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DEVELOPMENT OF EXTENDED RELEASE DOSAGE FORM OF NSAIDS USED IN COLON TARGETED DRUG DELIVERY.

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ABSTRACT

In the present work, extended release matrix tablets of Diclofenac Sodium was formulated above its site of absorption.Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities. 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. Antipyretic effect may be due to action in hypothalamus, resulting in peripheral dilation, increased cutaneous blood flow and subsequent heat dissipation. Diclofenac sodium is a benzene acetic acid derivative, designated chemically as 2-[(2, 6-dichlorophenyl) amino] benzene acetic acid, monosodium salt. Formulation of Diclofenac sodium was formed by different techniques like direct compression and wet granulations having 100 mg strength

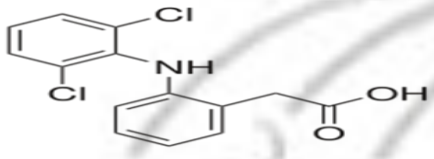
Keywords: Diclofenac Sodium, matrix tablet, COX, granulation, prostaglandin synthesis.

INTRODUCTION

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities. 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. Antipyretic effect may be due to action in hypothalamus, resulting in peripheral dilation, increased cutaneous blood flow and subsequent heat dissipation. Diclofenac sodium 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 156-158^{o}C. 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



Diclofenac is used to relieve pain and swelling (inflammation) from various mild to moderate painful conditions, for conditions related to inflammation, swelling, stiffness, pain, for relief of signs and symptoms of osteoarthritis, for relief of signs and symptoms of rheumatoid arthritis, for acute or long-term use in the relief of signs and symptoms of ankylosing spondylitis, for treatment of muscle aches, backaches, dental pain, menstrual cramps and sports injuries.

Pharmacokinetics

Table 1: Pharmacokinetics of Diclofenac Sodium

Bioavailability	40-45%
Plasma Half Life	2 hrs.
Plasma Protein Binding	99%
Peak Plasma Concentration	1- 4.5 hours
Excretion	Renal Excretion (65%) Metabolic Excretion (35%)
Drug Interaction	Diclofenac, like other NSAIDs is associated with several suspected or probable interactions that affect the action of other drugs. Some examples are discussed below. Diclofenac may increase the blood levels of lithium (Eskalith) by reducing the excretion of lithium by the kidneys. Increased levels of lithium may lead to lithium toxicity. Diclofenac may reduce the blood pressure lowering effects of blood pressure medications. This may occur because prostaglandins play a role in the regulation of blood pressure. When diclofenac is used in combination with aminoglycoside antibiotics [for example, gentamicin (Garamycin)] the blood levels of the aminoglycoside may increase, presumably because the elimination of aminoglycosides from the body is reduced. This may lead to more aminoglycoside-related side effects. Individuals taking oral blood thinners or anticoagulants [for example, warfarin (Coumadin)] should avoid diclofenac because diclofenac also thins the blood, and excessive blood thinning may lead to bleeding. Combining NSAIDs with methotrexate (Rheumatrex, Trexall) may reduce the elimination of methotrexate from the body and result in increased side effects from methotrexate.

MATERIAL AND METHODS

Diclofenac sodium was obtained from AmoliOrgenics; 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

Preparation of Extended Release Matrix Tablets of Diclofenac Sodium

The composition of different formulations of extended release matrix tablets was shown in table 2. The ingredients were weighed accurately and mixed thoroughly. Tablets of Diclofenac Sodium were prepared by direct compression & wet compression method and their release profiles were compared to select the manufacturing process for further studies. Two batches with different grades of Ethyl cellulose (Ethocel 20cps &Ethocel 45cps) 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 Ethylcellulose (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 4: Formulation of Diclofenac sodium tablet using Ethyl cellulose Standard Premium grades with wet granulation method

Batch no.	**M 3**	**M 4**	**M 5**	**M 6**
Grade	Ethocel 45cps	Ethocel 20cps	Ethocel 10cps	Ethocel 7cps
Hardness	7.0-8.0kp	5.0-6.0kp	7.0-8.0kp	7.0-8.0kp
Intragranular Ingredients	mg/tab	mg/tab	mg/tab	mg/tab
Diclofenac sodium	100	100	100	100
Ethyl cellulose	100	100	100	100
Microcrystalline cellulose	79	79	79	79
Polyvinylpyrollidine (K-30)	15	15	15	15
Ethanol	q.s.	q.s.	q.s.	q.s.
Extragranular Ingredients				
Talc	3	3	3	3
Magnesium stearate	3	3	3	3
Total	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 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 increasing binder concentration in formula

Formulation batch was prepared with increased concentration of binder and was compared to formulated batch containing optimum binder concentration using Ethocel 7FP, Table 6.

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 $V_a$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 V_b 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)]/TD

Table 6: 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

2. 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 (W_0) 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% w/w.

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

Table 7: 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 releasestudies:

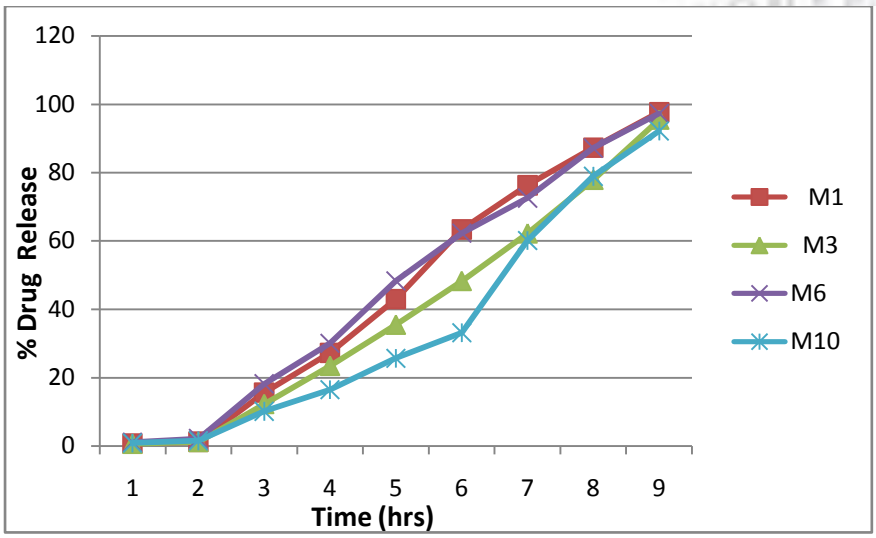
Studies were carried out using USP-III dissolution apparatus. Drug release studies were performed in 0.1 N HCl (2 hours), pH 7.5 Sorenson Phosphate Buffer (3 hours) and pH 7.5 Phosphate Buffered saline (PBS) with rat caecal contents. Samples of 1 ml were taken from the medium at the definite time intervals 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 7.10: 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 7.3: Percentage release of Diclofenac sodium in Phosphate Buffer pH 7.5 from tablets



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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