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Formulation and evaluation of diclofenac sodium delayed release tablets

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ABSTRACT

Delayed release tablets of Diclofenac sodium tablets were prepared by wet granulation method using different pH resistant polymers like HPMC, CAP and Eudragit to dissolve it in alkaline pH. F1-F4 trials were performed and evaluated. F4 was found to be satisfactory.F4 was seal coated using HPMC E-5 EP & PEG 400L(F5).F5 was enteric coated using HPMC(F6-F7), CAP(F8-F9), EUDRAGIT(F10-F11).Dissolution was carried out in 0.1 N HCl for first 2hrs and next 1hr in phosphate buffer pH6.8.Dissolution studies of EUDRAGIT polymer trail (F10) shows much better release then HPMC and CAP.

Key words: Diclofenac sodium, Enteric coated tablets, Delayed release tablets, pH resistant polymers.

INTRODUCTION

Diclofenac sodium is a non- steroidal anti inflammatory agent[1], which is widely used in the long term therapy for rheumatoid arthritis. The biological half life of diclofenac sodium is about 1-2h, therefore, it requires multiple dosing to maintain therapeutic drug blood level. The most frequent adverse side effect of Diclofenac sodium on long term administration are GI disturbences[8],peptic ulceration & gastro intestinal bleeding .Diclofenac sodium is poorly soluble in water & acidic pH (1-3) but rapidly soluble in alkaline pH(5-8)hence an attempt was made to formulate a delayed release[2] tablet i.e. enteric coating[3] of Diclofenac sodium which will released in alkaline pH(5-8) which eliminates GI disturbances [4]& provides better patient compliance.

MATERIAL AND METHODS

Diclofenac sodium delayed release tablets (F1-F4) were prepared by wet granulation method by using Lactose monohydrate[7], Maize starch, Povidone, Micro crystalline cellulose, Colloidal silicone dioxide, Magnesium stearate[11], PEG 400, HPMC E5 EP with various ratios of CAP,HPMC,& EUDRAGIT L30D55. Preformulation studies of pure drug and mixed blend were carried out for organoleptic properties, Angle of repose ,Bulk density, Tapped density, Carr's index & Hausner's ratio. After compression, the tablets were evaluated for Weight variation, Thickness, Hardness, Friability, drug content uniformity & *invitro* dissolution studies as per standards.

Preparation of core tablets (F1-F4)

Core tablets were prepared by wet granulation method[9] by using PVPK 30 binder solution[10].Which is mixed with diclofenac sodium, lactose monohydrate, corn starch were shifted through sieve no 40 and mixed for 10 min. Granules were dried and achieved LOD < 2.0%. Dried granules were passed through sieve no 18 .Micro crystalline cellulose PH102 & corn starch 400L which is passed through sieve no 40 should be added to above mixture. Megnesium sterate which is passed through sieve no 60 was to added to above mixture and compression was carried out by using 7mm punches. Results are shown in table 1

Table 1: Formulation of enteric coated tablets

Ingredients	Coretablet(mg/tab)					
	F 6	F 7	F 8	F 9	F 10	F 11
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	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*
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)						
HPMC E-5 EP	3.28	3.28	3.28	3.28	3.28	3.28
PEG 400 L	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	-	-	-	-
HPMCP	-	-	14.77	20.308	-	-
Eudragit L-30 D55[@]	-	-	-	-	14.00	19.25
Talc	0.520	0.715	-	-	2.320	3.19
Diethyl phthalate	2.400	3.300	1.55	2.132	-	-
Isopropyl Alcohol	-	-	-	-	q.s.*	q.s.*
Acetone	-	-	-	-	q.s.*	q.s.*
Water	q.s.*	q.s.*	q.s.*	q.s.*	-	-

Preparation of seal coated tablets F5

HPMC E5 was weighed & added water slowly under stirring. For this PEG 400L was added under stirring till clear solution obtained. Among F1-F4 core tablets one batch is optimized and taken for seal coating at suitable temperature &rpm.

Preparation of enteric coated tablets

Seal coated tablets were taken and coated with different enteric coated solutions using HPMC, CAP & EUDRAGIT table1.

Charcterization of blends

Prior to compression blends were evaluated for their characteristic parameters. The results were shown in table. 3

Characterization of tablets

The properties of coated tablets, such as thickness, weight variation, hardness, friability, disintegration time was determined using standard procedures .Briefly hardness was determined by

Table 2: Physical parameters of blend

Batch No.	Angle Angle of repose	Bulk bulk Density (gm/ml)	Tapped tapped Density (gm/ml)	%Comp ressibility	Hausner Hausner 'sRatio
F1	33.29	0.7620	0.8630	14.1	1.188
F2	31.30	0.7711	0.8723	13.9	1.178
F3	29.21	0.7810	0.8920	12.9	1.1499
F4	26.45	0.7812	0.8928	12.5	1.1412

Table 3:

Concentration(µg/ml)	Absorbance (nm)
0	0
5	0.153
10	0.301
15	0.483
20	0.643
25	0.812
30	0.97

using Monsanto hardness tester, friability was determined using Roche friabilator apparatus. The drug content was determined as described for blend. The results were shown in following table.

Evaluation of tablets [12]

Physical parameters of formulated tablets like Weight variation, Hardness, Thickness, Frianility & % of coating are shown in tables 4 &5.

Table 4: Evaluation of core tablets and seal coated tablets

Batch No.	Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	D.T. (Min)
F1	199.5	3.70	4.2	0.23	15
F2	200	3.75	4.1	0.32	12
F3	201.5	3.75	3.9	0.38	10
F4	200	3.77	3.8	0.29	8
		Seal coated tablets F5			
F5	204	3.78	8.0	0.32	10

Table 5: Evaluation of Enteric coated tablets

Batch No.	Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability	& Coating
F6	220.5	3.99	8.32	0.24	8%
F7	224.2	4.00	8.12	0.32	11%
F8	220.9	3.98	8.31	0.29	8%
F9	224.6	4.01	8.01	0.33	11%
F10	221.1	3.99	8.12	0.35	8%
F11	224.9	4.00	8.23	0.28	11%

Table 6: Data for dissolution study of formulation 6,8,10

Time in min	% Drug released in CAP (F6)	%Drug released HPMC (F8)	% Drug released in Eudragit (F10)
0	0	0	0
30	0	0	0
60	0	0	0
90	0	0	0
120	5.8	3.8	0
135	22.17	25.62	23.2
150	46.06	49.21	60.33
165	62.31	60.23	86.52
180	83.27	85.43	90.03

***In vitro* dissolution studies**[13-14]

The *invitro* dissolution studies were performed using USP II dissolution apparatus[15] paddle type at 50 rpm. The dissolution studies were carried out for 2hrs in 0.1 N Hcl and the subsequently with Phosphate buffer pH 6.8 for next 1 hr at 37°c. the release studies were conducted in triplicate . Aliquots of sample (5ml) were with drawn at specific time intervals and drug content was determined at spectrophotometrically at 278 nm. The *in vitro* release studies data obtained was treated to zero order equation,first order equation.Higuchi equation($Q=Kt_{1/2}$) and Korseymer peppas to know the drug release mechanism from enteric coated tablet.showin in figures 3,4,5 & 6.

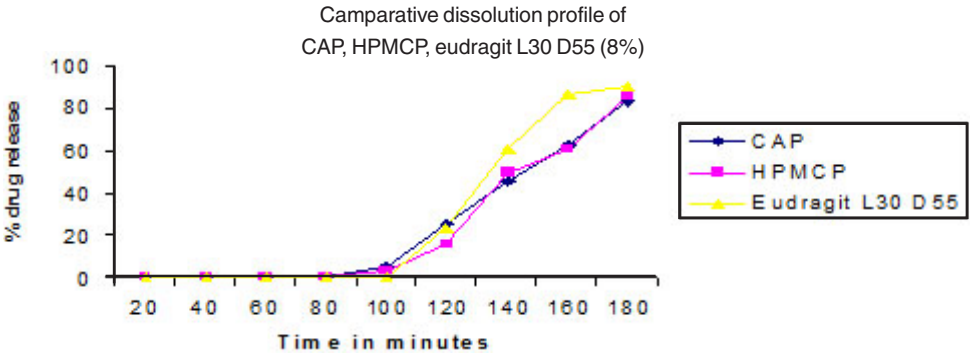

Fig. 1: Comparitive of Dissolution profile for F6, F8, F10

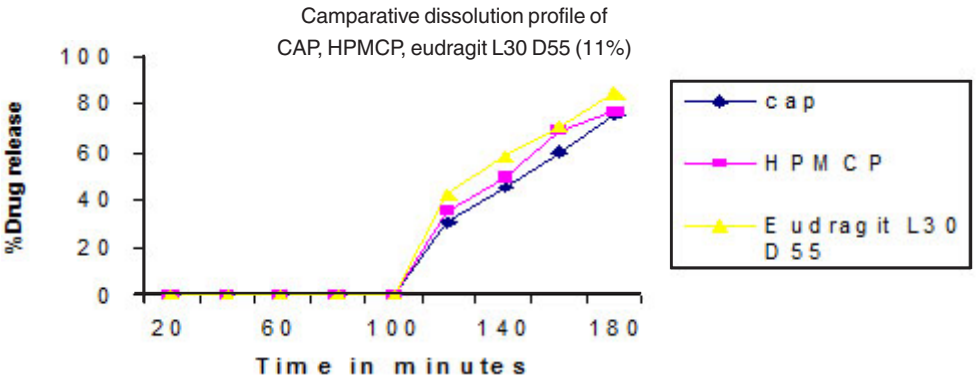

Fig. 2: Comparative dissolution profile of F7, F9, F11

RESULTS AND DISCUSSION

The blend for tablets were prepared and characterized with respect to angle of repose ,bulk density,tapped density,carr's index.the other parameters for blend were also determined and found to be in acceptable range.

The tablets of different formulations(F1-F10) were subjected to various evaluation tests such as weight variation ,friability,hardness& content uniformity according to procedure specified in IP.the weight variation and friability was less than 200.1mg & 0.29% for F1-F4,204.4 mg &0.32% for F5, 222.7mg&0.35% for F6-F11.drug content uniformity was more than 955 in all batches in vitro release profile different concentrations of HPMC (8%&11%) F6 &F7,CAP(8%&11%)F8&F9 & EUDRAGIT (8%&11%) F10& F11.the tablets with the tablets with 8% optimum concentration shows significant

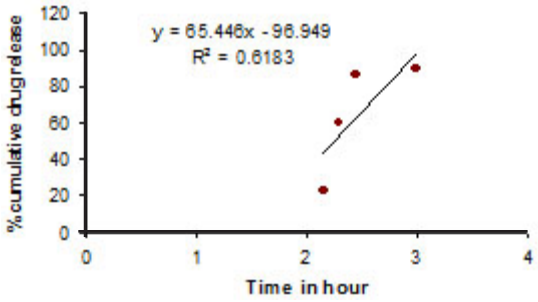

Fig. 3: Zero Order Plot

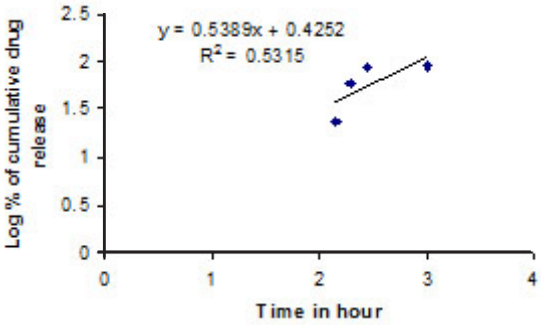

Fig. 4: First Order Plot

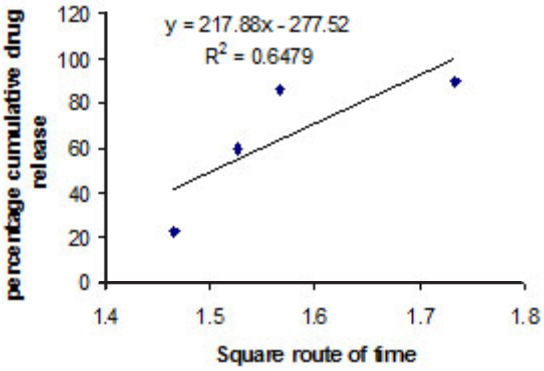

Fig. 5: Higuchi Plot

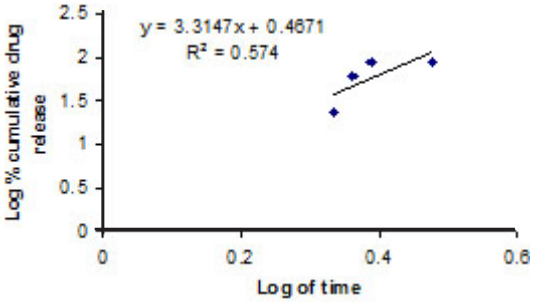

Fig. 6: Korsmeyer-Peppas Plot

Table 7: Data for dissolution study of F7, F9, F11

Time in min	% Drug released in CAP (F7)	%Drug released HPMC (F9)	% Drug released in Eudragit (F10)
0	0	0	0
30	0	0	0
60	0	0	0
90	0	0	0
120	0	0	0
135	30.12	35.23	42.21
150	45.21	49.65	58.42
165	60.23	69.22	70.34
180	75.24	76.54	84.23

release at 2 hr to 3hr. The EUDRAGIT polymer showed much better release than the other two polymers used for thw same purpose where as with the same weight given as that of HPMC,CAP& EUDRAGIT coated tablets showed release in 0.1 N Hcl. The % of coating is increase upto 11% in CAP & HPMC.there is no release in 0.1 N Hcl. Among the enteric coated tablets F 10 was the best.

CONCLUSION

Result of present study demonstrated that pH resistant polymers could be employed for successfully for formulated enteric coated tablets of Diclofenac sodium.. The investigated delayed release tablet was capble of release drug in alkaline pH but in acid pH. This can be expected to avoid the GI disturbance and reduces dose of administration.

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