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ETORICOXIB ORODISPERSIBLE TABLETS: FORMULATION AND *IN VITRO* EVALUATION

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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, etoricoxib 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. Tablets were prepared using direct compression technique and were evaluated for its thickness, hardness, friability, disintegration test, weight variation test, water Absorption ratio, wetting time, *In vitro* Dispersion Time & *In vitro* Dissolution. 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. The wetting time of all formulations was found between 13-36 sec. 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. 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.

Key words: Orodispersible, Superdisintegrants, Etoricoxib, Ac-Di-Sol.

INTRODUCTION:

The term 'Orodispersible Tablet' as appears in European Pharmacopoeia (Suppl. 4.1, IV Ed.) is defined as ''uncovered tablet for buccal cavity, where it disperses before ingestion''. They obviate the problem associated with conventional dosage forms, it has benefits like desired hardness, dosage uniformity, extremely easy administration and since no water is required for swallowing these tablets are suitable for geriatric, paediatric and travelling patients. These tablets display a fast and spontaneous de-aggregation in the mouth, soon after it comes in contact with saliva, dissolving the active ingredient and allowing absorption through all possible membrane it comes in contact during deglutition [1].

In the recent past, several new advanced technologies have been introduced for the formulation of orodispersible tablets with very interesting features, like extremely low disintegration time, exceptional taste masking ability, pleasant mouth feel and sugar free tablets for diabetic patients [2]. The technologies utilized for fabrication of orodispersible tablets include lyophilization, [3] moulding[4], direct compression[5], cotton candy process[6]., spray drying[7], sublimation[8], mass extrusion[9], nanonization [10] and quick dissolve film formation[11]. These techniques are based on the principles of increasing porosity and/or addition of superdisintegrants and water soluble excipients in the tablets[12]. The formulations prepared from these techniques differ from each other on the basis of the factors like mechanical strength of final product, drug and dosage form stability, mouth feel, taste, rate of dissolution of the formulation in saliva, rate of absorption from saliva and overall drug bioavailability and polymers [13].

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 [14].

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 [15].

MATERIALS AND METHODS

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 purchased from local market and all other chemicals and reagents were of analytical grade.

Methods

Preparation of tablets

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 5-7 minutes. The resulting uniform blend of composition per tablet as mentioned in table 1 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.

Weight variation[16]

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

Hardness[16]

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.

Table-1: Formulation design of tablets

Tablet ingredients (mg)	Formulation code					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
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 (mg)	400	400	400	400	400	400

Thickness[16]

Thickness of tablets was measured using Vernier calliper.

Friability[16]

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,

$f = (W_0\text{-}W) \times 100 / W_0$

Where, W_0 is the weight of the tablets before the test & W is the weight of the tablets after the test.

Content uniformity[16]

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[16]

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,

$R= (W_a- W_b) X 100 / W_b$

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**[16]

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 vitro* Dissolution Study**[16]

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 0.1N HCl maintained at 37 ± 0.5°C. 5ml 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 0.1N HCl, 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

Tablets were evaluated for its thickness, hardness, friability, disintegration test, weight variation test, water Absorption ratio, wetting time, *In vitro* Dispersion Time & *In vitro* Dissolution. The results were reported in table 2.

Table 2: Evaluation of tablets*

Tablet ingredients (mg)	Formulation code					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
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)	<21	<16	<36	<16	<13	<31
In vitro DT (sec)	<25	<20	<40	<20	<18	<35
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)

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 between13-36 sec. *In vitro* dispersion time is presented in Table 2. All tablets disintegrated rapidly without disc in the IP test especially when used at their optimum concentrations as reported in literature.

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.

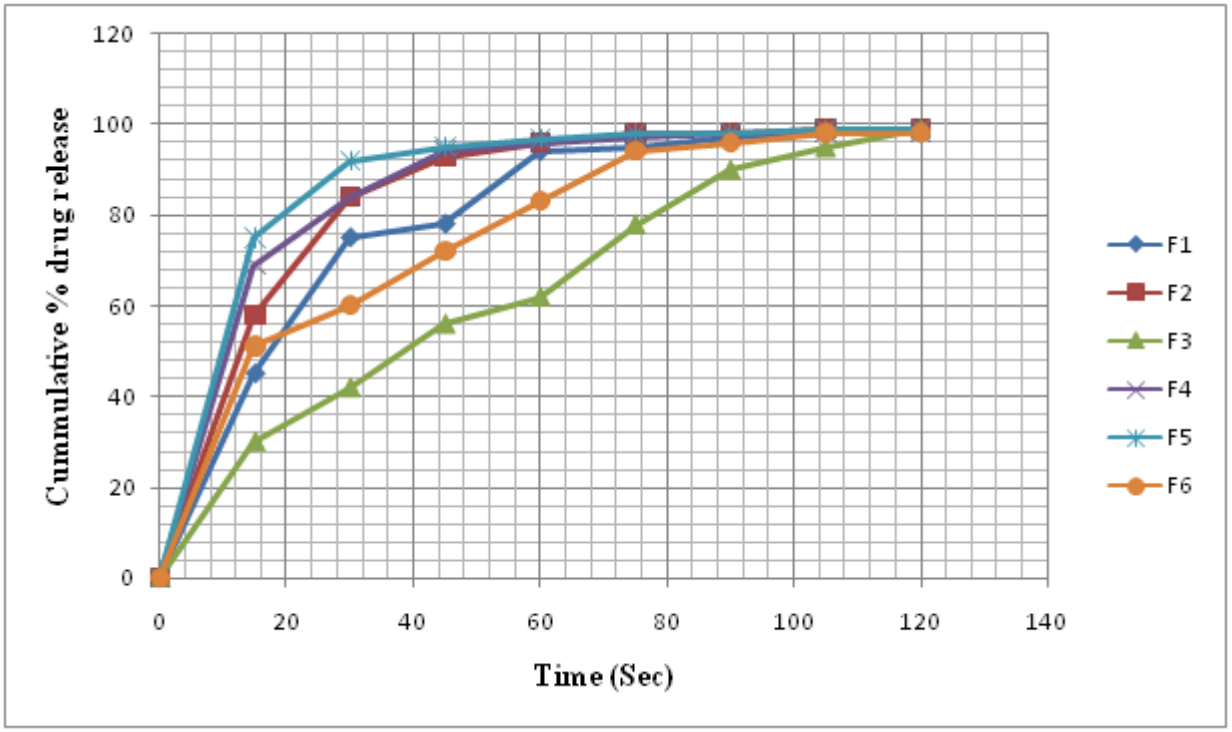

Figure 1: Comparative dissolution profile of etoricoxib dispersible tablets in 0.1 N HCl

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[18]. 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 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 2 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. The water absorption ratio was summarized in Table 2. 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.

CONCLUSION:

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.

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REFERENCES

1. Sharma, V., Philip, A., Pathak, K. Modified polysaccharides as fast disintegrating excipients for orodispersible tablets of roxithromycin. AAPS PharmSciTech.2008; 9 (1), 1530–32.
2. Shukla, D., Chakraborty, S., Singh, S. Mouth dissolving tablets II: an overview of evaluation techniques. Sci. Pharm.2009; 77, 327–341.
3. Virely, P., Yarwood, R. Zydis – a novel, fast dissolving dosage form. Manuf. Chem.1990; 61, 36–37.
4. Pebley, W.S., Jager, N.E., Thompson, S.J. Rapidly disintegrating tablet. US Patent 5, 1994; 298, 261.

5. Watanabe, Y. New compressed tablet rapidly disintegrating in the mouth using crystalline cellulose and a disintegrant. Biol. Pharm. Bull.1995; 18, 1308–10.
6. Myers, G.L., Battist, G.E., Fuisz, R.C., 1995. Process and apparatus for making rapidly dissolving dosage units and product there from. PCT Patent WO 95/34293-A1.
7. Allen, L.V., Wang, B. Process for making a particulate support matrix for making a rapidly dissolving tablet. US Patent 1996; 5,587,180.
8. Koizumi, K.I., Watanabe, Y., Morita, K., Utoguchi, N., Matsumoto, M. New method for preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material. Int. J. Pharm. 1997; 152, 127–131.
9. Bhaskaran, S., Narmada, G.V. Rapid dissolving tablets a novel dosage form. Indian Pharmacist. 2002; 1, 9–12.
10. Khan, S., Kataria, P., Nakhat, P., Yeole, P. Taste masking of ondensetron hydrochloride by polymer carrier system and formulation of rapid disintegrating tablets. AAPS PharmSciTech. 2007; 8 (2), 46–57.
11. Biradar, S.S., Bhagavati, S.T., Kuppasad, I.J. Fast dissolving drug delivery system: a brief overview. Internet J. Pharmacol.2006; 4 (2), 32–38.
12. Kuchekar, B.S., Badhan, A.C., Mahajan, H.S., 2003. Mouth dissolving tablets: a novel drug delivery system. Pharma. Times 2003; 35 (June),7-9
13. A. Mahajan, R. Sharma, COX-2 Selective Nonsteroidal Anti-inflammatory Drugs: Current Status, *Journal of the Association of Physicians of India*, 2005; Vol.53, 200-04.
14. S.R. Shahi et.al, Formulation And *In Vitro* Evaluation Of Oro-Dispersible Tablets Of Etoricoxib With Emphasis On Comparative Functionality Evaluation Of Three Classes Of Superdisintegrants, *Rasayan Journal of Chemistry*, 2008; 1(2) ,292-300.
15. Chaudhari PD, Chaudhari SP, Lanke SD, Patel N. Formulation and in vitro evaluation of taste masked orodispersible dosage form of Levocetirizine dihydrochloride, *Indian Journal of Pharmaceutical Education & Research*, 2007; 41 (4), 319-28.
16. K.S.G. Vijaya, D.N. Mishra, Rapidly disintegrating oral tablets of meloxicam by direct compression method, *Indian Drugs*,2006;.43(2), 117-21.