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Research Article

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Formulation development and optimization of chirally pure S (+) Etodolac extended release tablets for the management of arthritis

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ABSTRACT

Etodolac is a non-steroidal anti-inflammatory drug effectively used in treatment of rheumatoid arthritis, osteoarthritis and in the relief of moderately severe post-surgical pain. S (+) Etodolac shows almost all the pharmacological activity, and more potent than its racemate, while R-Etodolac is almost inactive. The main objective of the present study was to formulate chirally pure S(+) Etodolac extended release tablets.S(+) Etodolac 300 mg is equivalent to Etodolac 600 mg. Based on the pre-formulation studies; excipients are selected for formulation development. The major criterion considered during the development of formulation was to match the dissolution profile of the drug product with the reference product.The extended release tablets were prepared by wet granulation technique using excipients likeCarbopol 974 P, HypromelloseK4M, PEG 6000, Povidone, and Colloidal Silicon Dioxide. Tablets were subjected to film coating to enhance aesthetic appeal. Formulation was designed to release the drug in extended release manner over a period of 16 hours using polymers like Carbopol 974 P and Hypromellose K4M. Several trials were taken to optimize the physical parameters of the tablets and the release kinetics of the drug product. The prepared tablets were evaluated for pre and post compression parameters. To analyze the in vitro release data various kinetic models were used to describe the release kinetics. In vitro drug release data were plotted in various models to find out the best fit model with higher correlation coefficient. Stability study was also performed and desirable results were obtained.

Keywords: S (+) Etodolac, Extended release tablets, Compatibility Study, Dissolution Study, Accelerated stability study.

INTRODUCTION

Extended release drug formulations have been used since 1960's. These formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance.[1] Many drugs have been developed as a racemic mixture (50:50) of the S- and R-enantiomers. Nonsteroidal anti-inflammatory drugs (NSAIDs) of 2-arylpropionate class are an important group of racemic medication. The S-isomer of NSAIDs is generally thought to express pharmacological activity and/or be associated with clinical efficacy[2].

Etodolac (ET; (1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4- 6]indol-1-yl) acetic acid) is a nonsteroidal anti-inflammatory agent prescribed for the treatment of acute pain, osteoarthritis, and rheumatoid arthritis. It has also been reported to be effective in the treatment of gout by lowering uric acid blood levels in humans. The drug shows high therapeutic index between gastric irritation and anti-inflammatory effects. Etodolac acts by a preferential

inhibition of cyclo-oxygenase-2 (COX-2) enzyme. The inhibition of the enzyme cyclooxygenase, that synthesizes prostaglandins results in low concentrations of prostaglandins and thus the conditions like inflammation, pain and fever are reduced. It is used for rheumatoid arthritis, including juvenile idiopathic arthritis, osteoarthritis, and for the treatment of acute pain. It has an elimination half-life of 7 h, and the recommended oral dose, 200 to 400 mg, is given every 6 to 8 h to a maximum of 1.2 g daily[3-6].

S-(+)-Etodolac shows almost all the pharmacological activity, while R-(-)-Etodolac shows little. S-Etodolac possesses almost all of the anti-inflammatory activity of Etodolac while R-Etodolac is almost inactive. S-(+)-Etodolac is 2.6 times more potent than the racemate and 100 times more potent than R-enantiomer. Furthermore, S-Etodolac achieves greater concentrations in synovial fluid than plasma compared to R-Etodolac. R- and S-Etodolac competitively interact with each other for binding to human serum albumin and are displaced by each other. S-Etodolac rapidly attains the peak plasma concentration and is rapidly cleared from plasma compared to R-Etodolac[6, 7].

The pivotal objective of the present research work was to formulate extended release tablets of S (+) Etodolac in order to avoid the first pass metabolism and to match the dissolution pattern in line with racemic reference listed drug. Trials were taken by using different polymers, punch size shape, and percentage weight gainof core tablets during coating.

EXPERIMENTAL SECTION

Materials: S (+) Etodolac was procured from Emcure Pharmaceuticals, Pune, Maharashtra; Hypromellose K4M was received from Dow Chemicals, Carbomer was received from Lubrizol USA, Dibasic Sodium Phosphate Dihydrate was received from Canton laboratories Pvt. Ltd, Lactose Monohydrate, was received from Dynamix dairy, Povidone [PVP K-30] was received from BASF Corporation, Polyethylene glycol 6000, was received from Viswaat chemicals Ltd, Magnesium Sterate was received from Sunshine oraganic, Colloidal silicon dioxide was received from Cabot Sanmar.

Method: S (+) Etodolac, Dibasic Sodium Phosphate Dihydrate, Lactose Monohydrate and Hydroxy propyl methyl cellulose K4M were sifted through 40 # seive. Sifted materials were mixed in Rapid Mixer Granulator for about 20 min. Binder solution was prepared by dissolving Povidone PVP K -30 in isopropyl alcohol and Methylene chloride under stirring. Binder solution was added in above material and mixed in Rapid Mixer Granulator. Wet mass milling was performed through # 10 sieve. Wet mass was dried in fluidized bed dryer at $50^0C \pm 5^0C$ to achieve LOD 3-4 % w/w. Dried granules were passed through # 20 sieves. Prelubrication was done by sifting Purified talc, Colloidal silicon dioxide through # 40, and Polyethylene Glycol (PEG 6000) through # 60 seive and mixed with dried granules in double cone blender for about 10 minutes. Magnesium stearate was passed through 60 # and above material was lubricated with magnesium stearate for about 1 minute in double cone blender; lubricated blend was compressed into tablets by using specified punch tooling.

Preparation of coating suspension: Opadry white followed byColour Lake of indigo carminewas slowly added to the Purified Water IP with continuous stirring. Abovecoating suspension was filtered through nylon cloth and coating was performed.

Drug release Kinetics:

1. Zero order release model: To study the zero order release kinetics the release rate data are fitted to the following equation :

$$\mathbf{F= K_0t}$$

Here, F is the fraction of drug release, K_0 is the rate constant, and T is the release time.

2. First order release model : This model has also been used to describe absorption and /or elimination of some drug, the release of the drug which followed first order kinetic can be expressed by the equation :

$$\mathbf{Log\ C = logC_0\text{-}Kt/2.303}$$

Where, C_0 is the initial concentration of drug, K is the first order rate constant, t is the time.

3. Higuchi release model : To study the Higuchi release kinetics, the release rate data was fitted to the following equation :

$$\mathbf{F = K_H.t^{½}}$$

Where, F is the amount of drug release, K_H is the release rate constant, t is the release time

4. Hixson–Crowellrelease model : The release rate data were fitted to the following equation,

$$\mathbf{W_0^{1/3} – W_t^{1/3} = K_s\ t}$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, Wt is the remaining amount of drug, in the pharmaceutical dosage form at time t and $K_s$is a constant incorporating the surface–volume relation.

5. Korsmeyer and peppas release model : The release rate data were fitted to the following equation,

$$\mathbf{Mt/M\infty = K_M.t^n}$$

Where, Mt/M∞ is the fraction of drug release, KM is the release constant, t is the release time.

Preformulation studies: Preformulation is an exploratory activity that begins early in pharmaceutical development. Preformulation studies are designed to determine the compatibility of initial excipients with the active substance for a biopharmaceutical, physicochemical, and analytical investigation in support of promising experimental formulations.

Drug excipients compatibility study: Compatibility of S (+) Etodolac with excipients was studied by keeping S (+) Etodolac individually and with each excipient in 1:1 ratio and exposed to Room Temperature (RT), and 40°C/75% RH for 15 days.

Table: 1. Drug excipients compatibility study

Sr. No.	Sample	Initial		40°C/75% RH	
		Any Individual impurity (%)	Total Impurities (%)	Any Individual impurity (%)	Total Impurity (%)
1.	API	BDL	0.27	BDL	0.24
2.	API + Lactose monohydrate	BDL	0.26	BDL	0.24
3.	API + Di Basic Sodium Phosphate Dihydrate	BDL	0.27	0.06	0.46
4.	API + Hypromellose	BDL	0.27	BDL	0.24
5.	API + Carbomer	BDL	0.27	0.03	0.27
6.	API + Povidone (PVPK 30)	BDL	0.24	BDL	0.24
7.	API + Polyethylene Glycol	BDL	0.27	0.12	0.65
8.	API + Purified Talc	BDL	0.28	0.02	0.26
9.	API + Colloidal silicon dioxide	0.12	0.56	0.11	0.78
10.	API + Lake of indigo carmine	BDL	0.29	BDL	0.24
11.	API + Opadry White	BDL	0.27	0.03	0.65
12.	API + Magnesium Stearate	BDL	0.29	0.04	0.38
13.	API + Composite sample	BDL	0.26	0.08	0.53

**BDL: Below Detection Limit*

RESULTS AND DISCUSSION

Extended release tablets of S (+) Etodolac were formulated by wet granulation technique using different grades and concentration of excipients. (Table 2). Two different strengths of S (+) Etodolac 300 mg and 200 mg were formulated. Drug excipients compatibility study was performed and API was found compatible with all the excipients used in formulation. The Precompression parameters such as Bulk density, Tapped density, Compressibility index and Hausner's ratio evaluated were found within prescribed limits and indicated good flow property. (Table 3). Post compression parameters such as Weight, Thickness, Hardness, and Friability were evaluated found satisfactory and compiled in table 4. In vitro dissolution was carried out and test sample dissolution was matched with reference drug. Similarity and dissimilarity factor was also calculated. (Table 5). The in vitro release data obtained from final formulation were applied to various kinetic models. Correlation coefficient of final formulation F7 was calculated with different models and it shows higher correlation coefficient value with Higuchi model than first order than zero order respectively. (Table 6). Dose proportionate formulation of S (+) Etodolac 200 mg was developed and the physiochemical parameters were optimized by using punches of different size. Evaluation of core and coated tablets of S (+) Etodolac 200 mg were performed and results are compiled in table 7, and 8 respectively. Comparison of in vitro dissolution of tablets compressed with four different sizes of punches is given in table 9. Accelerated stability study was performed on both the strength for 6 M at 40°C/75% RH, and results were found well within the specified limit.(Table 10).

Table: 2. Formulation of S (+) Etodolac Extended Release Tablets

Ingredients	Formulations							
	F1	F2	F3	F4	F5	F6	F7	F8
Dry mix								
S (+) Etodolac	300.00	300.00	300.00	300.00	300.00	300.00	300.00	300.00
Hypromellose	52.00	52.00	52.00	60.00	60.00	60.00	60.00	60.00
Dibasic Sodium Phosphate Dihydrate	52.00	52.00	52.00	52.00	52.00	52.00	52.00	52.00
Carbomer	15.00	7.50	-	-	-	-	-	-
Lactose Monohydrate	QS	QS	QS	QS	QS	QS	QS	QS
Binder								
Povidone	-	-	-	-	5.00	5.00	10.00	10.00
Polyethylene Glycol	-	-	10.00	-	-	-		
Isopropyl Alcohol	QS	QS	QS	QS	QS	QS	QS	QS
Methylene chloride	QS	QS	QS	QS	QS	QS	QS	QS
Lubrication								
Polyethylene Glycol	-	-	-	10.00	10.00	10.00	10.00	10.00
Colloidal silicon dioxide						5.00	5.00	5.00
Purified Talc	1.50	3.50	3.50	6.50	6.50	6.50	6.50	6.50
Magnesium Stearate	5.25	7.00	7.00	10.00	10.00	10.00	10.00	10.00
Coating								
Opadry 06G28430	10.0%	10.0%	-	-	-	10.0%	10.0%	10.0%
Colour Lake of Indigo carmine	0.1%	0.1%	-	-	-	0.1%	0.1%	0.1%
Purified water	QS to 100 %	QS to 100 %	-	-	-	QS to 100 %	QS to 100 %	QS to 100 %

Table: 3 Evaluation of powder blend

Formulation	Bulk Density (gm/cm^2)	Tapped Density(gm/cm^2)	Carr's Index	Hausner's Ratio
F1	0.400	0.508	21.20	1.27
F2	0.498	0.567	12.16	1.13
F3	0.485	0.613	20.8	1.26
F4	0.485	0.613	20.8	1.26
F5	0.485	0.613	20.8	1.26
F6	0.499	0.617	19.12	1.23
F7	0.489	0.591	17.25	1.20
F8	0.489	0.607	18.94	1.24

Table: 4 Evaluation of extended release tablet of S (+) Etodolac 300 mg strength

Formulation	Weight (mg)	Thickness (mm)	Hardness kg/cm2	Friability (% w / w)
F1	525 mg	5.2	8 – 9	0.10%
F2	525 mg	5.2	9 – 10	0.15 %
F3	525 mg	5.1	9 – 10	0.15%
F4	525 mg	5.1	9 – 10	0.98%
F5	525 mg	5.2	9 – 10	0.86%
F6	525 mg	5.2	7 – 9	0.85%
F7	525 mg	5.1.mm	12 – 14	0.1%
F8	525 mg	5.1.mm	12 – 14	0.1%

Table: 5. Comparative dissolution profile of S (+) Etodolac ER Tablets 300 mg test samplewith Etodolac ER Tablets 600 mg reference drug product

Sr. No.	Sampling Time Points (hrs.)	Tablets 600 mg (Reference)	Tablets 300 mg (Test)
1	0	0	0.00
2	3	24.78	27.5
3	6	45.67	50.6
4	10	73.20	73.9
5	16	97.87	94.5
f2	**77.08**		
f1	**4.85**		

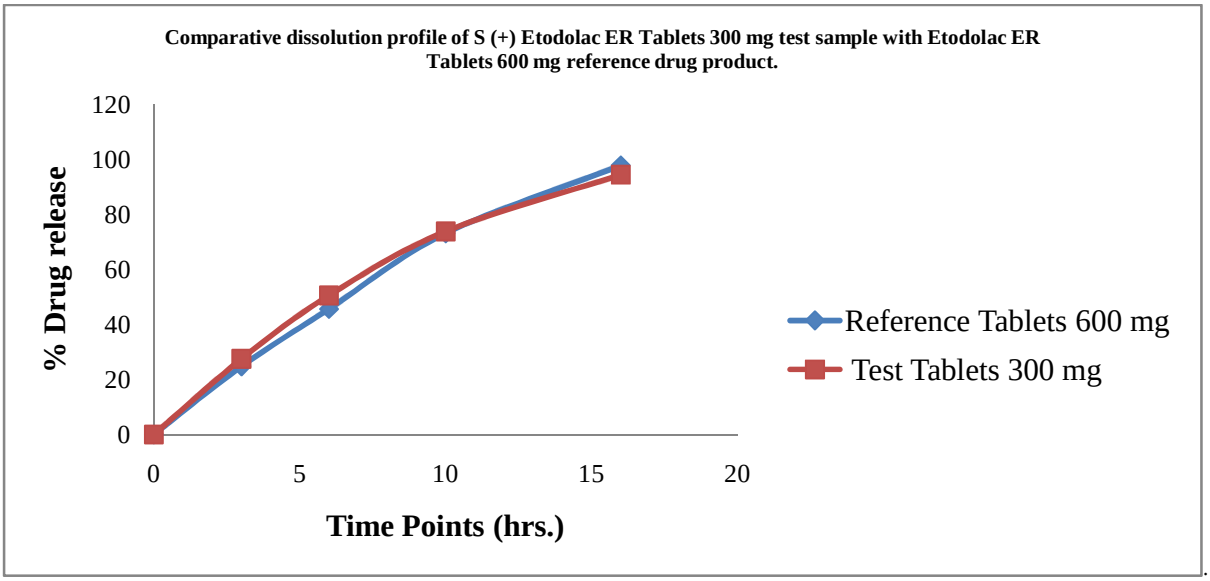

Figure: 1. Comparative dissolution profile of S (+) Etodolac ER Tablets

Table: 6. Release kinetics of final formulation (F7)

Time (hrs.)	% cumulative drug released	log % cumulative drug released	% cumulative drug remaining (x)	log % cumulative drug remaining	log T	√T	(x)⅓
0	0	0	100	2	0	0	4.641
3	27.5	1.5058	72.5	1.8603	0.4771	1.7320	4.169
6	50.6	1.7696	49.4	1.6937	0.7781	2.4494	3.669
10	73.9	1.9362	26.1	1.4166	1.0000	3.1622	2.966
16	94.5	2.0162	5.5	0.7403	1.2041	4	1.765

Figure: 2. Release kinetic models for S (+) Etodolac extended release tablets

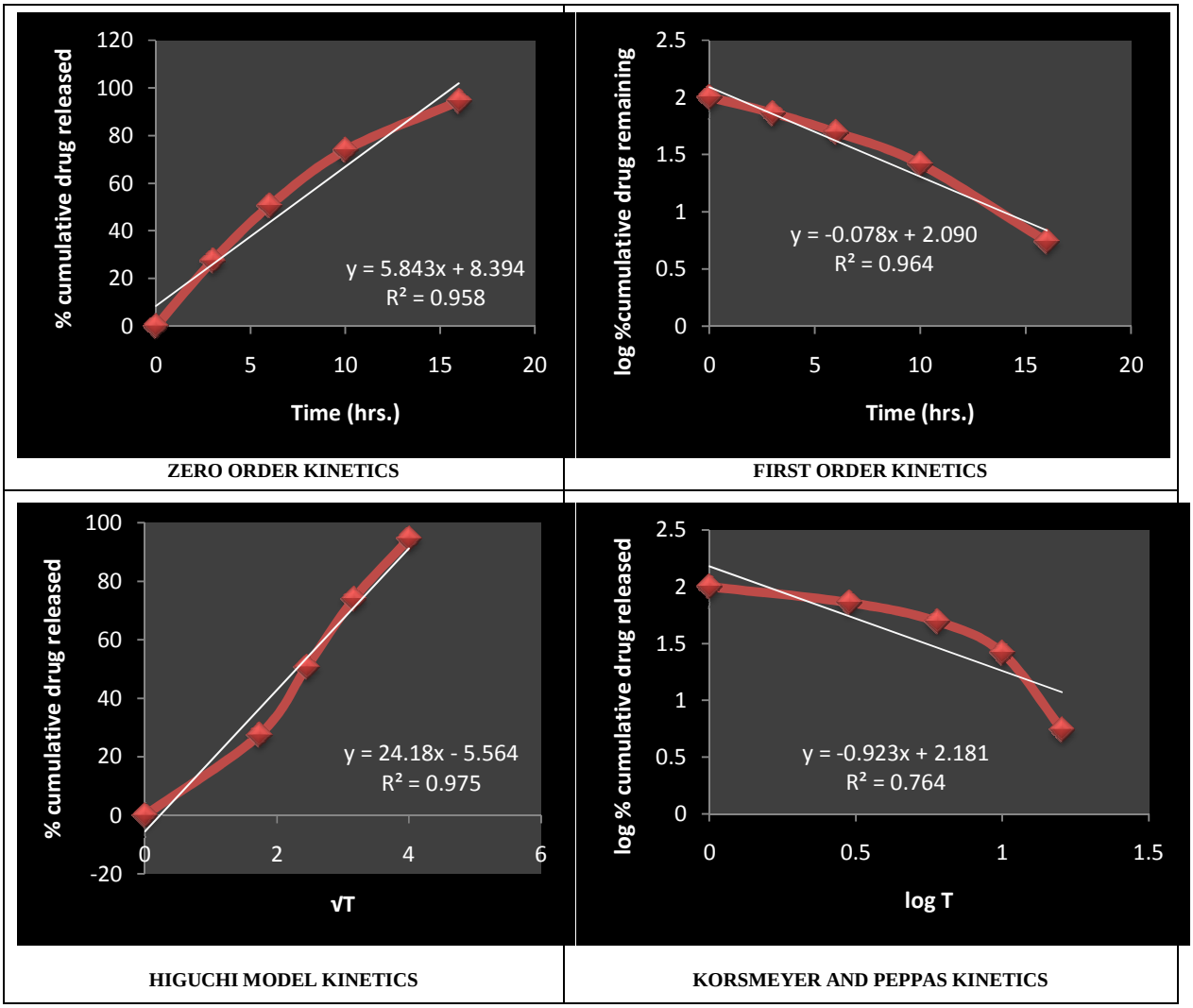

Table: 7. Evaluation of extended release tablet of S (+) Etodolac 200 mg strength

Formulation	Avg. Weight (mg)	Avg. Thickness (mm)	Avg. Hardness kg/cm2	Avg. Friability (% w / w)
9.5 mm standard concave	350.7	4.75	18.16	0.01%
10.5 mm standard concave	351.8	4.17	16.96	0.01%
9.0 mm standard concave	350.3	5.22	16.83	0.01%
13*17.2 mm standard concave	350.1	4.54	15.6	0.01%

Table: 8. Evaluation of coated tablet of S (+) Etodolac 200 mg strength

Formulation	Avg. Weight (mg)	Avg. Thickness (mm)	Avg. Hardness kg/cm2	Avg. Friability (% w / w)
9.5 mm standard concave	361.6	4.82	23.4	0.01%
10.5 mm standard concave	360.3	4.23	22.93	0.01%
9.0 mm standard concave	359.3	5.29	20.33	0.01%
13*17.2 mm standard concave	360.9	4.62	18.81	0.01%

Table: 9. Effect of different sizes of punches on dissolution of S (+) Etodolac 200 mg

Time interval	% Drug release			
	9.5 mm standard concave	10.5 mm standard concave	9.0 mm standard concave	13*17.2 mm standard concave
0	0	0	0	0
3	32.7	34.4	31.2	33.0
6	60.1	56.5	53.8	57.8
10	81.8	81.9	77.1	81.8
16	92.1	94.7	92.5	95.7

Table: 10. Stability Results: Stability results of final formulations

Sr. No.	Test	Specification		(200mg)	(300mg)
				6 M40°C/75% RH	
1	Assay (By HPLC) Content of S(+) Etodolac	S (+) Etodolac per tablet i.e. Not less than 90.0% and not more than 110.0% of the labeled amount.		96.93	97.11
2	**Related Substance**				
	Any individual impurity	**Not more than 0.2%**		0.08	0.11
	Total impurities	**Not more than 1.0%**		0.42	0.43
3	**Dissolution**	**Time in hours**	**Amount dissolved**		
		3	Between 15% and 45 %	35.7	27.6
		6	Between 35% and 75 %	63.9	50.9
		10	Between 60% and 95 %	86.9	75.4
		16	Not less than 70 %	100.1	96.7

CONCLUSION

In the present study two different strengths of S (+) Etodolac Extended release tablets were formulated and evaluated. Different release models were applied to investigate the mode of release and the best fit was found with Higuchi model. From the present research work it can be concluded that final formulation F7 was best suited according to all parameters evaluated. The drug release was found to be within the limit as per USP recommendation for Etodolac at the end of 1st, 3rd, 10th and 16th hour.Based on the above experiments followed by their observations it can be concluded that the designed and developed formula was stable, robust and reproducible.

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