Intragranular Ingredients	mg/tab	mg/tab
Diclofenac sodium	100	100
Ethyl cellulose	100	100
Microcrystalline cellulose (Avicel 101)	94	94
Extragranular Ingredients		
Talc	3	3
Magnesium stearate	3	3
Total	300	300

Wet granulation

Batch was prepared with Ethyl cellulose (Ethocel 20cps) using wet granulation method and compared with formulation of direct compression method. Formula is given in Table 3.

Table 3: Formulation of Diclofenac sodium tablet using Ethyl cellulose for 100mg strength with direct compression and wet granulation methods

Batch no.	M 1	M 3
Grade	Ethocel 20cps	Ethocel 20cps
Hardness	5.0-6.0kp	5.0-6.0kp
Intragranular Ingredients	mg/tab	mg/tab
Diclofenac sodium	100	100
Ethyl cellulose	100	100
Microcrystalline cellulose(Avicel 101)	94	94
Extragranular Ingredients		
Talc	3	3
Magnesium stearate	3	3
Total	300	300

Effect of different viscosity grades

Formulation batches were prepared using different viscosity grades of Ethyl cellulose Standard Premium (Ethocel 45cps, Ethocel 20cps, Ethocel 10cps, Ethocel 7cps), Table 4

Table 5: Formulation of diclofenac sodium tablets using Ethyl cellulose FP grades with wet granulation method.

Batch no.	M 7	M 8	M 9	M 10	M 5	M 6
Grade	Ethocel 100FP	Ethocel 10FP	Aqualon 10cps	Ethocel 7FP	Ethocel 10cps	Ethocel 7cps
Hardness	8.0-8.5kp	10-11kp	11-12kp	11-12kp	7.0-8.0kp	7.0-8.0kp
Intragranular Ingredients	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab
Diclofenac sodium	100	100	100	100	100	100
Ethyl cellulose	100	100	100	100	100	100
Microcrystalline cellulose (Avicel 101)	79	79	79	79	79	79
Polyvinylpyrollidine (K-30)	15	15	15	15	15	15
Ethanol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Extragranular Ingredients						
Talc	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3
Total	300	300	300	300	300	300

Effect of particle size

Formulation batches were prepared using different Ethyl cellulose FP grades and compared with Ethyl cellulose Standard Premium grades. Formula is given in Table 5.

Table 6: Formulation of Diclofenac sodium tablets by increasing binder concentration in formula with respect to optimum binder concentration batch.

Batch no.	M 11	M 10
Grade	Ethocel 7FP	Ethocel 7 FP
Hardness	9.0-10.0kp	11.0-12.0kp
Intragranular Ingredients	mg/tab	mg/tab
Diclofenac sodium	100	100
Ethylcellulose	100	100
Microcrystalline cellulose (Avicel101)	74	79
Polyvinylpyrrolidine (K-30)	20	15
Ethanol	q.s.	q.s.
Extragranular Ingredients		
Talc	3	3
Magnesium stearate	3	3
Total	300	300

Effect of particle size

Formulation batches were prepared using different Ethyl cellulose FP grades and compared with Ethyl cellulose Standard Premium grades. Formula is given in Table 5.

Table 6: Formulation of Diclofenac sodium tablets by increasing binder concentration in formula with respect to optimum binder concentration batch.

Batch no.	M 11	M 10
Grade	Ethocel 7FP	Ethocel 7 FP
Hardness	9.0-10.0kp	11.0-12.0kp
Intragranular Ingredients	mg/tab	mg/tab
Diclofenac sodium	100	100
Ethylcellulose	100	100
Microcrystalline cellulose (Avicel101)	74	79
Polyvinylpyrrolidine (K-30)	20	15
Ethanol	q.s.	q.s.
Extragranular Ingredients		
Talc	3	3
Magnesium stearate	3	3
Total	300	300

Effect of increasing polymer concentration

Formulation batch was prepared by increasing the polymer concentration in the formula with Ethyl cellulose (Ethocel 7FP) and microcrystalline cellulose and compared with less polymer concentration. Formula is given in Table 7

Table 7: Formulation of diclofenac sodium tablets with increased polymer concentration and compared to less polymer concentration.

Batch no.	M 12	M 10
Grade	Ethocel 7FP	Ethocel 7FP
Hardness	19.0-20.0kp	11.0-12.0kp
Intragranular Ingredients	mg/tab	mg/tab
Diclofenac sodium	100	100
Ethylcellulose	150	100
Microcrystalline cellulose (Avicel 101)	129	79
Polyvinylpyrrolidine (K-30)	15	15
Ethanol	q.s.	q.s.
Extragranular Ingredients		
Talc	3	3
Magnesium stearate	3	3
Total	400	300

Effect of various diluents with their elastic or plastic properties

Formulations were prepared using different diluents as Lactose, Dicalciumphosphate and microcrystalline cellulose with Ethyl cellulose (Ethocel 7FP) and compared to select the best diluent for further formulations. Formula is given in Table 8

Table 8: Formulation of Diclofenac sodium tablets using different diluents with Ethylcellulose (Ethocel 7FP) with wet granulation method.

Batch no.	M 13	M 14	M 10
Grade	Ethocel 7FP	Ethocel 7FP	Ethocel 7FP
Hardness	11.5-12.0kp	10.0kp	11.0-12.0kp
Intragranular Ingredients	mg/tab	mg/tab	mg/tab
Diclofenac sodium	100	100	100
Ethyl cellulose	100	100	100
Dicalcium phosphate	79	-	-
Lactose (200M)	-	79	-
Microcrystalline cellulose (Avicel 101)	-	-	79
Polyvinylpyrrolidine (K-30)	15	15	15
Ethanol	q.s.	q.s.	q.s.
Extragranular Ingredients			
Talc	3	3	3
Magnesium stearate	3	3	3
Total	300	300	300

In – Vitro evaluation

1. **Evaluation of granules** Bulk Density (BD): Bulk density was determined according to Method I as reported in USP XXXII. The drug powder was passed through BSS # 25 screens to break up agglomerates. The drug powder was introduced into a dry 100 ml tarred measuring cylinder. The powder was then carefully labeled, if necessary, without the application of force and the unsettled volume (bulk volume) was noted. The weight of the powder was also noted and the bulk density was calculated as

   Bulk density (g/ml) = Weight of powder (g) / Bulk volume (ml)

Tapped density (TD)

After the initial volume Va was observed, the cylinder containing the sample was mechanically tapped by raising the cylinder and allowing it to drop under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further changes was observed in volume was noted and tapped volume Vb was noted. The tapped density was calculated from the formula given below:

Tapped Density (g/ml) = Weight (g) / Tapped volume (ml)

The flow properties of granules before compression were characterized in terms of angle of repose, Carr's index and Hausner ratio. For determination of angle of repose, the granules were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0cm above hard surface. The granules were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The tan-1 of the (height of the pile/ radius of its base) gave the angle of repose. Granules were poured gently through a glass funnel into a graduated cylinder cut exactly to 10ml mark. Excess granules were removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0cm until the time when there was no more decrease in the volume. Bulk density and tapped density were calculated.

Hausner's Ratio = Tapped density / Bulk density

Carr's Index (%Compressibility Index) = [100× (TD-BD)]/TDC)

Table 9: Results of flow properties of granules

Batch No.	Bulk Density	Tapped Density	Angle of Repose	Hausner's ratio	Carr's index
M1	0.520	0.580	25.5	1.11	10.34
M2	0.500	0.605	25.0	1.21	17.35
M3	0.520	0.580	25.5	1.11	10.34
M4	0.530	0.598	26.0	1.12	11.37
M5	0.544	0.610	26.57	1.12	10.81
M6	0.575	0.665	28.56	1.15	13.53
M7	0.610	0.665	31.81	1.09	8.27
M8	0.625	0.685	32.93	1.09	8.75
M9	0.645	0.705	35.31	1.09	8.51
M10	0.650	0.720	37.2	1.10	9.72
M11	0.680	0.730	38.65	1.07	6.84
M12	0.450	0.521	22.25	1.15	13.62
M13	0.512	0.550	25.1	1.07	6.90
M14	0.490	0.534	24.9	1.08	8.23
M15	0.504	0.524	25.05	1.03	3.81
M16	0.650	0.721	37.2	1.10	9.84
M17	0.450	0.542	22.25	1.20	16.97

Evaluation of colon targeted matrix tablets Weight variation tests of tablets

Weight variation of the formulation was performed as per USP. 20 tablets were weighed using a Scale-Tec electronic balance individually and compared with the average weight of the twenty tablets.

Hardness of the tablets

The hardness of five tablets was determined using Pfizer type hardness tester and the average values were calculated.

Friability of tablets

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W0) or a sample of tablets were dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%

% Friability = $(W_0\text{-}W)/W0 \times 100$

Table 10: Results of evaluation of parameters of tablets from different batches

Batch no.	Average weight(mg)	Friability %	Hardness (kp)
M1	290	0.8620	4
M2	300	0.7200	2
M3	295	0.3589	5
M4	305	0.3591	4
M5	297	0.3728	5
M6	300	0.3207	3
M7	295	0.2216	4
M8	299	0.1705	6
M9	301	0.372	5
M10	299	0.1864	4
M11	298	0.2518	6
M12	305	0.3390	5
M13	303	0.1963	2
M14	295	0.2388	5
M15	298	0.2366	4
M16	300	0.1897	3
M17	296	0.3566	4

Drug release studies:

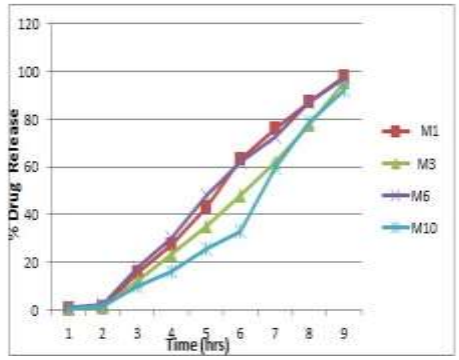
Studies were carried out using USP-III dissolution apparatus. Drug release studies were performed in 0.1 N HCl (2 hours), pH 7.5 Sorenson Phosphate Buffer (3 hours) and pH 7.5 Phosphate Buffered saline (PBS) with rat caecal contents. Samples of 1 ml were taken from the medium at the definite time intervals and diluted to ten times by same dissolution media. The samples were assayed by using double beam UV spectrophotometer.

Results of drug release studies in various dissolution media

Table 11: Percentage release of Diclofenac sodium in Phosphate Buffer pH 7.5 from tablets

Time(hrs)	M1	M3	M6	M10
1	0.75	0.60	1.07	0.85
2	1.25	1.12	2.12	1.52
4	15.65	12.25	18.15	10.15
6	27.26	23.41	29.98	16.45
8	42.98	35.45	48.29	25.65
12	63.35	48.24	62.23	33.12
16	76.25	62.15	72.51	60.11
20	87.25	77.84	87.12	78.88
24	97.64	95.45	97.28	92.12

Figure 2: Percentage release of Diclofenac sodium in Phosphate Buffer pH 7.5 from tablets



Study of Release Kinetics of batch M1

Table 12: *In vitro* drug release parameters for Batch M1

Time (hours)	% CDR	Log % CDR	Cube root of % drug remaining	Log % cumulative drug remaining	Square root time	Log time
1	0.75	-0.1249	4.598	1.9967	1	0
2	1.25	0.0969	4.622	1.9945	1.414	0.3010
4	15.65	1.1945	4.385	1.9260	2.00	0.6021
6	27.26	1.4355	4.174	1.8617	2.449	0.7782
8	42.98	1.6332	3.849	1.7560	2.828	0.9031
12	63.35	1.8017	3.321	1.5640	3.464	1.0792
16	76.25	1.8822	2.874	1.3756	4.000	1.2041
20	87.25	1.9407	2.336	1.1055	4.472	1.3010
24	97.64	1.9896	1.331	0.3729	4.899	1.3802

Fig 3: Diclofenac Sodium release kinetics of batch M1 according to Zero order kinetics.

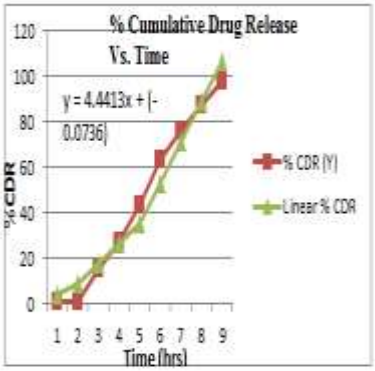


Fig 4: Diclofenac Sodium release kinetics of batch M1 according to First order kinetics.

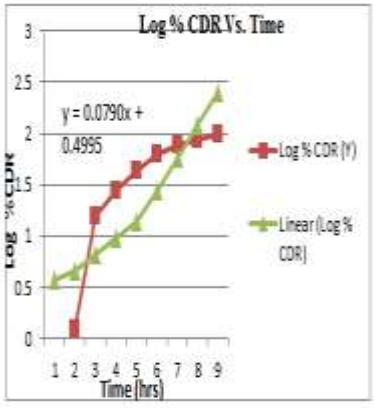


Fig 5: Diclofenac sodium release kinetics of batch M1 according to Hixon-Crowell's kinetics

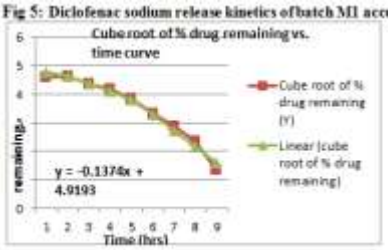


Fig 6: Diclofenac Sodium release kinetics of batch M1 according to Higuchi kinetics.

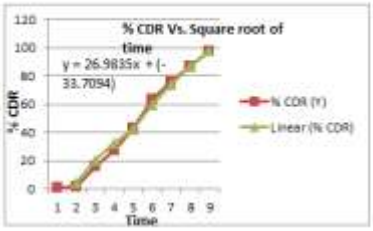
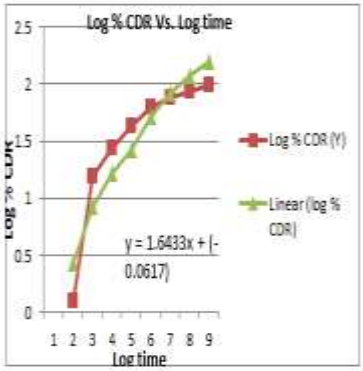


Fig 7: Diclofenac Sodium release kinetics of batch M1 according to Korsmeyer- Peppas kinetics.



The statistical kinetics values for the batch M1 is represented in Table 13

Table 13: Statistical kinetics values of batch M1

Kinetic models	R^2	Slope
Zero-order	0.9892	4.4413
First-order	0.9875	0.0790
Higuchi kinetics	0.9912	26.9835
Hixon-crowell	0.9905	-0.1374
Korsmeyer-peppas	0.9870	1.6433

Study of Release Kinetics of batch M3

Table 14: *In vitro* drug release parameters for Batch M3

Time (hours)	% CDR	Log % CDR	Cube root of % drug remaining	Log % cumulative drug remaining	Square root time	Log time
1	0.60	-0.2218	4.631	1.9973	1	0
2	1.12	0.0492	4.624	1.9951	1.414	0.3010
4	12.25	1.0881	4.443	1.9432	2.00	0.6021
6	23.41	1.3694	4.246	1.8841	2.449	0.7782
8	35.45	1.5496	4.011	1.8098	2.828	0.9031
12	48.24	1.6834	3.727	1.7139	3.464	1.0792
16	62.15	1.7934	3.357	1.5780	4.000	1.2041
20	77.84	1.8912	2.808	1.3455	4.472	1.3010
24	95.45	1.9797	1.657	0.6580	4.899	1.3802

Fig 8: Diclofenac Sodium release kinetics of batch M3 according to Zero order kinetics.

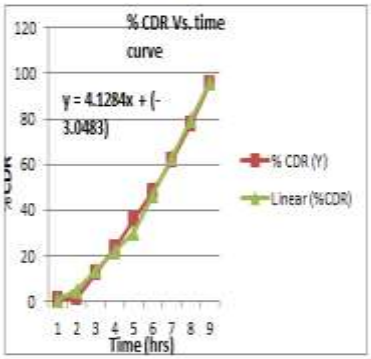


Fig 9: Diclofenac Sodium release kinetics of batch M3 according to First order kinetics.

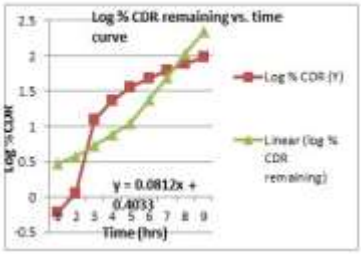


Fig 10: Diclofenac Sodium release kinetics of batch M3 according to Hixon-Crowell's kinetics.

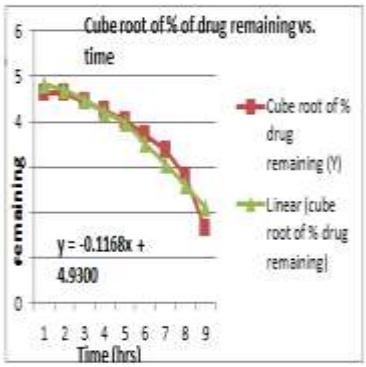


Fig 11: Diclofenac Sodium release kinetics of batch M3 according to Higuchi kinetics.

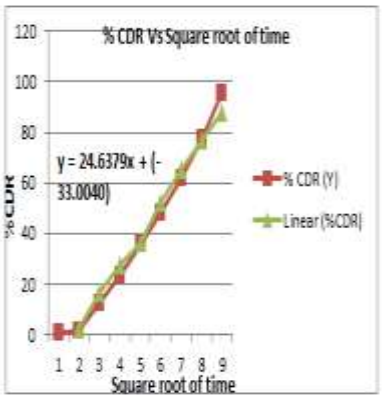
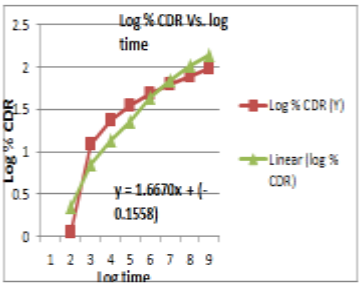


Fig 12: Diclofenac Sodium release kinetics of batch M3 according to Korsmeyer- Peppas kinetics.



The statistical kinetics values for the batch M3 is represented in Table 15

Table 15: Statistical kinetics values of batch M3

Kinetic models	R^2	Slope
Zero-order	0.9902	4.1284
First-order	0.9865	0.0812
Higuchi kinetics	0.9932	24.6379
Hixon-crowell	0.9892	-0.1168
Korsmeyer-peppas	0.9887	1.6670

Among the entire kinetic model studied for the batch (M3), it was found that the batch followed Higuchi kinetics because of having maximum R2 value of 0.9932 (closest to 1.0).

Table 16: *In vitro* drug release parameters for Batch M6

Time (hours)	% CDR	Log % CDR	Cube root of % drug remaining	Log % cumulative drug remaining	Square root time	Log time
1	1.07	0.0293	4.625	1.9953	1	0
2	2.12	0.3263	4.608	1.9906	1.414	0.3010
4	18.15	1.2588	4.341	1.9130	2.00	0.6021
6	29.98	1.4768	4.121	1.8452	2.449	0.7782
8	48.29	1.6838	3.725	1.7135	2.828	0.9031
12	62.23	1.7939	3.355	1.5771	3.464	1.0792
16	72.51	1.8603	3.018	1.4391	4.000	1.2041
20	87.12	1.9401	2.344	1.1099	4.472	1.3010
24	97.28	1.9880	1.396	0.4345	4.899	1.3802

Fig 13: Diclofenac Sodium release kinetics of batch M6 according to Zero order kinetics

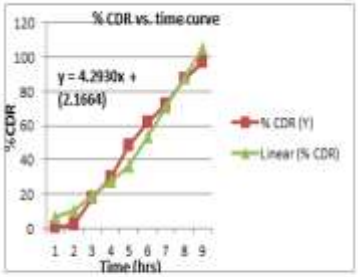


Fig 14: Diclofenac Sodium release kinetics of batch M6 according to First order kinetics

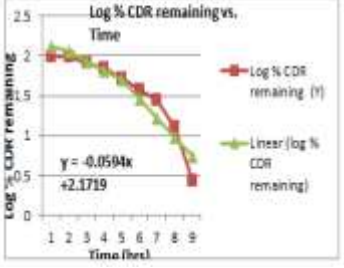


Fig 15: Diclofenac Sodium release kinetics of batch M6 according to Hixon-Crowell's kinetics

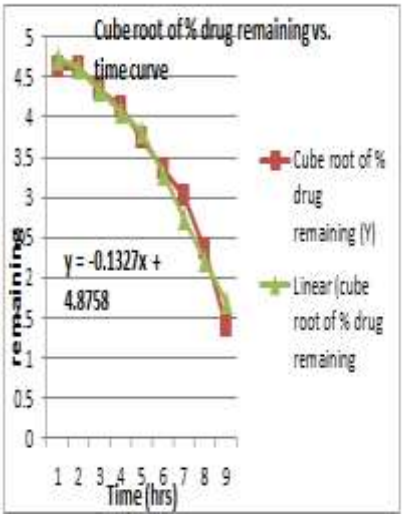


Fig 16: Diclofenac Sodium release kinetics of batch M6 according to Higuchi kinetics.

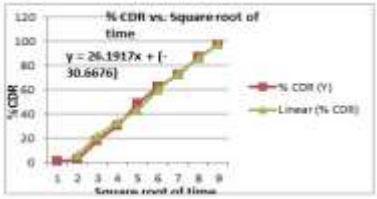
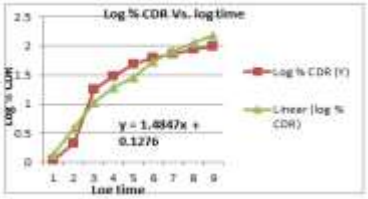


Fig 17: Diclofenac Sodium release kinetics of batch M6 according to Korsmeyer- Peppas kinetics.



The statistical kinetics values for the batch M6 is represented in Table 17

Table 17: Statistical kinetics values of batch M6

Kinetic models	R^2	Slope
Zero-order	0.9888	4.2930
First-order	0.9865	-0.0594
Higuchi kinetics	0.9913	26.1917
Hixon-crowell	0.9896	-0.1327
Korsmeyer-peppas	0.9882	1.4847

Among the entire kinetic model studied for the batch (M6), it was found that the batch followed Higuchi kinetics because of having maximum R2 value of 0.9913 (closest to 1.0).

Study of Release Kinetics of batch M10

Table 18: *In vitro* drug release parameters for Batch M10

Time (hours)	% CDR	Log % CDR	Cube root of % drug remaining	Log % cumulative drug remaining	Square root time	Log time
1	0.85	-0.0705	4.628	1.9962	1	0
2	1.52	0.1818	4.617	1.9933	1.414	0.3010
4	10.15	1.0064	4.478	1.9535	2.00	0.6021
6	16.45	1.2161	4.371	1.9219	2.449	0.7782
8	25.65	1.4090	4.205	1.8712	2.828	0.9031
12	33.12	1.5200	4.059	1.8252	3.464	1.0792
16	60.11	1.7789	3.417	1.6008	4.000	1.2041
20	78.88	1.8969	2.764	1.3246	4.472	1.3010
24	92.12	1.9643	1.990	0.8965	4.899	1.3802

Fig 18: Diclofenac Sodium release kinetics of batch M10 according to Zero order kinetics.

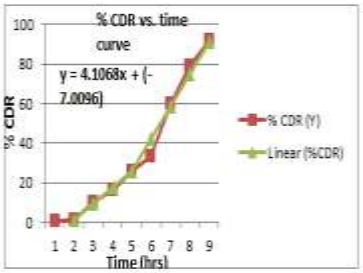


Fig 19: Diclofenac Sodium release kinetics of batch M10 according to First order kinetics.

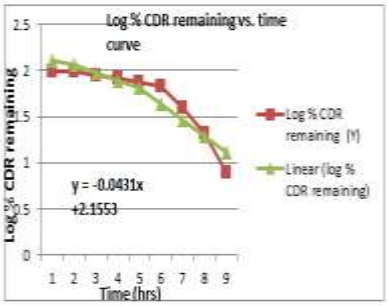


Fig 20: Diclofenac Sodium release kinetics of batch M10 according to Hixon-Crowell's kinetics.

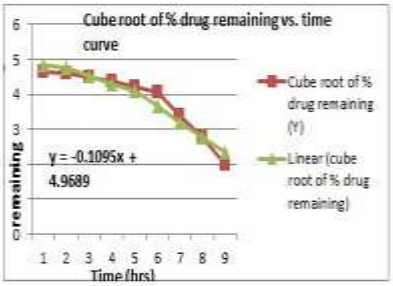


Fig 21: Diclofenac Sodium release kinetics of batch M10 according to Higuchi kinetics.

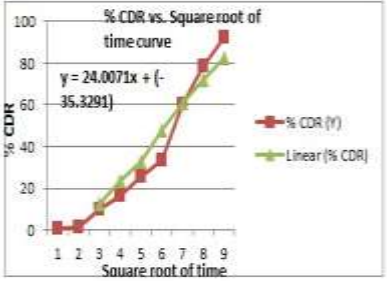
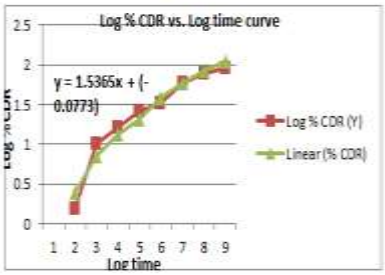


Fig 22: Ibuprofen release kinetics of batch M10 according to Korsmeyer- Peppas kinetics.



The statistical kinetics values for the batch M10 is represented in Table 19

Table 19: Statistical kinetics values of batch M 10

Kinetic models	R^2	Slope
Zero-order	0.9892	4.1068
First-order	0.9867	-0.0431
Higuchi kinetics	0.9904	24.0071
Hixon-crowell	0.9872	-0.1095
Korsmeyer-peppas	0.9867	1.5365

Among the entire kinetic model studied for the batch (M10), it was found that the batch followed Higuchi kinetics because of having maximum R2 value of 0.9904 (closest to 1.0).

Conclusion

Seventeen batches of extended release colon targeted tablets were made using various grade of ethyl cellulose in their maximum and minimum concentrations. Various effects of different grades on the drug release were noted. Formulation of Diclofenac sodium was formed by different techniques like direct compression and wet granulations having 100 mg strength. Batch M1 was formed by direct compression and batch M3 was formed by wet granulations. Four batches (M3, M4, M5 and M6) were formed to check the effect of different viscosity grade of ethyl cellulose. Four batches (M7, M8, M9 and M10) were formed to check the effect of different fine particle grade of ethyl cellulose. Batches M10 and M11 shows the comparisons on the basis of different concentrations of the binder (Microcrystalline cellulose). Batches M10 and M12 shows the comparisons on the basis of different concentrations of the ethyl cellulose. Batches M13 and M14 shows the comparisons on the basis of different concentrations of the diluents with their elastic and plastic properties. Batches M15 and M16 show the comparisons with batch M10 and M13 using different diluents in double concentrations.

Results show that when ethyl cellulose was used alone in a same concentration in batch M1 and M3 with direct compression and wet granulation respectively, the batch M3 give the best evaluation parameter like weight variation, flow property, friability and hardness etc. as comparison to M1. The wet granulation technique is the best suitable technique for extended release dosage forms as comparison to direct compression. The M3 batch show less release as comparison to M1, it means this technique is best for extended release. When the percentage of microcrystalline cellulose was increased in batch M10 as comparison to other batches, the tablet shows the best extended release than the other batches. Some batches show the effect of different concentrations of diluents but the major effect of the binder was shown for the release of the drug in the formulations.

The overall studies show that the formulation techniques were shown an effect on extended release dosage forms. The wet granulation technique is the best technique for extended release dosage forms. This technique gives the best evaluation parameters of the tablets. Another studies show that the concentration of binder plays an important role in the release of extended release. When the concentration of the binder is increased, the release of the dosage form will decrease which is necessary for extended release. Out of all batches the batch M10 is the best suitable batch for the extended release. The data obtained from in vitro dissolution studies were fitted in different models to determine the mechanism of drug release like Zero-Order Kinetics, First-Order Kinetics, Higuchi Kinetics, Hixon-Crowell`s Kinetics and Korsmeyer-Peppas Kinetics. The batch M10 shows the best result of release as comparison to the other batches.

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