The Pharma Innovation Journal 2017; 6(5): 29-33

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating 2017: 5.03
TPI 2017; 6(5): 29-33

www.thepharmajournal.com
Received: 15-03-2017
Accepted: 16-04-2017

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# Comparative evaluation of quality control parameters of some etoricoxib generic tablets available in Bangladesh

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**Abstract**
Etoricoxib is a highly selective cyclooxygenage-2 (COX-2) inhibitor administered orally as an analgesic drug that has shown some improved efficacy versus traditional NSAIDs. The study was intended to evaluate different physicochemical parameters of generic etoricoxib tablet from different manufacturers using *in vitro* tests. The tested brand products had satisfactory hardness, average weight, friability, disintegration and potency. All the brands released more than 80% drug in the first 45 minutes except for brand E9. The dissolution profiles were compared with the use of difference factor (f1) and similarity factor (f2), showing that all the brands except E9 are similar with brand E1 and can be used interchangeably.

**Keywords:** Etoricoxib, *In vitro* equivalence, Dissolution, Difference factor ($f_1$), Similarity factor ($f_2$).

## 1. Introduction
The oral route of drug administration is the most important method of administering drugs for systemic effects. Tablets represent unit dosage forms in which one usual dose of the drug has been accurately placed. The main purpose of designing and manufacturing of the compressed tablet is to deliver orally the correct amount of drug in the proper form, at or over the proper time and in the desired location, and to have its chemical integrity protected to that point. Manufacturing methods and the excipients used in the production process could affect the quality and release profile of medicament. Therefore, to ensure the necessary quality, drug manufacturers are required to examine their products during and after manufacturing at various time intervals. So, the selection of one product from several generic drug products of the same active ingredients is very important for healthcare workers [1].

The non-steroidal anti-inflammatory drugs (NSAIDs) are widely used long term for the treatment of rheumatoid and osteoarthritis to relieve the pain and inflammation [2]. The intermediate iso enzymes responsible for prostaglandin biosynthesis, cyclo-oxygenase (COX) 1 and 2, have been the target of arthritis therapy using non-steroidal anti-inflammatory drugs [3]. NSAIDs are associated with a number of adverse effects. These include alterations in renal function, effects on blood pressure, hepatic injury and platelet inhibition which may result in increased bleeding [4]. COX-2 has been shown to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation and fever. Selective inhibition of COX-2 by etoricoxib decreases these clinical signs and symptoms of pain with decreased potential for GI toxicity and effects on platelet aggregation [5].

Etoricoxib, [5-chloro-2-(6-methylpyridin-3-yl)-3-(4-methylsulfonylphenyl) pyridine], is an orally active agent that selectively inhibits COX-2. It is a widely prescribed anti-inflammatory drug available in tablet strengths of 30, 60, 90, and 120 mg. It is a poorly soluble and highly permeable BCS class 2 drug [6]. Its aqueous solubility is low and highly pH-dependent. Pharmacokinetic studies, however, show that when administered orally, etoricoxib is completely and rapidly absorbed, with an oral bioavailability of up to 100% [7]. It is used in the treatment of rheumatoid arthritis, osteoarthritis, post-operative dental pain, chronic musculo-skeletal back pain, primary dysmenorrhoea and acute gout. Moreover, recent studies evidenced its efficacy in patients with ankylosing spondylitis. But it's very low aqueous solubility and poor dissolution can cause formulation problems and limit its therapeutic application by delaying the rate of absorption and the onset of action [8]. Etoricoxib is available in 55 countries in Europe, Latin America and the

Asia-Pacific region and is under development in the US. There have been an estimated 2.4 million patient-years of exposure with etoricoxib 60, 90, and 120 mg outside the United States since 2001.

The purpose of the study is to make a comparison of product quality control parameters, differentiate visual uniqueness and identify differences in physicochemical properties between different marketed etoricoxib tablets in Bangladesh.

## 2. Materials and Methods

### 2.1 Collection of Sample Products

Standard of etoricoxib was a kind gift from a reputed pharmaceutical company in Bangladesh. Etoricoxib tablets (60 mg) of nine different brands were purchased from registered pharmacy stores of Dhaka, Bangladesh. The samples were properly checked for their physical appearance, name of manufacturer, batch number, manufacturing date, expiry date, manufacturing license number, DAR number and maximum retail price. For ethical concerns, the tablets were randomly coded as E1, E2, E3, E4, E5, E6, E7, E8 and E9 so that the identity of the manufacturer can be blinded. The label information of nine different brands of etoricoxib tablets are shown in (Table 1).

**Table 1:** Label information of nine different brands of etoricoxib tablets

| Brand code | Mfg. date | Exp. date | Pack size found | Price of pack found (BDT) | Price / 10 units (BDT) |
|---|---|---|---|---|---|
| E1 | April 2016 | April 2018 | 100 | 500 | 50 |
| E2 | May 2016 | May 2018 | 100 | 550 | 55 |
| E3 | June 2016 | June 2018 | 100 | 550 | 55 |
| E4 | June 2016 | June 2018 | 100 | 600 | 60 |
| E5 | June 2016 | June 2018 | 100 | 600 | 60 |
| E6 | October 2016 | October 2018 | 100 | 650 | 65 |
| E7 | July 2016 | July 2018 | 100 | 600 | 60 |
| E8 | March 2016 | March 2018 | 100 | 600 | 60 |
| E9 | April 2016 | April 2018 | 100 | 600 | 60 |

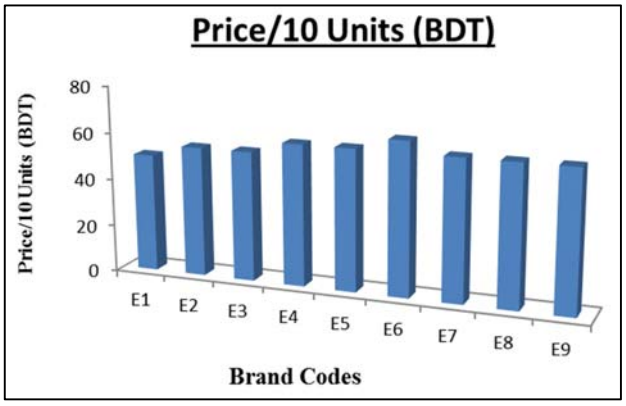


**Fig 1:** Price fluctuation among different brands of etoricoxib available in local market of Bangladesh

### 2.2 Diameter and thickness inspection

Twenty tablets from each brand were selected for diameter and thickness test. Diameter and thickness were determined by using digital slide caliper. Mean thickness, diameter and their standard deviations (SD) were calculated.

### 2.3 Hardness test

Crushing strength (N) was determined with an automatic hardness tester (VEEGO, INDIA). Twenty tablets were randomly selected from each brand and the pressure required to crush each were recorded.

### 2.4 Friability test

Twenty tablets from each brand were weighed and subjected to rotation by employing a VEEGO friabilator (VFT-2, India) which was operated at 25 RPM for 4 minutes. All tablets were weighed before and after 100 revolutions.

### 2.5 Weight variation

For weight variation twenty tablets from each brand were weighed individually using an analytical balance (TE214S, Sartorious Germany).

### 2.6 Standard assay preparation

The powder equivalent to 100 mg of etoricoxib was taken and dissolved in 0.1 N HCl (pH 1.2). Then it was diluted to produce a final concentration of 0.010 mg/ml (10 µg/ml) for working solution. Then this solution was again serially diluted to get concentrations of 1 µg/ml, 2 µg/ml, 3 µg/ml, 4 µg/ml, 5 µg/ml, 6 µg/ml, 7 µg/ml, 8 µg/ml, 9 µg/ml and 10 µg/ml respectively. Absorbance values were then measured at the maximum wavelength (λ max) of etoricoxib using a UV-VIS spectrophotometer (UV-1700, Shimadzu, Japan). Maximum wavelength (λ max) was obtained by scanning samples at different wavelength ranging from 200 to 400 nm and it was found to be 234 nm.

### 2.7 Disintegration test

Disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mesh screen. It has to be pointed out that a product which fails disintegration will presumably fail dissolution criteria [9]. Six tablets from each brand were employed for the test in distilled water at 37 °C using a tablet disintegration tester ED-20 (Electrolab, Mumbai, India) as per condition described by United State Pharmacopeia, 2014 [10]. The disintegration time (DT) was noted down and by definition, it's the time taken for the entire tablet to disintegrate completely.

### 2.8 Measurement of potency

Analysis of drug potency in tablets is to evaluate the tablets potential for efficacy by monitoring the presence of drug in dosage form and also requisite for the establishment of stability data. Sample was prepared by weighing and crushing 10 tablets, transferring amount of drug powder equivalent to 10 mg in 0.1 N HCl (pH 1.2) solution and placing it in sonicator. The portion of solution was filtered and the filtrate was suitably diluted to give concentrations of 1 µg/ml, 2 µg/ml, 3 µg/ml, 4 µg/ml, 5 µg/ml, 6 µg/ml, 7 µg/ml, 8 µg/ml, 9 µg/ml and 10 µg/ml respectively. Absorbance was taken at 234 nm by using UV-visible spectrophotometer. Finally the

potency of different tablets was determined by using the following equation:

$$\% \text{ Potency} = \frac{\text{Drug content}}{\text{Therapeutic value}} \times 100$$

### 2.9 Dissolution Test

The dissolution test was undertaken for six randomly selected tablets using dissolution apparatus paddle (Electrolab, India). The dissolution medium was 900 ml of 0.1 N HCl (pH 1.2) which was maintained at 37±0.5 °C. Rotations were 50 revolutions per minute. 10 ml of sample was withdrawn after 5 and 15 minutes and then after every 15 minutes. Standard solution was prepared accordingly. Absorbance was measured at 234 nm. To determine the concentration of samples, help from the standard curve of pure API was taken. Using the Y= mX + C equation, sample concentration was calculated.

## 3. Results and discussion

### 3.1 Price fluctuation

Price, manufacturing and expiry date of etoricoxib tablets were observed in the drug outlets on single visit during medicine collections. The highest price was for brand E6 (6.5 taka per tablet) and minimum for brand E1 (5 taka per tablet) while there was no major variation in the physical appearance of the tablets (Figure 1).

### 3.2 Diameter and thickness test

As the weight of a compressed tablet is dependent on density, diameter, and thickness, determination of the diameter and thickness of the tablets at regular intervals during the production may prevent potential problems related to tablet weight and content uniformity at an early stage [11]. Among six brands, brand E4 had the highest average diameter (13.38 mm) whereas brand E8 had the lowest average diameter (6.48 mm). The average thickness was found to be between the ranges of 3.10 mm-5.25 mm (Table 2).

### 3.3 Hardness test

Hardness is referred to as non-compendial test. The hardness of the tablet depends on the materials used, amount of binder, space between the upper and lower punches at the time of compression and pressure applied during the process of compression [12]. The testing of tablet hardness and friability plays a pivotal role in both product development and subsequent quality control because high hardness values may result in increased disintegration time and decreased dissolution time. As opposed to this situation, high friability values may be observed in case of low hardness values. Measuring the hardness of a tablet is not a reliable indicator for tablet strength as some formulations when compressed into very hard tablets tend to cap or lose their crown portions on attrition [13]. Tablet hardness was found between 76-183 N. A force of about 40 N is the minimum requirement for a satisfactory tablet [14]. So, the tablets of all the brands complied with this requirement were considered as of good quality.

### 3.4 Friability test

It is the tendency of tablets to powder, chip, or fragment and this can affect the elegance appearance, consumer acceptance of the tablet and also add to tablet's weight variation or content uniformity problems [15]. Tablet hardness is not an absolute indicator of strength and therefore another measure of a tablet's strength, its friability, is often measured which is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping which can lead to capping, chipping, abrasion or even breakage of the tablets. Friability test is now included in the United States Pharmacopeia as a compendial test [16]. The compendial specification for friability is 1%. Usually harder the tablets less will be the percentage friability and vice versa [17]. It was found that nine different brands of etoricoxib tablets were in accordance with the stated USP guideline (Table 2).

### 3.5 Test of uniformity of weight

The weight variation test would be a satisfactory method of determining the drug content uniformity of tablets if the tablets were all or essentially all (90 to 95%) active ingredient, or if the uniformity of the drug distribution in the granulation or powder form from which the tablets were made were perfect [15]. The average weight of tablets of each brands were between 130 mg-324 mg and USP specification for weight variation of tablets is ±7.5% for this average weight range. From the results, it can be said depending upon the USP specification that, the % deviations of all the brands of etoricoxib 60 mg tablets are within range ±7.5% deviation. So, all brands comply with USP specification.

### 3.6 Disintegration test

Disintegration time depends on the product, the stirring speed etc [15]. Disintegration time affects release of drug content from its dosage form. It has to be pointed out that a product which fails disintegration will presumably fail dissolution criteria because the disintegration tests do serve as a component in the overall quality control of tablets manufacturing [9]. According to BP specification, film coated tablets should disintegrate within 30 min, while the USP specifies that both uncoated and film coated tablets should disintegrate within 30 min. Here all brands of etoricoxib tablets were film coated and maximum time for disintegration was found 7.06 min in case of brand E3 (Table 2)

**Table 2:** A summary of the quality control tests undertaken on different brands of etoricoxib tablets

| Brands | Diameter (mm) | Thickness (mm) | Friability (%) | Hardness (N) | Weight Variation (gm) | DT (min) | Potency (%) |
|---|---|---|---|---|---|---|---|
| E1 | 8.07±0.01 | 3.10±0.02 | 0.25 | 84.67±0.83 | 164.64±1.49 | 2.17±0.52 | 98.03 |
| E2 | 8.28±0.02 | 3.40±0.02 | 0.14 | 61±0.87 | 190.29±1.53 | 2.82±0.55 | 95.79 |
| E3 | 10.44±0.01 | 3.84±0.02 | 0.23 | 53±0.91 | 180.57±1.66 | 7.06±0.52 | 91.68 |
| E4 | 13.38±0.01 | 5.25±0.03 | 0.03 | 126±0.73 | 368±1.88 | 1.88±0.59 | 99.56 |
| E5 | 10.08±0.03 | 3.15±0.06 | 0.04 | 183±0.80 | 123±1.33 | 2.47±0.57 | 95.77 |
| E6 | 7.13±0.03 | 3.72±0.04 | 0.09 | 96.66±0.80 | 153±1.75 | 1.54±0.52 | 90.75 |
| E7 | 9.20±0.03 | 3.32±0.03 | 0.19 | 76±0.83 | 147.05±1.22 | 2.2±0.66 | 97.59 |
| E8 | 6.48±0.01 | 3.46±0.03 | 0.11 | 89.33±0.97 | 121.3±2.12 | 1.57±0.69 | 100.93 |
| E9 | 10.56±0.01 | 4.34±0.03 | 0.1 | 130.67±0.87 | 260.1±1.06 | 3.3±0.88 | 90.52 |

*Values are expressed as mean± SD

### 3.7 Potency test

Potency of all the brands was found within 90.52-100.93%. Etoricoxib is an INN drug; no official specification for the drug's potency is available yet. For highly potent, low-dose drugs this range is usually not less than 90% and not more than 110% of the labeled amount. Since the present study was conducted with large dose etoricoxib tablets (60 mg), percent potency should be within 95%-105% [10]. All the brands met this specification (Table 2).

### 3.8 Dissolution test

Intra-brand comparison of the drug release profile of all the brands indicated increase in drug release after every 15 minutes although this increase varied from brand to brand. After 60 minutes interval, brand E4 showed maximum drug release (98.8%) and brand E9 exhibited minimum drug release (72.1%). Since all the brands released more than 80% drug in the first 45 minutes except for brand E9, it can be assumed that all the brands possessed good dissolution profile although the brands were manufactured by different companies using different excipients in different ratio (Table 3)

**Table 3:** Dissolution profile of nine brands of etoricoxib tablets

| Time (min) | % Drug Release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | E1 | E2 | E3 | E4 | E5 | E6 | E7 | E8 | E9 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 24.4±0.66 | 25.6±0.88 | 22.5±0.53 | 28.1±0.72 | 28.9±0.83 | 22.9±0.78 | 39.3±0.75 | 39.6±0.86 | 32.6±0.61 |
| 15 | 44.3±0.53 | 42±0.86 | 43.7±0.56 | 45.3±0.78 | 44.8±0.88 | 44.1±0.75 | 46.9±0.79 | 53±0.86 | 40±0.69 |
| 30 | 84.6±0.61 | 84.4±0.86 | 80.5±0.58 | 85.5±0.75 | 84.1±0.82 | 76.8±0.71 | 68.4±0.79 | 74±0.80 | 55.6±0.63 |
| 45 | 92.7±0.66 | 93.3±0.86 | 89±0.59 | 95.3±0.72 | 92.6±0.88 | 87.2±0.78 | 89±0.75 | 92.5±0.86 | 61.6±0.63 |
| 60 | 97.4±0.68 | 98.6±0.82 | 94.2±0.52 | 98.8±0.79 | 95.6±0.88 | 90.1±0.75 | 98.4±0.73 | 96.8±0.89 | 72.1±0.61 |

*Values are expressed as mean± SD

### 3.9 Comparison of dissolution data

Difference factor (f1) and similarity factor (f2) were calculated to compare the dissolution profile. The following equations were used to calculate f1 and f2. Where n is the number of time points, $R_t$ is the dissolution value of reference product at time t and $T_t$ is the dissolution value for the test product at time t. Similarity factor (f2) has been adopted by FDA and the European Agency for the Evaluation of Medicinal Products by the Committee for Proprietary Medicinal Products (CPMP) to compare dissolution profile. According to the FDA guidance, dissolution profiles are similar if f1 values are between 0 and 15 and f2 values are between 50 and 100. Table 4 shows the f1, f2 values of different brands in respect of brand E1 as a reference brand [18]

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} X100$$

$$f_2 = 50 \log \left\{ \left( 1 + \frac{1}{n} \sum_{i=1}^{n} (R_t - T_t)^2 \right)^{-0.5} X100 \right\}$$

**Table 4:** f1 and f2 of nine brands of etoricoxib tablets tested

| Pair Comparison | Difference Factor (f1) | Similarity Factor (f2) |
|---|---|---|
| E2 vs E1 | 1.65 | 73.85 |
| E3 vs E1 | 3.95 | 58.2 |
| E4 vs E1 | 2.8 | 82.35 |
| E5 vs E1 | 2.12 | 82.5 |
| E6 vs E1 | 6.46 | 65 |
| E7 vs E1 | 11.12 | 52 |
| E8 vs E1 | 10.27 | 53.5 |
| E9 vs E1 | 28.49 | 35 |

It can be seen from the Table 4 that, all the brands except E9 has difference factor between 0 and 15, and similarity factor between 50 and 100. So, all the brands except brand E9 can be used interchangeably with brand E1.

## 4. Conclusion

Quality of product refers to its confining to the standards pre-set to assure the desired purpose. A quality product gives not only better therapeutic efficacy but also gives consumer satisfaction and increases its market demand. So, a pharmaceutical industry follows the international standards to ensure quality product and to give proper safety and efficacy. In the current industrial practice, to compare with the multi brand generic molecules and to provide enough therapeutic activity of the dosage form, *in-vitro* tests play a significant role. Drug release and potency were satisfactory for all brands. As a result, patients can safely switch from one brand to another

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