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FORMULATION AND *IN VITRO* EVALUATION OF DICLOFENAC SODIUM DELAYED RELEASE TABLETS

BHARGHAVA BHUSHAN RAO PATHANGE*, K. E. V. NAGOJI, PRAVEEN GADDAM, RAJU JUKANTI and MANOJ KUMAR JALAGAM [a]

Department of Pharmaceutics, Hindu College of Pharmacy, GUNTUR, (A. P.) INDIA
[a]K. V. S. R. Siddhartha College of Pharmacy, Siddhartha Nagar, VIJAYWADA (A. P.) INDIA

ABSTRACT

Diclofenac sodium, a non-steroidal anti-inflammatory drug inspite of its absorption throughout the G. I tract irritates the G. I wall and is more likely to cause ulcer in stomach. In the present work so as to protect from gastric ulcer, Diclofenac sodium was formulated as delayed release through enteric coating. All the physical parameters like hardness, friability were found to be within the limits through wet granulation process while showing good flow properties. Drug and excepients were confirmed to be standard without any incompatibility by authenticated DSC samples. Disintegrating time (DT) was found to be matched in F4 as that of core innovator. F 11 tablets, which were coated with Eudragit polymers showed better release characteristics compared to that of HPMC and CAP. The optimized formulation F11 were subjected to stability studies as per ICH guidelines, which were found to be intact without any deterioration for 3 months in comparison to innovator sample. All the results were found to be in correlation, by which the stable delayed release Eudragit enteric coated tablets can be subjected for further *in vivo* studies.

Key words : Diclofanac sodium, Delayed release

INTRODUCTION

Modified-release tablets are coated or uncoated tablets that contain special excipients or are prepared by special procedures, or both, designed to modify the rate, the place or the time at which the active substance (s) are released.

The majority of modern enteric coatings rely on polymers containing carboxylic acid groups as the functional moiety. As the pH level rises above the point of dissolution, the polymer is ionized and the drug is released. In the past, enteric coating systems have

* Author for correspondence; E-mail : bharghavsmpharm@yahoo.co.in

required the use of non-aqueous solvents for application; how ever, the majority of new enteric coating developments are based on aqueous enteric polymeric systems. The advantages offered by aqueous systems include :

(i) Avoidance of capital cost for solvent recovery and explosion-proof equipment, with a safer working environment in development and production.

(ii) Environmentally friendly.

(iii) Faster processing time, while still providing reliable enteric performance.

(iv) Faster development and scale-up process.

Enteric coatings form a sub-group of modified release coatings and a simple definition of such a coating would be one that resists the action of stomach acids but rapidly breaks down to release its contents; once it has passed into the duodenum. These coatings will come with in the definition of delayed release forms as specified in USP.

The use of enteric coatings is for:

(i) Prevention of the drug's destruction by gastric enzymes or by the acidity of the gastric fluid,

(ii) Prevention of nausea and vomiting caused by the drug's irritation of the gastric mucosa,

(iii) Delivering the drug to its local site of action in the intestine, and

(iv) Providing a delayed action.

Delivering a drug primarily absorbed in the intestine to that site, at the highest possible concentration.

EXPERIMENTAL

Materials and methods

Diclofenac sodium, lactose monohydrate, maize starch, povidone, micro crystalline cellulose, colloidal silicone dioxide, magnesium stearate, HPMC 6000EP, PEG 4000, PEG 8000, polysorbate 80, antifoam silicone, CAP, HPMC, Eudragit L30D55.

Table 1: Composition of diclofenac sodium core tablets

Ingredients (mg)	F I	F II	F III	FIV
Diclofenac sodium	50	50	50	50
Lactose monohydrate	100	80	70	60
Starch	20	40	50	56
Povidone	4	4	4	4
Sodium starch glycolate	--	--	--	4
Water	Qs	Qs	Qs	Qs
Micro crystalline cellulose	18.5	18.5	18.5	18.5
Silicon dioxide	5	5	5	5
Magnesium stearate	2.5	2.5	2.5	2.5

Details of core tablets

F I : The disintegration time of the core tablet does not match with that of the innovator. The disintegration time of the innovator is 7 to 8 min. But in this formulation, the disintegration time is 15 min. Hence, this formulation is changed.

F II : In this formulation, starch quantity is increased by decreasing diluent lactose quantity. The disintegration time of the core tablet improved to 12-13 min., still more than innovator.

F III : In this formulation, starch quantity is again increased by decreasing further lactose quantity but their is no marked improvement in the disintegration time of the core tablet. DT is in the range of 10-12 min.

F IV : Sodium starch glycolate is incorporated in the same formula i. e. F III, which resulted in the core tablets having DT in the range of 7-8 min. which is more or less similar to that of reference sample. This formula is finalized for evaluation of seal coat and enteric coat performance.

Evaluation of core tablets

Tablets are evaluated for the following parameters–

Weight variation, friability, disintegration time, hardness.

Coating of the tablets

Precoating of the core tablets

Weigh HPMC E-5 and add water slowly under stirring. Weigh and add PEG 400 under stirring and stir for 1 hr till clear solution is obtained. Required amount of the core tablets are taken and coated by using the seal coat solution. Dedust tablets before loading in coating pan. Tablets were preheated to 45-50ºC. Coating was done by suitably adjusting the Pan rpm and spray rate as required. The percentage of weight builds up is 2.0. The coating process was carefully monitored to avoid any process problems.

Table 2 : Composition of diclofenac sodium seal coated tablets

Ingredients (mg)	F V	F VI
Core tablet (mg/tab)		
Diclofenac sodium	50	50
Lactose monohydrate	60	60
Starch	56	56
Povidone	4	4
Sodium starch glycolate	4	4
Water	Qs*	Qs*
Microcrystalline cellulose	18.5	18.5
Silicon dioxide	5	5
Magnesium stearate	2.5	2.5
Seal coat		
HPMCE-5 EP	3.64	3.28
PEG 400	0.36	0.72
Qs* : Quantity sufficient		

Details of seal coated tablet

F V : In this formulation, the above prepared core tablets are taken and by using HPMCE-5 EP, PEG 400 as seal coating materials tablets are coated up to 2.0 % and tested

for their dissolution in pH 6.8 buffer. This formulation failed, since there is formation of crack at the edge in 6.8 buffer.

F VI : In this formulation, the above prepared core tablets are taken and by using HPMCE-5 EP, PEG 400 as seal coating material, tablets are coated up to 2.0 % and tested for their dissolution in pH 6.8 buffer. There is no formation of crack.

Evaluation of seal coated tablets

Weight variation, disintegration time (DT).

Enteric coating of the seal coated tablets

Eudragit L30D55 and talc were added to water under stirring condition, stirred for 20 min. and filtered through nylon cloth. Required amount of the seal coated tablets are taken and coated by using the enteric coat solution. Tablets were preheated to 45-50°C. Coating was done by suitably adjusting the Pan rpm and spray rate as required. Tablets were coated for a weight gain of 8 %. Coating process was carefully monitored to avoid any process problems.

Table 3: Composition of diclofenac sodium enteric coated tablets

Ingredients (mg)	F VII	F VIII	F IX	FX	F XI	F XII
Core tablet (mg/tab)						
Diclofenac sodium	50	50	50	50	50	50
Lactose monohydrate	60	60	60	60	60	60
Starch	56	56	56	56	56	56
Povidone	4	4	4	4	4	4
Sodium starch glycolate	4	4	4	4	4	4
Water	Qs*	Qs*	Qs*	Qs*	Qs*	Qs*
Microcrystalline cellulose	18.5	18.5	18.5	18.5	18.5	18.5
Silicon dioxide	5	5	5	5	5	5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
Seal coat (mg/tab)						

Cont…

Ingredients (mg)	F VII	F VIII	F IX	FX	F XI	F XII
HPMC E-5 EP	3.28	3.28	3.28	3.28	3.28	3.28
PEG 400	0.72	0.72	0.72	0.72	0.72	0.72
Enteric coat (mg/tab)						
Percentage of coating	8%	11%	8%	11%	8%	11%
Cellulose acetate phthalate	13.400	18.425	--NA--	-NA-	-NA-	-NA-
HPMCP	-NA-	- NA -	14.77	20.308	- NA -	- NA -
Eudragit L-30 D55[@]	- NA -	-NA -	- NA -	- NA -	14.00	19.25
Talc	0.520	0.715	- NA -	- NA -	2.320	3.19
Diethyl phthalate	2.400	3.300	1.55	2.132	-NA -	- NA -
Isopropyl alcohol	- NA -	- NA -	- NA -	- NA -	q. s. *	q. s. *
Acetone	- NA -	- NA -	- NA -	-NA -	q. s. *	q. s. *
Water	q. s. *	q. s. *	q. s. *	q. s. *	-NA -	-NA -
Colour coat (mg/tab)						
Opadry yellow	4.68	4.56	4.68	4.56	4.68	4.56
Water	q. s. *	q. s. *	q. s. *	q. s. *	q. s. *	q. s. *

Details of enteric coated tablet

F VII : In this formulation, the seal coated tablets are taken and enteric coating was done by using cellulose acetate phthalate and tested for dissolution in 0.1N HCl, followed by pH 6.8 buffer.

F VIII : In this formulation, the seal coated tablets are taken and enteric coating is done by using cellulose acetate phthalate up to 11% and tested for their dissolution in 0.1N HCl, followed by pH 6.8 buffer.

F IX : In this formulation, the seal coated tablets are taken and by using HPMCP as enteric coating, material tablets are coated and tested for their dissolution in 0.1N HCl, followed by pH 6.8 buffer.

F X : In this formulation, the seal coated tablets are taken and by using HPMCP as enteric coating material tablets are coated up to 11% and tested for their dissolution in

0.1N HCl, followed by pH 6.8 buffer.

F XI : In this formulation, the seal coated tablets are taken and by using EUDRAGIT L30D55 as enteric coating material tablets are coated and tested for their dissolution in 0.1N HCl, followed by pH 6.8 buffer.

F XII : In this formulation, the seal coated tablets are taken and by using EUDRAGIT L30D55 as enteric coating material tablets are coated up to 11% and tested for their dissolution in 0.1N HCl, followed by pH 6.8 buffer.

Evaluation of enteric coated tablets

Weight variation, disintegration time, Dissolution

Colour coating

The required quantity of Opadry yellow was added to water under stirring for 30 min. It was filtered through nylon cloth. Required amount of the enteric coated tablets are taken and coated by using the colour coat solution. Tablets were preheated to 45-50°C. Coating was done by suitably adjusting the Pan rpm and spray rate as required. Tablets were coated for a weight gain of 2 %. Coating process was carefully monitored to avoid any process problems.

Details of colour coating

Enteric coated tablets are taken and colour coating is given up to 2 % and finally the weight of the tablets reaches up to 220 mg, which matches with that of the innovator

***in vitro* drug release studies**

The dissolution test for diclofenac sodium enteric coated tablets was performed in triplicate using USP 24 paddle (Type II) method. The medium is 900 mL of 0.1N HCl for 2 hours, followed by phosphate pH 6.8 buffer, maintained at a temperature of 37° C ± 0.5° C. The paddles are rotated at 50 rpm.

10 mL of sample are withdrawn at an interval 15, 30, 45, 60 min and replaced with the same amount of pH 6.8 buffer to maintain the perfect sink conditions. The percent release is calculated by using HPLC apparatus.

Comparison with marketed formulation

In comparison with marketed (Voltarene) formulation, the following parameters

are considered :

Physical parameters

Physical appearance

Weight, Thickness, Hardness, Assay

Dissolution profile

RESULTS AND DISCUSSION

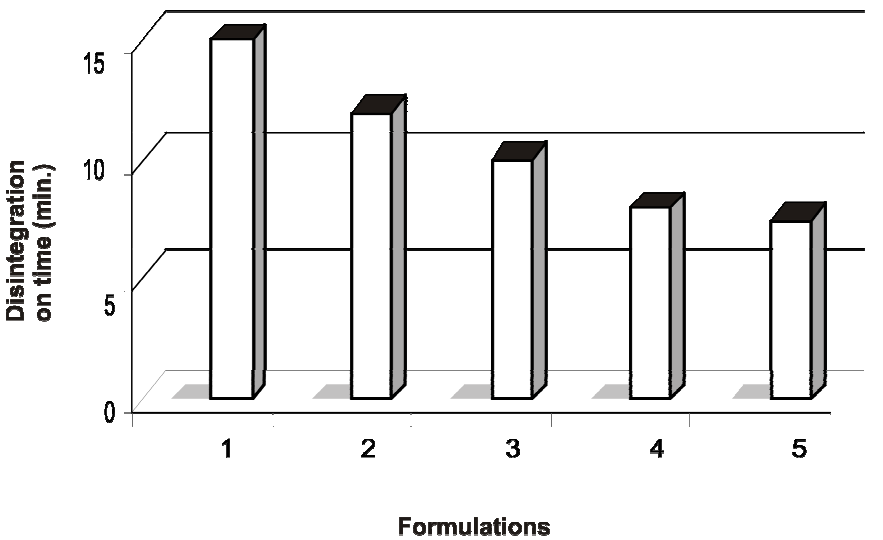

Fig. 1

Table 4 : Comparison of seal coated tablets

Formulation number	Physical appearance	Weight (Mg)	Thickness (mm)	Hardness (N)	Disintegration time	Assay (%)
FV	Round, circular, biconcave	204	3.77	89	9 min	99.3
FV1	Round, circular, biconcave	204	3.78	90	9.3 min	99.7

Results show that the formulation F IV has comparative disintegration time as that of the innovator. Since there is an addition of sodium starch glycolate, which made tablet to disintegrate fast and hence, this formulation is finalized for the sake of the seal coating.

Results show that both the formulations have comparative disintegration time as that of the innovator. But in the formulation F V, there is a formation of crack at the edge. Hence in formulation FV, the quantity of PEG 400 is increased. Finally, this formulation is finalized for the sake of enteric coating.

Table 5. Comparison of physical parameters for enteric coated tablets

Batch number	Weight (mg)	Thickness (mm)	DT in 0.1 N HCl for 2 hrs	DT in 6.8 buffer (min)	% Coat-ing	Assay
F VII	224.9	3.99	Failed	12	8%	101.3
F VIII	230	4.00	Passed	15.6	11%	101.6
F IX	225	3.98	Failed	11.5	8%	100.3
F X	230	4.01	Passed	15.5	11%	100.6
F XI	225	3.99	Passed	16	8%	101.2
F XII	230	4.00	Passed	17.5	11%	101.2
Innovator	225	3.98	Passed	15.30	NA	101.3

Results show that the formulations coated with 8 % (F VII, F IX) failed in DT. The same formulations with 11% coating (F VIII, F X) passed in DT, but there is increase in weight gain, which does not match with that of the innovator.

The formulation (F XI) with enteric coating 8 % passed in DT. The same formulation with 11% coating (F XII) also passed in DT, but there is increase in weight gain. Hence, the formulation FXI is finalized.

Dissolution profile of diclofenac sodium using cellulose acetate phthalate (8 %) F VII

Medium : 0.1 N HCl for 2 hrs, followed by 6.8 buffer.

Agitation : 50 rpm

Volume : 900 mL

F VII : Results show that the tablets coated with CAP fails in the dissolution since there is formation of crack at the edge in 0.1 N HCl and there is release of drug at the end of 2nd hour. The 8% enteric coating given to the tablet is not sufficient. Hence the % of coating is increased up to 11%, which shows good result.

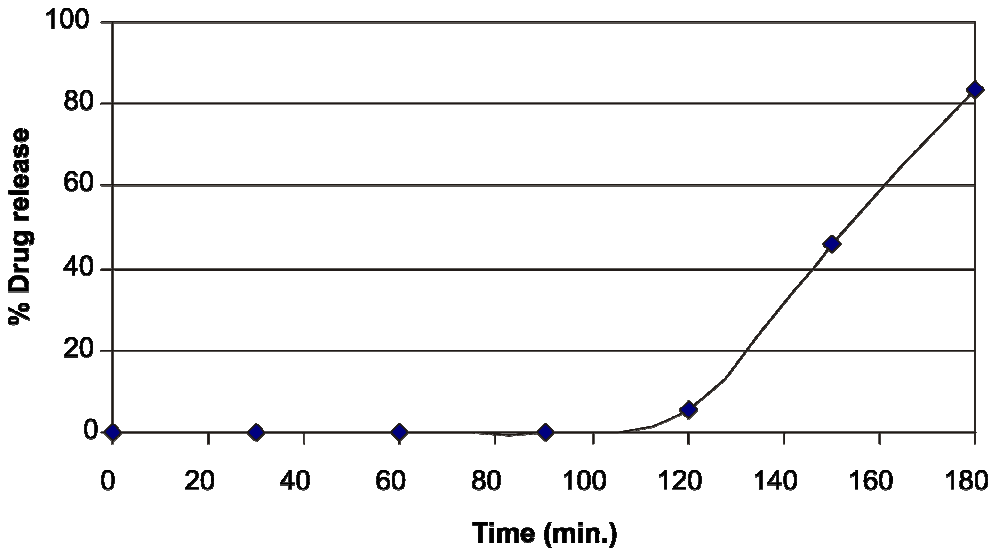

Fig. 2

Dissolution profile of diclofenac sodium using cellulose acetate phthalate 11% (F VIII)

F VIII : In this formulation, the % of coating is increased up to 11%. This formulation is passed. Since there is no crack at the edge in 0.1 N HCl and there is no release of drug at the end of 2nd hour. Hence, this formulation was passed, but there is increase in the final tablet weight.

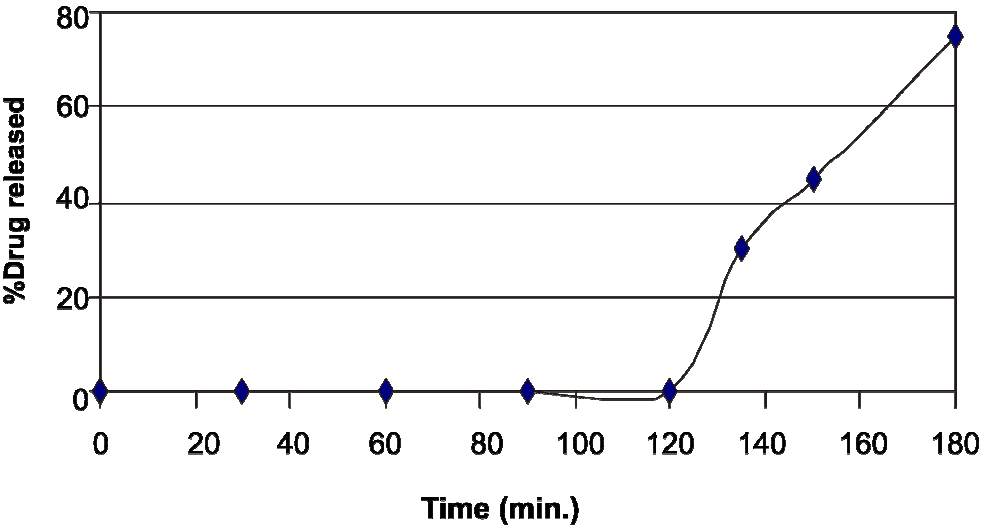

Fig. 3

Dissolution profile of diclofenac sodium using HPMCP 8% (F IX)

F IX : Results show that the tablets coated with HPMCP fails in the dissolution since there is formation of crack at the edge in 0.1 N HCl and there is release of drug at the end of 2nd hour. The 8 % enteric coating given to the tablet is not sufficient and hence, the % of coating was increased up to 11%, which shows good result.

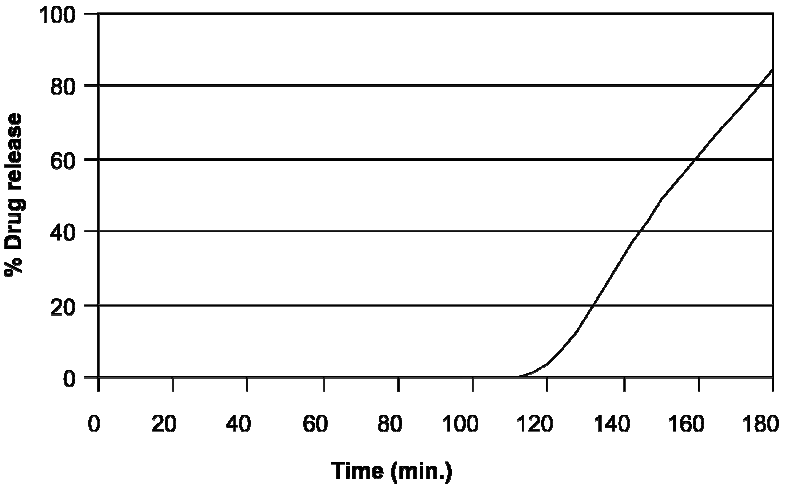

Fig. 4

Dissolution profile of diclofenac sodium using HPMCP 11% (F X)

F X : In this formulation, the % of coating was increased up to 11%. This formulation is passed. Since there is no crack at the edge in 0.1 N HCl and there is no release of drug at the end of 2nd hour. Hence, this formulation was passed, but there is increase in the final tablet weight.

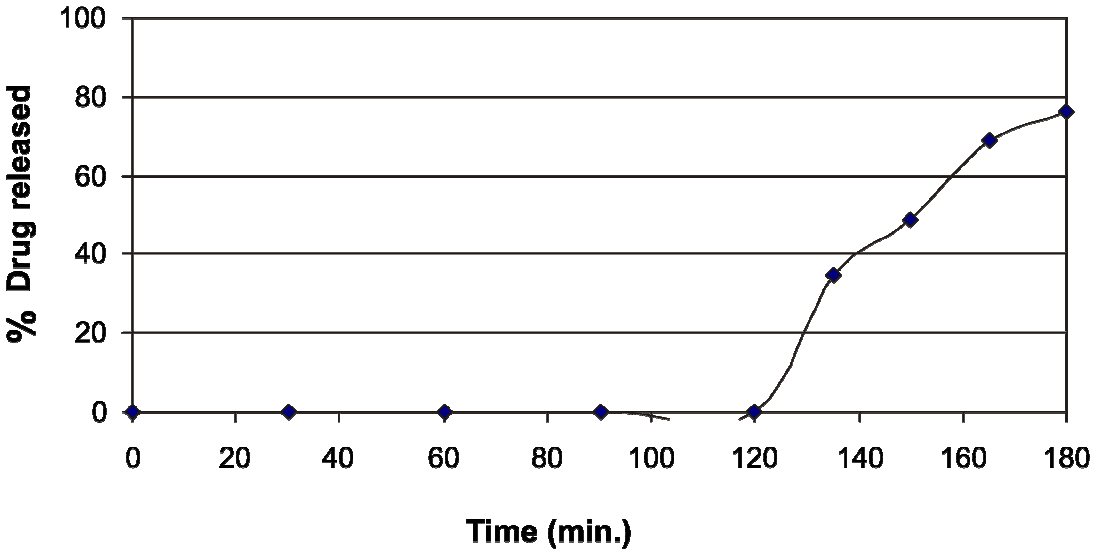

Fig. 5

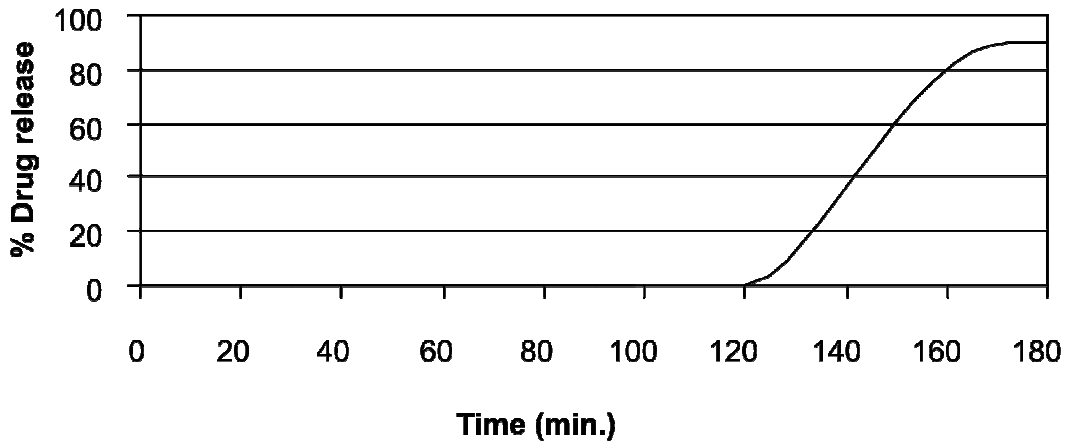

Fig. 6

Dissolution profile of diclofenac sodium using eudragit L30D55 (8%) (F XI)

F XI : Results show that the tablets coated with Eudragit L30D55 passes in the test since there is no formation of crack at the edge in 0.1 N HCl and there is no release of drug at the end of 2nd hour. The 8% enteric coating given to the tablet is sufficient and hence, this formulation is finalized. The weight of the tablet matches with that of the innovator.

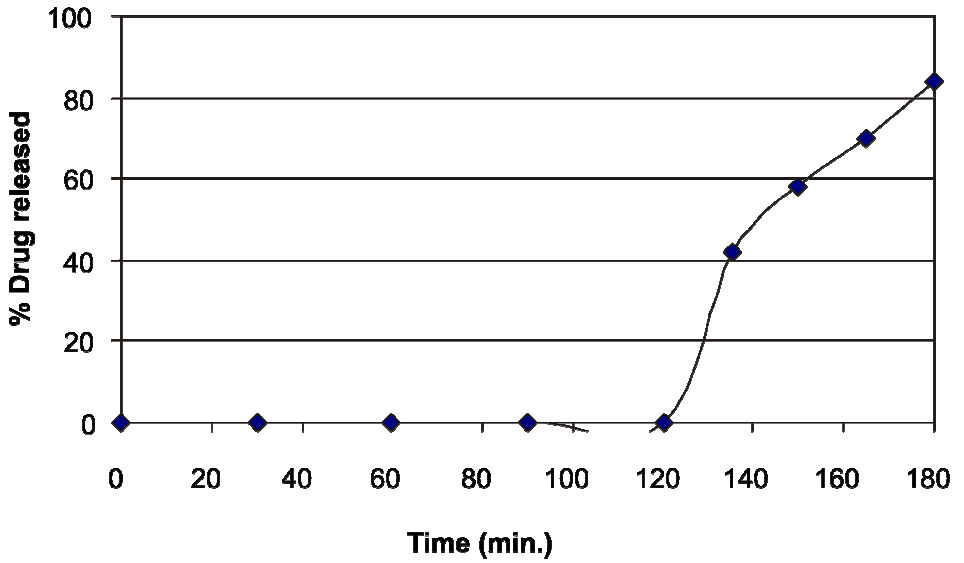

Fig. 7

Dissolution profile of diclofenac sodium using eudragit l30d55 (11%) (FXII)

F XII : In this formulation, the % of coating was increased up to 11 %. This formulation is passed. Since there is no crack at the edge in 0.1 N HCl and there is no release of drug at the end of 2nd hour. Hence, this formulation was passed, as the weight of the tablet is increased, which does not match that of the innovator

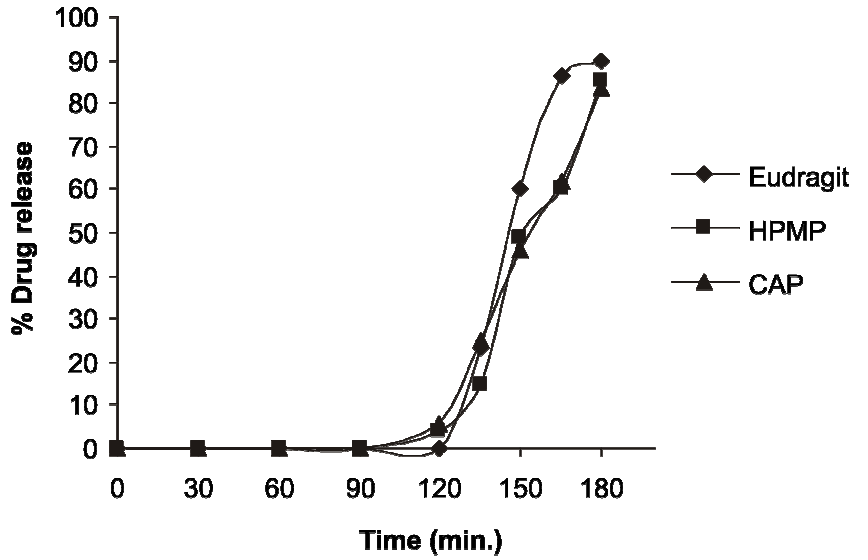

Fig. 8 : Comparison of dissolution of enteric coating polymers

Results show that the tablets coated with Eudragit L30D55 passes in the test since there is no formation of crack at the edge in 0.1 N HCl and there is no release of drug at the end of 2nd hour. The 8 % enteric coating given to the tablet is sufficient.

Comparison of dissolution profiles of three polymers (11%)

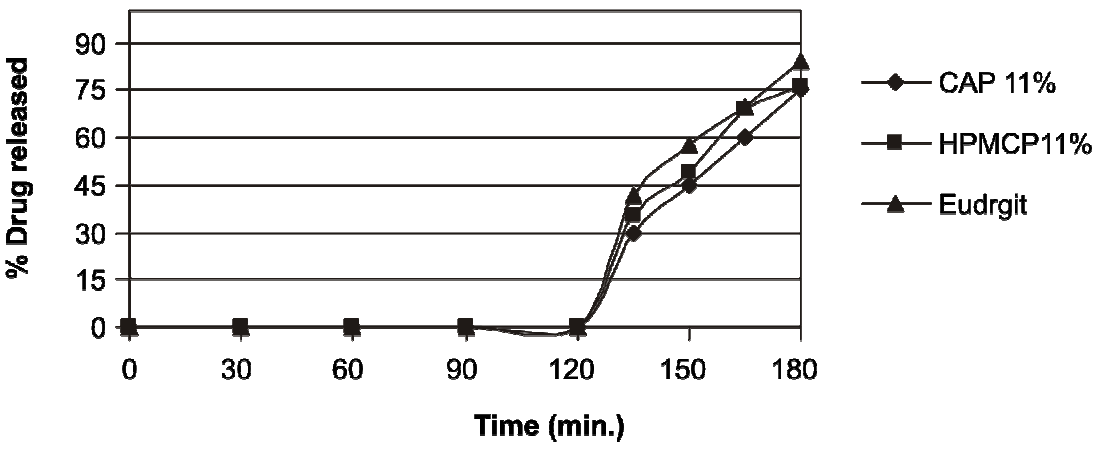

Fig. 9

Comparison of dissolution profile of innovator and F XI

Results show that the % drug release of the formulation F XI has comparative results as that of the innovator.

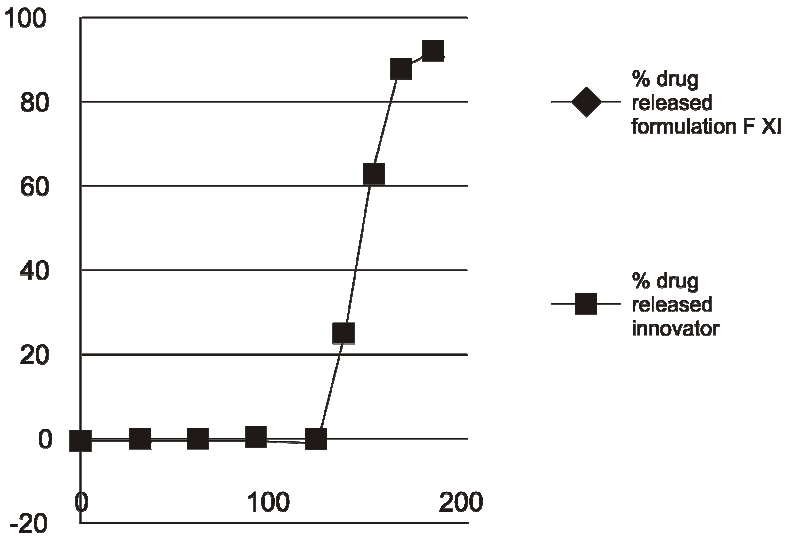

Fig. 10

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SUMMARY AND CONCLUSION

Diclofenac sodium is non-steroidal anti-inflammatory drug having absorption through out GI tract. Due to irritation to GI wall, it is more likely that the drug may cause ulcer in the stomach. In the present study, an attempt has been made to formulate diclofenac sodium using enteric coating and formulated as delayed release tablets. The formulation is developed to protect from gastric ulcer.

Standardization of drug and excipients were confirmed by authentication of sample DSE studies, which showed no incompatibility between ingredients.

Wet granulation method was selected to make the formulation. The granules so

obtained were having good flow properties and tablets had shown satisfactory results with respect to physical parameters like hardness and friability. Among core tablets formulations, F IV is the best formulation, which matched the disintegration time of the core innovator.

Dissolution results showed that tablets coated with Eudragit polymer showed much better release than the other two polymers used for the same purpose. Where as with same weight gain as that of Eudragit, CAP and HPMCP coated tablets showed the release in 0.1 HCl. The % of coating is increased up to 11 in CAP, HPMCP, there is no release in 0.1 HCl, but there is increase in weight. Among enteric coated formulations F XI was suited formulation having no drug release in 0.1 N HCl and showed release in pH 6.8 buffer. The results obtained were compared with that of the innovator and showed a correlation. The optimized formulation was subjected for stability studies as per ICH guidelines. During stability study, it was found that the drug is stable for 3 months. Innovator sample was also kept during stability study and there releases were compared and good correlations were found among formulations.

Thus, it can be concluded that stable delayed release formulation can be prepared.

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