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STUDIES ON EFFECT OF SUPERDISINTEGRANTS ON ETORICOXIB TABLET FORMULATIONS

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ABSTRACT:
Etoricoxib is a selective COX-2 inhibitor, a potent widely prescribed anti-inflammatory and analgesic drug, belongs to Class II under 'BCS' and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Five formulations were developed with various superdisintegrants. The formulations were tested in-vitro drug release and hardness, friability disintegration and other tablet properties. Hardness of the tablets was in the range 5.5 -6.5 kg / sq.cm in all the batches of tablets. The correlation coefficient (r) value between log percent un dissolved and time was in the range 0.9620 -0.9977 with various tablet formulations. Tablets formulated with Prosolve, modified starch and croscarmellose sodium exhibited higher dissolution rates and dissolution efficiency among all and these tablets also fulfilled all official (I.P) and GMP requirements of compressed tablets.
Key Words: *Etoricoxib, COX-2 inhibitor, Tablets, Dissolution rate.*

INTRODUCTION:

Bioavailability is the most important property of a dosage form. It is the ability of the dosage form to deliver the active ingredient to its site of action in an amount sufficient to elicit the desired pharmacological response. It is affected by a number of factors related to the drug, dosage form and patient. It is well known that the drug bioavailability and efficacy are severely limited by its poor aqueous solubility and dissolution rate. The drug in a solid dosage form (tablet) must undergo dissolution before it is available for absorption in the gastrointestinal tract. Dissolution forms the rate limiting step in the absorption of drug from solid dosage forms especially when the drug is poorly soluble. Many of the modern drugs belong to the Class II category under biopharmaceutical classification system [(1)] (BCS), which are characterized by low solubility and high permeability. The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug product development. Etoricoxib is a selective COX-2 inhibitor, a potent widely prescribed anti-inflammatory and analgesic drug [(2-5)], belongs to Class II under 'BCS' and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Etoricoxib is superior form of other NSAIDs as it has selectivity for COX-2 a beneficial COX inhibitor, well tolerated, better GI tolerability and improved cardiovascular safety when compared to other selective COX-2 inhibitors. As such oral absorption of etoricoxib is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. The present investigation was undertaken with an overall objective of developing etoricoxib formulations. Studies were carried out on etoricoxib tablets to evaluate the effect of formulation variables such as superdisintegrants on the tablet qualities and dissolution rate of etoricoxib from compressed tablets with a view to optimize the formulation of etoricoxib tablets.

EXPERIMENTAL:

Material and Methods:

Etoricoxib, Primogel, Croscarmellose sodium, Crospovidone, Modified Starch was a gift sample from M/s Natco Pharma Ltd. Hyderabad. Prosolve (gift sample from M/s Orchid Health Care Ltd., Chennai) Acacia (Loba Chemie) Magnesium stearate I.P, Talc I.P, all other materials used was of Pharmacopoeial grade.

Method:

A Spectro photometric method based on the measurement of absorbance at 273 nm in phosphate buffer of pH 7.2 was used in the present study for the estimation of etoricoxib.

Stock Solution:

The stock solution (1mg/ml) of etoricoxib was dissolved in methanol and the volume was made up to 100ml with methanol.

Preparation of calibration curve:

The stock solution of etoricoxib was subsequently diluted with phosphate buffer of pH 7.2 to obtain a series of dilutions containing 2, 4, 6, 8 and 10 µg of etoricoxib in 1 ml solution. The absorbance of these solutions was measured in Elico-SL 159, UV-Vis Spectrophotometer at 273 nm using phosphate buffer of pH 7.2 as blank. Reproducibility of the above method was studied by analyzing six individually weighed samples of etoricoxib. The percent relative standard deviation (RSD) of the determinations found to be less than 1.0%. (Table. 1, Fig. 1)

Table 1: Calibration Curve for the Estimation of Etoricoxib:

Etoricoxib Concentration (µg/ml)	Absorbance	
	X	RSD
2	0.071	0.32
4	0.134	0.26
6	0.186	0.07
8	0.238	0.12
10	0.302	0.13

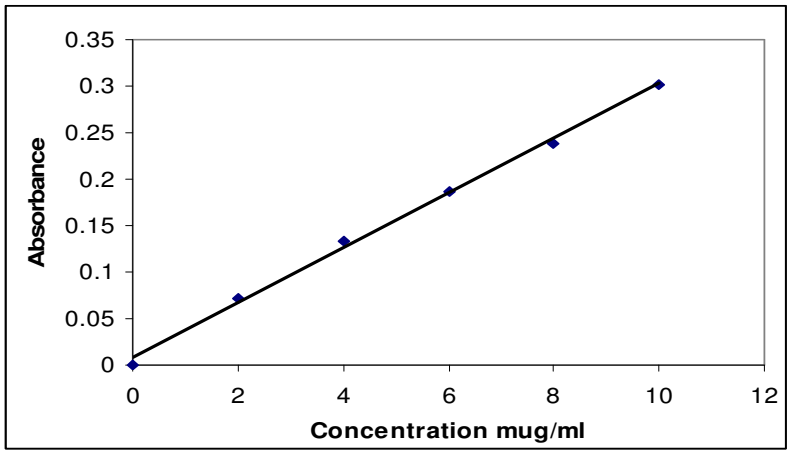

Fig. 1 Calibration Curve for the Estimation of Etoricoxib

Preparation of Etoricoxib Tablets:

Compressed tablets each containing 60 mg of etoricoxib were prepared by conventional wet granulation method using various superdisintegrants as per the formulae given in Table 5.6. All superdisintegrants except prosolve were used at 4% concentration and prosolve was used at 10% concentration. Acacia (2.5%) was used as binder in the form of aqueous mucilage in all the formulations.

Method:

The required quantity of medicament and other ingredients (Table 2) was mixed thoroughly with binder solution to form dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60°C for 4 hr. The dried granules were passed through mesh No. 16 to break the aggregates. The superdisintegrants, talc (2%) and magnesium stearate (2%) were passed through mesh No. 100 onto dry granules and blended in a polyethylene bag. The tablet granules were then compressed into tablets on a rotary multi-station tablet punching machine (M/s. Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 6-7 kg/sq.cm using 9 mm round and flat punches.

Content of active ingredient:

Five tablets were accurately weighed and powdered. Tablet powder equivalent to 60 mg of the medicament was taken into a boiling test tube and extracted with 4 x 10 ml quantities of methanol. The methanolic extracts were collected and the volume was made up to 50 ml with methanol. The solution was subsequently diluted with phosphate buffer of pH 7.2 and absorbance was measured by using UV Spectro photometric at 273 nm.

Hardness:

Hardness of the tablets was tested using a Monsanto hardness tester.

Friability:

Friability of the tablets was determined in a Roche friabilator.

Disintegration time:

Disintegration times were determined in thermonic tablet disintegration test machine using distilled water as fluid.

Dissolution rate study:

The dissolution rate of etoricoxib from the tablets was studied in 900 ml of phosphate buffer of pH 7.2 using Disso

2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature of 37°C ± 1°C was maintained throughout the study. One tablet containing 60 mg of etoricoxib was used in each test. Samples of dissolution media (5 ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitably diluted and assayed for etoricoxib at 273 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were conducted in triplicate.

Table.2: Formulae of Etoricoxib Tablets Prepared with Various Superdisintegrants:

Ingredient (mg/tab)	Formulation				
	TF1	**TF2**	**TF3**	**TF4**	**TF5**
Etoricoxib	60	60	60	60	60
Acacia	3.75	3.75	3.75	3.75	3.75
Modified Starch	6	-	-	-	-
Primogel	-	6	-	-	-
Crospovidone	-	-	6	-	-
Croscarmellose sodium	-	-	-	6	-
Prosolve	-	-	-	-	15
Talc	3	3	3	3	3
Magnesium stearate	3	3	3	3	3
Lactose up to (mg)	150	150	150	150	150

RESULTS AND DISCUSSION:

Content, Hardness, Friability and Disintegration time:

Etoricoxib tablets could be prepared by wet granulation method employing various superdisintegrants. Superdisintegrants were added after drying the wet granules and before compression. Etoricoxib content, hardness, friability and disintegration time of various tablets are given in Table.3. All the tablets were found to contain the etoricoxib within 100 ± 3% of the label claim. Hardness of the tablets was in the range 5.25 - 6.5 kg/sq.cm in all the batches of tablets. The percentage weight loss in the friability test was less than 1.1 with all the batches of tablets. All the tablets formulated were disintegrated in 5-10 min. All tablets prepared were of good quality fulfilling the official (I.P) and GMP requirements of tablets.

Dissolution characteristics of various tablets prepared were shown in Table.4 and in Fig.2.

Table.3: Drug Content, Hardness, Friability and Disintegration Time of Etoricoxib Tablets Formulated with Various Superdisintegrants:

Tablet Formulation	Drug content (mg/Tab)	Hardness (kg/sq. cm)	Friability (%)	Disintegration (min)
TF1	58.7	6.5	0.95	5.5
TF2	59.1	6.5	0.9	8.0
TF3	60.3	5.5	0.91	6.0
TF4	58.5	6.0	0.9	6.5
TF5	59.2	5.5	1.03	5.0

Table.4: Dissolution Profiles of Etoricoxib Tablets Formulated Employing Various Superdisintegrants:

Time (min)	Percent Drug Dissolved (x ± s.d.) (n=3)				
	TF1	TF2	TF3	TF4	TF5
5	08.70± 1.51	10.53± 1.32	15.73± 1.24	16.84±1.11	12.56± 1.44
10	13.97± 1.32	16.35± 1.25	20.03±1.14	25.54± 1.42	31.05± 1.22
20	27.62±1.67	27.90± 1.52	25.61± 1.53	32.72± 1.35	46.04± 1.55
30	38.23± 1.15	31.84± 1.43	30.65± 1.72	40.15±1.24	56.08± 1.23

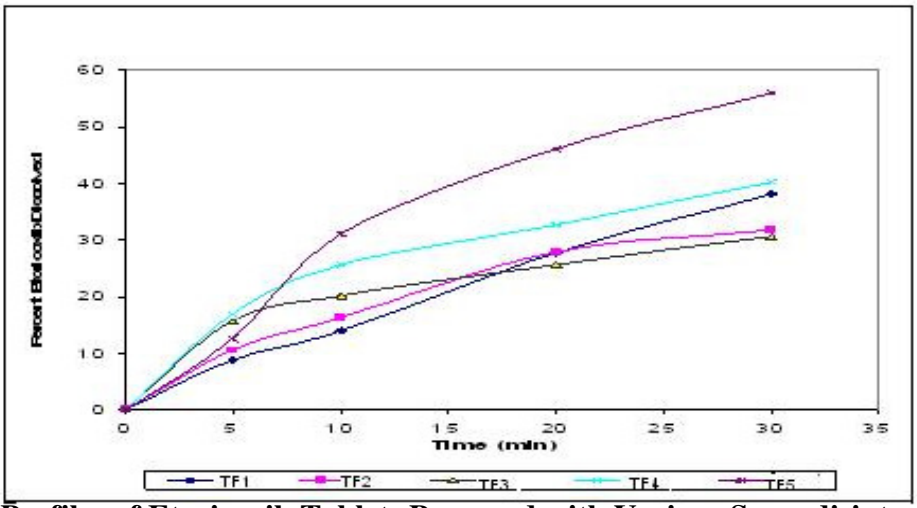

Fig.2. Dissolution Profiles of Etoricoxib Tablets Prepared with Various Superdisintegrants

Dissolution of etoricoxib from all the tablets prepared followed first order kinetics. The correlation coefficient (r) between log percent undissolved and time was in the range 0.962 - 0.997 with various tablet formulations (Table. 5). Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[4]. Much variation was observed in the dissolution characteristics of tablets prepared with various superdisintegrants (Table. 6).

Table.5: Correlation Coefficient (r) Values in the Analysis of Dissolution Data, as per Zero order and First order Models:

Formulation	Correlation coefficient value	
	Zero order model	First order model
TF 1	0.9970	0.9977
TF2	0.9529	0.9620
TF3	0.9899	0.9944
TF4	0.9657	0.9798
TF5	0.9318	0.9727

Table.6: Dissolution Parameters of Etoricoxib Tablets Formulated with Various Superdisintegrants:

Formulation	T_{50} (min)	K_1 (min^{-1})	DE_{30} (%)	Percent Drug Dissolved in 10 min
TF1	39	0.0159	20.52	13.97± 1.32
TF2	47	0.0112	20.44	16.35± 1.25
TF3	49	0.0076	21.27	20.03± 1.14
TF4	37	0.0125	26.79	25.54± 1.42
TF5	22	0.0265	34.54	31.05± 1.22

Another parameter suitable for the evaluation of in vitro dissolution data has been suggested by Khan[4] who introduced the parameter dissolution efficiency (DE). DE is defined as the area under dissolution curve up to a certain time T expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

$$\text{Dissolution Efficiency } (DE) = \left[\frac{\int_0^t y\,dt}{y100.t} \right] 100$$

The dissolution efficiency can have a range of values depending on the time intervals chosen. In any case, constant time intervals should be chosen for comparison. For example the index DE_{30} would relate to the dissolution of drug from a particular formulation after 30 min and could only be compared with DE3o of other formulations. Summation of the large dissolution data into a single figure DE enables ready comparison to be made between a large numbers of formulations.

Dissolution characteristics of various tablets prepared were shown in Table.4 and in Fig. 2. Dissolution of etoricoxib from all the tablets prepared followed first order kinetics. The correlation coefficient (r) between log percent undissolved and time was in the range 0.962 - 0.997 with various tablet formulations (Table.5, Fig.3). Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[5]. Much variation was observed in the dissolution characteristics of tablets prepared with various superdisintegrants (Table.6). The order of performance of superdisintegrants based on increasing dissolution rate was found to be Prosolve > modified starch > croscarmellose sodium > Primogel > crospovidone.

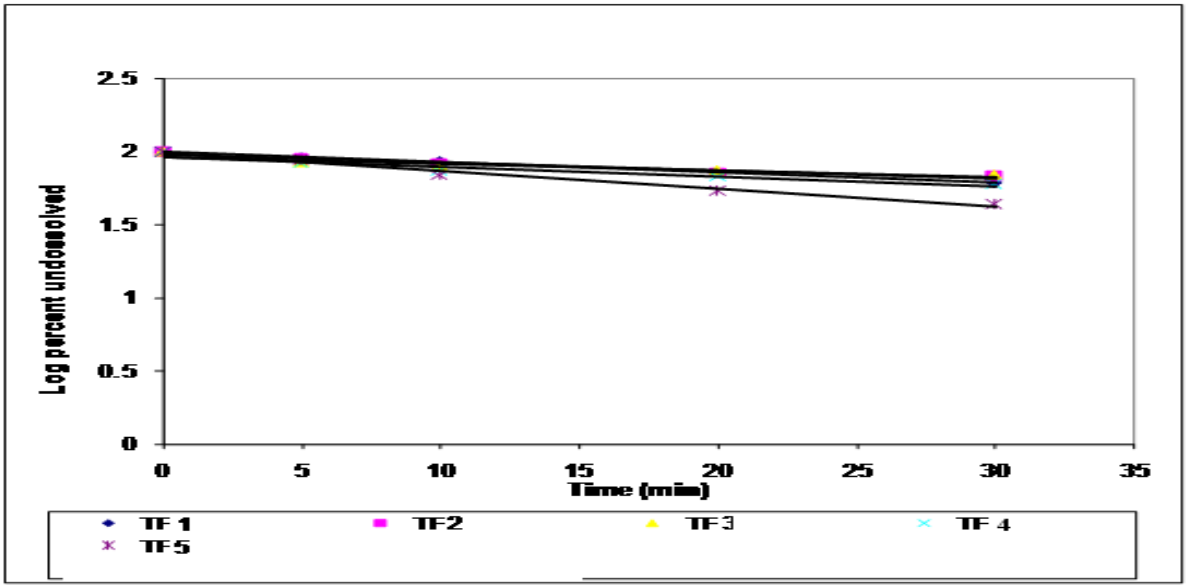

Fig.3. First order Plots of Dissolution Profiles of Etoricoxib Tablets Prepared with Various Superdisintegrants

CONCLUSIONS:

The superdisintegrant used has significant influence on the tablet qualities and dissolution rate of etoricoxib from the tablets. The order of performance of the superdisintegrants based on increasing dissolution rate was Prosolve > modified starch > croscarmellose sodium > Primogel > crospovidone. Tablets formulated with Prosolve, modified starch and croscarmellose sodium exhibited higher dissolution rates and dissolution efficiency values fulfilling all other official (I.P) and GMP requirements of compressed tablets. Prosolve, modified starch and croscarmellose sodium were found to be better superdisintegrants for etoricoxib tablets.

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