FORMULATION AND *IN VITRO* EVALUATION OF ORO-DISPERSIBLE TABLETS OF ETORICOXIB WITH EMPHASIS ON COMPARATIVE FUNCTIONALITY EVALUATION OF THREE CLASSES OF SUPERDISINTEGRANTS

S.R. Shahi*[1], G.R. Agrawal[1], N.V. Shinde[1], S.A. Shaikh[2], S.S. Shaikh[3], V.G. Somani[1], P.B. Shamkuvar[1] and M.A. Kale[1]

*[1]Government College of Pharmacy, Vedant Road, Aurangabad, M.S.-431005
[2]Jeevanjyoti Herbaceuticals, Beed-by-pass Road, Aurangabad, M.S.-431002
[3]Kamala Nehru College of Pharmacy, Rouza Baugh, Aurangabad, M.S.-431001
E-mail: sadhanashahi@yahoo.com

ABSTRACT

Etoricoxib is a novel, selective second generation cyclo-oxygenase-2 inhibitor administered orally as an analgesic and anti-inflammatory drug that is used for the treatment of osteoarthritis, rheumatoid arthritis and gouty arthritis. The poor aqueous solubility of the drug leads to variable dissolution rates. In the present investigation an attempt has been made to prepare oro-dispersible tablets of etoricoxib with enhanced dissolution rate. The another purpose of the present investigation was to evaluate effect of superdisintegrants like Crospovidone (Polyplasdone XL), Croscarmellose Sodium (Ac-Di-Sol) and Sodium starch glycolate (Primojel) on dissolution of poorly soluble, selective COX-2 inhibitor in oro-dispersible tablets. In the study, the effect of superdisintegrants specifically at 2 and 4 % level in oro-dispersible tablet formulation on the in vitro dissolution was evaluated. These levels included optimum concentrations of selected superdisintegrants. It was concluded that oro-dispersible tablets of etoricoxib with enhanced dissolution rate can be made using selected superdisintegrants.

Keywords: *Etoricoxib, Oro-dispersible tablet, Crospovidone (Polyplasdone XL), Croscarmellose Sodium (Ac-Di-Sol) and Sodium starch glycolate (Primojel).*

INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, scientists have developed innovative drug delivery systems known as "melt in mouth" or "mouth dissolve (MD)" tablets. Their growing importance was underlined recently when European Pharmacopoeia (European Pharmacopoeia 4.1, 2002) adopted the term *"Oro-dispersible tablet" as a tablet to be placed in mouth where it disappears rapidly before swallowing*. Oro-dispersible tablets are also known as quick dissolves, fast melts, fast dissolving, fast disintegrating, rapid-dissolve, or orally dissolving tablets. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market.[1]

Despite increasing interest in controlled-release drug delivery systems, the most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract (GIT). The proper choice of disintegrant and its consistency

of performance are of critical importance to the formulation development of such tablets. In more recent years, increasing attention has been paid to formulating not only fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in the mouth.[2-4]

Non-steroid anti-inflammatory drugs (NSAID) are widely used in clinical practice for the treatment of pain, inflammation and fever. The pharmacological effects are due to their ability to block prostaglandin synthesis by inhibiting the enzyme cyclo-oxygenase (COX). COX exists in two isoforms in man, COX-1 and COX-2. COX-1 is required for many physiologic housekeeping functions, such as protection of the gastric mucosa, maintenance of renal homeostatic and platelet aggregation. Conversely, COX-2 is responsible for synthesis of prostaglandins, which mediate responses to pathologic processes such as pain, fever and inflammation. Etoricoxib (5-chloro-2-[6-methyl pyridin-3-yl]-3-[4-methylsulfonylphenyl] pyridine) is a novel, selective second generation cyclooxygenase-2 inhibitor administered orally as an analgesic and anti-inflammatory drug that is used for the treatment of osteoarthritis, rheumatoid arthritis and gouty arthritis. Etoricoxib can be categorized as class II drugs according to the Biopharmaceutics Classification System. These drugs are poorly water soluble, but once they are dissolved they are easily absorbed over the gastro-intestinal membrane.[5]

In any solid dosage forms, an important variable is the rate at which the active substance goes into solution or dissolves. Dissolution of the active substance is essential for it to be absorbed through the biological membranes into systemic circulation for eliciting its desired pharmacological activity. For many solid dosage forms, disintegration occurs prior to drug dissolution and superdisintegrants such as Crospovidone (Polyplasdone XL), Croscarmellose Sodium (Ac-Di-Sol) and Sodium starch glycolate (Primojel) are now frequently used in tablet formulations to improve the rate and extent of tablet disintegration and thus increase the rate of drug dissolution.

EXPERIMENTAL

Materials

Etoricoxib was procured as gift sample from Torrent Research Center, Ahmedabad. Aspartame, Mannitol (granular), Croscarmellose Sodium, Crospovidone, Sodium starch glycolate, Colloidal silicon dioxide, Mixed fruit flavor and Magnesium stearate were procured as gift samples from Concept Pharmaceuticals Ltd., Aurangabad and all other chemicals and reagents were of analytical grade.

Methods

Blending

Etoricoxib, aspartame, mannitol, superdisintegrant (croscarmellose sodium/ Crospovidone/ Sodium starch glycolate), colloidal silicon dioxide and mixed fruit flavor were sifted through the sieve #44 and admixed for about 15 minutes to make a uniform blend. Magnesium stearate was passed through sieve #100 and mixed with the above blend for sufficient time, usually 5-7 minutes.

Characterization of powder blends of active pharmaceutical ingredient & excipients[6]

The powder blend was evaluated for flow properties as follows and reported in table 1:

Angle of Repose

Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (q) was calculated using the following formula,

$$q = \tan^{-1}\frac{h}{r}$$

Bulk Density

Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density (ρ_b) was calculated using following formula,

$$\rho_b = \frac{V_b}{M}$$

Tapped Density

The measuring cylinder containing a known mass of blend (M) was tapped for a fixed time (100 tapping). The minimum volume (V_t) occupied in the cylinder and weight of the blend was measured. The tapped density (ρ_t) was calculated using following formula,

$$\rho_t = \frac{V_t}{M}$$

Compressibility Index

The simplest method of measurement of free flow of powder is compressibility, an indication of the ease with which material can be induced to flow is given by compressibility index (I) which is calculated as follows,

$$I = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

The value below 15% indicates a powder which usually gives rise to excellent flow characteristics, whereas above 25% indicate poor flowability.[8]

Hausner's Ratio (H)

This is an indirect index of ease of powder flow. It is calculated by the following formula,

$$\mathrm{H} = \frac{\rho_t}{\rho_b}$$

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Tableting

The resulting uniform blend of composition per tablet as mentioned in table 2 was directly compressed using 10 mm; round flat faced tooling to make the tablets of about 4.2 ± 0.1 mm thickness. The weight of tablets was kept 400 ± 5mg. The hardness of tablets was kept 4.5 ± 0.2 kg/cm^2. The tablet press setting was kept constant across all formulations.

Evaluation of Tablets

The tablets evaluated for the following parameters and the results reported in table no.3

Weight variation[7]

Twenty tablets were selected at randomly and average weight was determined. Then individual tablets were weighed and was compared with average weight.

Hardness[7]

Hardness or tablet crushing strength (F_c), the force required to break a tablet in a diametric compression, was measured using Monsanto tablet hardness tester.

Thickness[7]

Thickness of tablets was measured using Vernier calliper.

Friability[6]

Friability of the tablets was determined using Roche Friabilator. Pre-weighed sample of tablets was placed in the friabilator and subjected to 100 revolutions (25 rpm). The tablets were de-dusted using a soft muslin cloth and reweighed. The friability (f) is given by the formula,

$$f = (1 - \frac{W_o}{W}) \times 100$$

Where, W_o is the weight of the tablets before the test &

W is the weight of the tablets after the test.

Content uniformity[7]

One tablet was dissolved in sufficient quantity of 0.1N HCl. The solution was filtered through Whatmann filter paper (no.41), suitably diluted with 0.1N HCl, and analyzed at 233 nm, using a UV-Visible double beam spectrophotometer. Each sample was analyzed in triplicate. The same procedure was repeated for remaining 9 tablets.

Water Absorption Ratio[7]

A piece of tissue paper folded twice was placed in a small petri dish (10 cm diameter) containing 6 ml of water. A tablet was put on the tissue paper and allowed to wet completely. The wetted tablet was then reweighed. Water absorption ratio, R was determined using following equation,

$$R = 100 \times \frac{W_a - W_b}{W_b}$$

Where, W_a= weight of tablet after water absorption &

W_b= weight of tablet before water absorption.

Wetting time

A piece of tissue paper folded twice was placed in a small petri dish (10 cm diameter) containing 10 ml of water. A tablet was put on the tissue paper and allowed to wet completely. The time required to wet completely the tablet was then recorded.

In vitro Dispersion Time[7]

Disintegration or more specifically dispersion times were measured in 900 ml purified water according to the I.P. method without disc at room temperature (25°C ± 2°C). The disintegration times of 6 individual tablets were recorded and the average DT was noted.

In vivo Dispersion Time[7]

The time required for the tablets to disperse in mouth cavity was determined by holding the tablets in mouth. The test was performed in five healthy human volunteers in the age group of 23 to 28 years.

In vitro Dissolution Study[7]

Dissolution profiles of etoricoxib tablets were determined using the USP 24 Method II with paddle speed at 50 rpm. Dissolution was performed in 900 ml 0.1NHCl maintained at 37 ± 0.5°C (figure 1). Five milliliters of samples were withdrawn at specified time intervals. The volume of dissolution fluid was adjusted to 900 ml, by replacing each 5 ml aliquot withdrawn with 5 ml of 0.1NHCl, pre-warmed at 37± 0.5°C. Samples withdrawn were filtered through Whatmann filter paper (no.41), suitably diluted with 0.1N HCl, and analyzed at 233 nm, using UV-Visible double beam spectrophotometer. The data given in table 4 are the mean of 6 individual determinations.

RESULTS AND DISCUSSION

In the present investigation, etoricoxib oro-dispersible tablets were prepared in six formulations with varying concentration of three superdisintegrants: Crospovidone (Polyplasdone XL), Croscarmellose Sodium (Ac-Di-Sol) and Sodium starch glycolate (Primojel) and mannitol (granular) was used as diluents. For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The powder blend was compressed using direct compression technique. Bulk density was found in the range of 0.567-0.586 g/cm^3 and the tapped density between 0.667 and 0.684 g/cm^3. Using above two density data, Hausner's ratio and compressibility index were calculated. The powder blends of all formulations with Hausner's ratio (<1.25) indicated better flow properties. The compressibility index was found between 14.09 and 14.84 and the compressibility-flowabilty correlation data indicated an excellent flowability of all powder blends[8]. The better flowability of all powder blends was also evidenced from angle of repose (range of 23.95- 28.65), which is below 40º indicating good flowability[8].

Tablets were prepared using direct compression technique. Since the powder blends were free flowing, tablets were obtained of uniform weight due to uniform die fill, with acceptable weight variations as per pharmacopoeial specifications. The drug content was found in the range of 98.86 – 104.87 % and the hardness of tablets between 4.3-4.5 kg/cm^2. Friability of the tablets was found below 0.43-0.62 % indicating good mechanical resistance of tablets. Water absorption ratio of all formulations was found between 74.47 and 96.92 % as evidenced from water uptake study. This resulted in fast wetting of tablets of all formulations as reflected from wetting time ranging between12-35 sec.

In vivo & *in vitro* dispersion time is presented in Table 3. All tablets disintegrated rapidly without disc in the IP test especially when used at their optimum concentrations as reported in literature. The usual concentration of Sodium starch glycolate (Primojel) employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient[9]. Croscarmellose sodium (Ac-Di-Sol) at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process[9]. Crospovidone (Polyplasdone XL) is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods[9]. Basically both Primojel and Ac-Di-Sol give approximately the same disintegration times at 2 and

3% levels, so that using these at a 2% level generally suffices to obtain maximum disintegration efficiency[10]. Hence, the effect of superdisintegrants specifically at 2 and 4% level in oro-dispersible tablet formulation on the in vitro dissolution was evaluated for functionality comparison. These levels included optimum concentrations of selected superdisintegrants to be used in formulations.

In the study, the relatively larger fragments generated by tablets containing sodium starch glycolate (Primojel) were not small enough to pass through the screen of the disintegration vessels. Accordingly a longer disintegration time and a larger variation were observed, especially when the sodium starch glycolate (Primojel) was used at the lower concentration (2%). Croscarmellose sodium (Ac-Di-Sol) and cospovidone (Polyplasdone XL) disintegrated tablets more rapidly. Tablets formulated with 2% of those two disintegrants disintegrated nearly immediately, even when tested at room temperature. Tablets formulated with Ac-Di-Sol can be seen to rapidly disintegrate into more or less uniform *fine* particles, while tablets formulated with Primojel appeared to disintegrate much more slowly into more or less uniform *coarser* particles. Tablets containing Polyplasdone seemed to swell immediately despite the limited swelling capacity of this class of superdisintegrants. Polyplasdone XL was reported to exhibit a high capacity to retain deformation during postcompression[11]. The rapid swelling of these tablets upon wetting may partly be attributed to the recovery of deformation. When used at 2% concentration, tablets with this class of superdisintegrants disintegrated further into large irregularly shaped fragments. Considering the short disintegration times measured by the IP disintegration apparatus, these fragments must be weakly held particle associations that apparently persist under the conditions of this test. Ac-Di-Sol disintegrated tablets rapidly into relatively fine particles, Primojel disintegrated tablets more slowly into relatively larger fragments, and Polyplasdone XL disintegrated tablets into relatively large fragments of loosely associated particles, which easily dispersed under the oscillating movement of the IP disintegration apparatus.

The disintegration test is not discriminating since all superdisintegrants appear highly efficient, with disintegration times as short as 30 seconds when used at 2% concentration. However, as discussed above, differences in the particle size generated in the disintegrated tablets could affect drug dissolution since breaking tablets into finer fragments may promote drug dissolution by providing larger total surface areas for drug dissolution to take place. The disintegration times and dissolution profiles of etoricoxib oro-dispersible tablets formulated with 2% and 4% Ac-Di-Sol, Primojel, or Polyplasdone XL are given in Table 3 and Figure 1. At the same addition level, Ac-Di-Sol and Polyplasdone XL generally disintegrate tablets faster than Primojel. It was found that the disintegration time was comparable for tablets formulated with either 2% Ac-Di-Sol, 2% Polyplasdone XL, or 4% Primojel. However, the dissolution of etoricoxib from these tablets varied in the following decreasing order despite the closeness of their disintegration times: Polyplasdone XL > Ac-Di-Sol > Primojel. These results correlate with the apparent differences in particle size generated in the disintegrated tablets. To further investigate the importance of the total surface area in promoting drug dissolution, a water uptake study was performed on etoricoxib oro-dispersible tablets. Since drug has to dissolve from the interface between drug and water, the maximal water uptake volume can be taken as an estimation of the total surface area available for drug dissolution to take place. The water absorption ratio was summarized in Table 3. Each fiber can act as a hydrophilic channel to facilitate water uptake into the tablet matrix and help increase the total water contact area with drug.

Thus, it can be concluded that the three disintegrants representing each of three main classes of superdisintegrants differed in their ability to disintegrate etoricoxib oro-dispersible tablets into their primary particles when used at the same w/w percentage concentration. Such a difference can potentially affect drug disintegration and subsequently dissolution behavior. The etoricoxib oro-dispersible tablet appeared to successfully discriminate the ability of these superdisintegrants to promote drug dissolution and is proposed as a model formulation for disintegrant performance testing and quality control purposes.

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Table 1: Characterization of powder blends*

Formulation code	Evaluation parameters					
	Angle of Repose	Bulk Density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner's Ratio	Flowability
ETR-1	25.12	0.571	0.669	14.64	1.17	Excellent
ETR-2	26.35	0.586	0.684	14.32	1.16	Excellent
ETR-3	24.21	0.579	0.674	14.09	1.16	Excellent
ETR-4	28.65	0.568	0.667	14.84	1.17	Excellent
ETR-5	23.95	0.578	0.678	14.74	1.18	Excellent
ETR-6	27.84	0.588	0.688	14.53	1.18	Excellent

All values are mean ± SD, n=6

Table 2: Formulation design

Tablet ingredients (mg) /Formulation code	ETR-1	ETR-2	ETR-3	ETR-4	ETR-5	ETR-6
Etoricoxib	60	60	60	60	60	60
Aspartame	4	4	4	4	4	4
Mannitol (granular)	320	320	320	312	312	312
Croscarmellose Sodium	8	-	-	16	-	-
Crospovidone	-	8	-	-	16	-
Sodium starch glycolate	-	-	8	-	-	16
Colloidal silicon dioxide	2	2	2	2	2	2
Mixed fruit flavor	2	2	2	2	2	2
Magnesium stearate	4	4	4	4	4	4
Total weight	**400**	**400**	**400**	**400**	**400**	**400**

Table 3: Evaluation of tablets*

Evaluation parameters /Formulation code	ETR-1	ETR-2	ETR-3	ETR-4	ETR-5	ETR-6
Weight Variation (± %)	Passes	Passes	Passes	Passes	Passes	Passes
Hardness (Kg/cm^2)	4.5	4.3	4.3	4.4	4.5	4.5
Thickness (mm)	4.2	4.3	4.4	4.3	4.2	4.3
Friability (%)	0.44	0.52	0.43	0.48	0.59	0.62
Content Uniformity (%)	101.52	102.38	98.86	103.65	104.87	100.24
Water Absorption Ratio (%)	78.87	84.72	74.47	92.62	96.92	85.34
Wetting time (sec)	<20	<15	<35	<15	<12	<30
In vitro DT (sec)	<25	<20	<40	<20	<18	<35
In vivo DT (sec)	<32	<28	<48	<28	<25	<42
DP_{30} (sec)	75.83	89.04	42.24	86.98	97.50	62.52

All values are mean ± SD, n=6; DP30 (sec): Percent drug dissolved in 30 sec. (in 0.1N HCL)

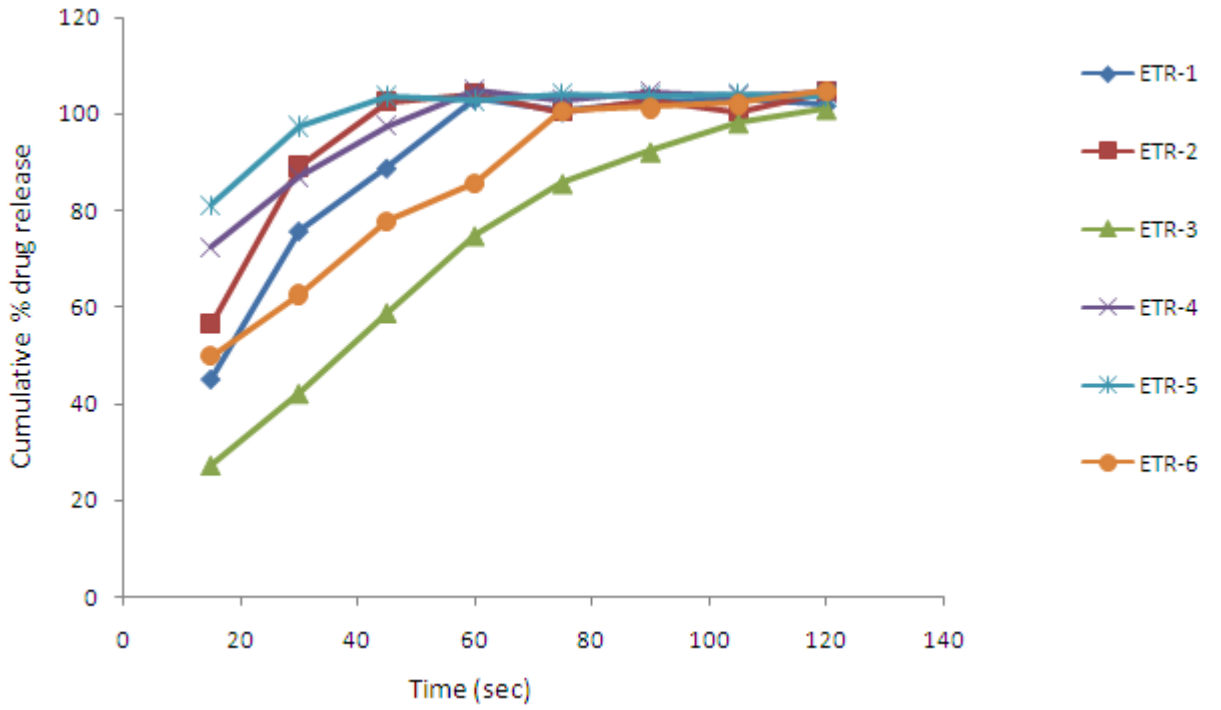

Fig 1: Comparative dissolution profile of etoricoxib oro-dispersible tablets in 0.1 N HCl

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