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STUDIES ON EFFECT OF BINDERS 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. Seven formulations were developed with various binders. The formulations were tested *in-vitro* drug release and hardness, friability disintegration and other tablet properties. Hardness of the tablets was in the range 5-6.5 Kg/sq.cm in all the batches of tablets except those prepared using methyl cellulose and HPMC as binders. The correlation coefficient (r) value between log percent undissolved and time was in the range 0.974-0.999 with various tablet formulations. Much variation was observed in the dissolution characteristics of tablets prepared with various binders.

Key words: Binder, Etoricoxib, Anti-inflammatory drug.

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

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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 binders 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 was a gift sample from M/s Natco Pharma Ltd., Hyderabad. Polyvinyl pyrrolidone (Mfg : BASF, PVP K-30) hydroxy propyl methyl cellulose (having a viscosity of 50 cps in a 2% weight aqueous solution at 20°C) Potato starch (Loba Chemie) Gelatin (oxoid) Acacia (Loba Chemie), Methyl cellulose (methoxyl content: 28-32%; viscosity : 65 cps) Sucrose, Talc I.P, Magnesium stearate I.P. all other materials used were of Pharmacopoeial grade.

A Spectrophotometric 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 (1 mg/mL) of etoricoxib was dissolved in methanol and the volume was made up to 100 mL 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

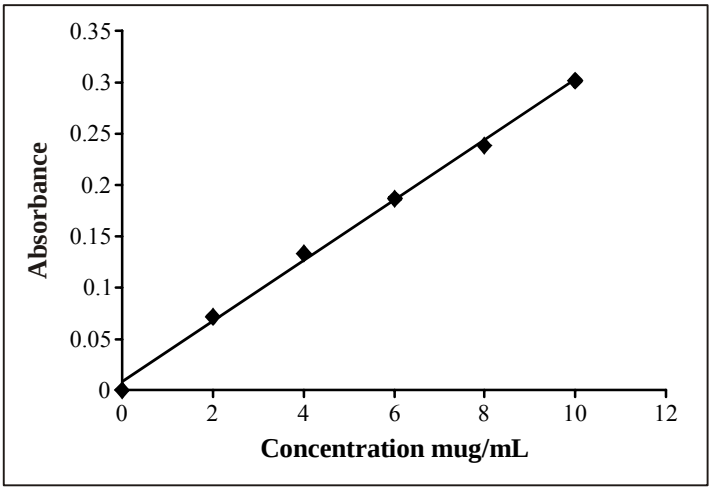

Fig. 1: Calibration curve for the estimation of Etoricoxib

Preparation of Etoricoxib tablets

Compressed tablets each containing 60 mg of etoricoxib were prepared by conventional wet granulation method using various binders as per the formulae given in Table 2. 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) were mixed and the binder solution was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 12 and wet granules were dried at 60°C for 4 hr. The dried granules were passed through mesh No. 16 to break the aggregates. 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.

Table 2: Formulae of Etoricoxib tablets prepared with various binders

Ingredient mg/tab.	Formulation						
	TF1	**TF2**	**TF3**	**TF4**	**TF5**	**TF6**	**TF7**
Etoricoxib	60	60	60	60	60	60	60
Acacia	3.75	-	-	-	4	-	-
Sucrose	-	3.75	-	-	-	-	-
PVP	-	-	3.75	-	-	-	-
MC	-	-	-	3.75	-	-	-
HPMC	-	-	-	-	3.75	-	-
Starch paste	-	-	-	-	-	3.75	-
Gelatin	-	-	-	-	-	-	3.75
Potato starch	30	30	30	30	30	30	30
Talc	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3
Lactose up to (mg)	150	150	150	150	150	150	150

Content of active ingredient

Five tablets were taken and powdered; 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 upto 50 mL with methanol. The solution was subsequently diluted with phosphate buffer of pH 7.2 and absorbance was measured by using UV Spectrophotometric 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 (0.45 μ) 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.

RESULTS AND DISCUSSION

Content, hardness, friability and disintegration time

Etoricoxib tablets could be prepared by wet granulation method employing the commonly used binders. 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 + 2% of the label claim. Hardness of the tablets was in the range 5-6.5 Kg/sq.cm in all the batches of tablets except those prepared using methyl cellulose and HPMC as binders. The tablets prepared using these binders were found to be relatively harder with hardness in the range 11-12 Kg/sq.cm. The percentage weight loss in the friability test was less than 1.2 with all the batches of tablets. Tablets formulated employing methyl cellulose and HPMC as binders did not fulfilled the official (IP) disintegration test of uncoated tablets. Though the tablets formulated with all other binders disintegrated within 4 min., variations were observed in their disintegration time in the range 0.5 - 4.0 min.

Table 3: Drug content, hardness, friability and disintegration time of etoricoxib tablets formulated with various binders

Tablet Formulation	Etoricoxib content (mg/Tab)	Hardness Kg/sq. cm.	Friability (%)	Disintegration Time (min.)
TF1	59.2	6.5	0.95	3.8
TF2	59.5	5.0	1.26	0.5
TF3	58.5	5.5	0.95	2.2 ,
TF4	60.2	12.0	0.42	19.0
TF5	60.5	11.5	0.52	15.0
TF6	59.6	6.25	0.93	1.0
TF7	59.8	6.5	0.94	1.0

Dissolution characteristics of various tablets prepared are shown in Table 4 and Fig. 2. The dissolution data were analysed as per zero order and first order kinetic models. The kinetic model that fits the dissolution data was evaluated by comparing the correlation coefficient (r) values obtained in zero order and first order models. The model that gave higher (r) value is considered as the best fit model. The correlation coefficient (r) values in the analysis of data as per zero and first order models are given in Table 5. The (r) values were found to be higher in the first order model than those in zero order model indicating that the dissolution of etoricoxib from all the tablets prepared followed first order kinetics. The correlation coefficient (r) value between log percent un dissolved and time (Fig. 3) was in the range 0.974 -0.999 with various tablet formulations. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[4].

Table 4: Dissolution profiles of etoricoxib tablets formulated employing various binders

Time (min)	Percent etoricoxib dissolved (x ± s.d.) (n = 3)						
	TF1	TF2	TF3	TF4	TF5	TF6	TF7
5	28.71 ± 1.3	45.00 ± 1.2	31.57 ± 1.4	5.91 ± 1.5	15.84 ± 1.1	30.69 ± 1.6	23.98 ± 1 .7
10	47.41 ± 1.1	49.40 ±1.6	37.84 ± 1.2	10.67 ± 1.3	26.95 ± 1.4	43.34 ± 1.5	31.90 ± 1.3
20	60.50 ± 1.6	56.59 ± 1.3	48.84 ± 1.1	26.88 ± 1.4	43.01 ± 1.2	59.18 ± 1.7	44.33 ± 1.5
30	70.07 ± 1.2	61.93 ± 1.4	54.78 ± 1.3	38.83 ± 1.6	49.94 ± 1.5	69.85 ± 1.1	54.45 ± 1.7

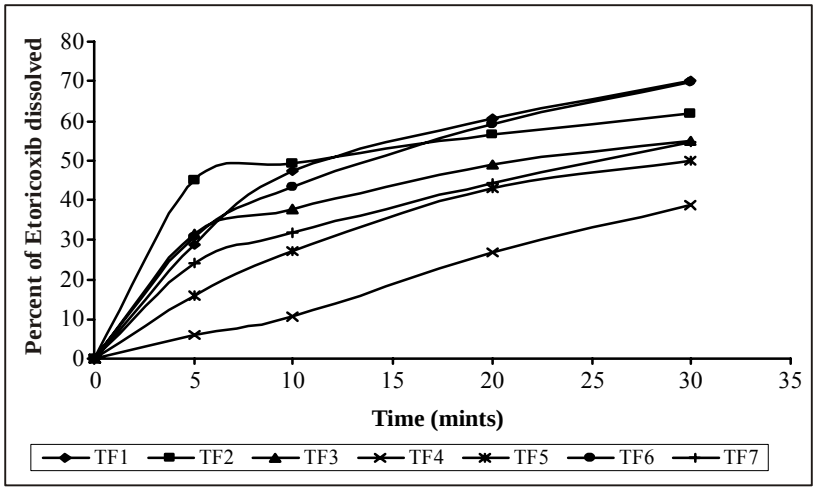

Fig. 2: Dissolution profiles of Etoricoxib tablets prepared using various binders

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
TF1	0.9193	0.9753
TF2	0.9905	0.9976
TF3	0.9768	0.9887
TF4	0.9941	0.9939
TF5	0.9535	0.9748
TF6	0.9743	0.9974
TF7	0.9930	0.9997

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 upto a certain time T expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

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

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 DE_{30} 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.

The dissolution parameters of various tablets prepared are summarized in Table 6. Much variation was observed in the dissolution characteristics of tablets prepared with various binders. The order of performance of binders based on increasing dissolution rate was found to be acacia > starch paste > sucrose > gelatin > PVP > HPMC > MC. Based on the dissolution efficiency the order of performance of binders was sucrose > acacia > starch

Table 6: Dissolution parameters of etoricoxib tablets formulated with various binders

Formulation	T_{50} (min)	K_1 (min^{-1})	DE_{30} (%)	Percent drug dissolved in 10 min
TF1	16	0.0332	41.37	47.41 ± 1.1
TF2	18	0.0147	49.03	49.40 ± 1.6
TF3	28	0.0167	40.14	37.84 ± 1.2
TF4	39	0.0177	19.08	10.67 ± 1.3
TF5	31	0.0209	32.03	26.95 ± 1.4
TF6	17	0.0330	47.31	43.34 ± 1.5
TF7	27	0.0204	35.82	31.90 ± 1.3

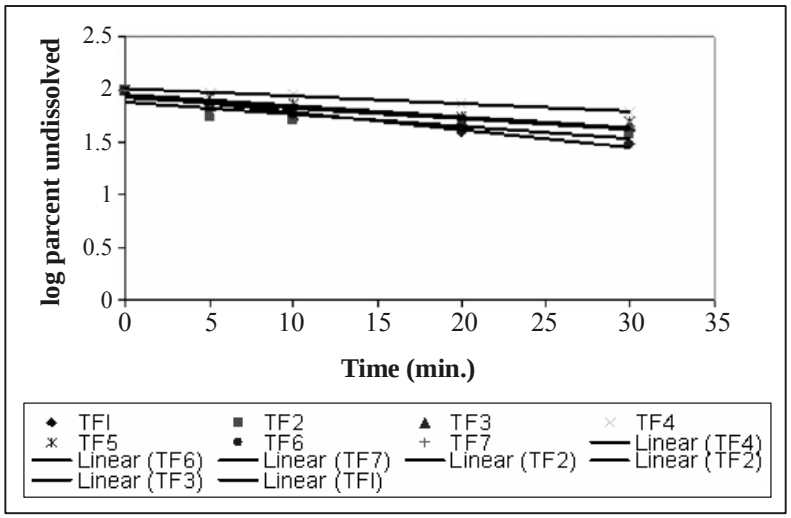

Fig.3: First order plots of dissolution profiles of Etoricoxib tablets prepared with various binders

paste > PVP > gelatin > HPMC > MC. Tablets formulated with acacia, starch paste and sucrose exhibited higher dissolution rates and dissolution efficiency values among all and these tablets also fulfilled all official (IP) and GMP requirements of compressed tablets. Overall acacia, starch paste and sucrose were found to be suitable binders for etoricoxib tablets.

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