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Research Article

COMPARATIVE IN VITRO ANALYSIS OF PHYSICOCHEMICAL PROPERTIES OF SOME ACECLOFENAC GENERIC TABLETS MARKETED IN BANGLADESH

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ABSTRACT

Aceclofenac is a non-steroidal anti-inflammatory drug analog of diclofenac and works by inhibiting the action of cyclooxygenase (COX) that is involved in the production of prostaglandin (PG) and accountable for pain, swelling, inflammation, and fever. Present study was targeted to assess various physicochemical parameters of aceclofenac tablets marketed in Bangladesh by different manufacturers using *in vitro* quality control tests. Brand products tested in our study had acceptable hardness, average weight, friability, disintegration and potency. All the brands released more than 80% of drug in the first 30 minutes except for brand A9. The dissolution profiles were compared utilizing difference factor (f1) and similarity factor (f2) which showed that all the brands except A6 are similar with brand A3 and can be used in exchange for A6.

Keywords: Aceclofenac, NSAID, dissolution, disintegration, difference factor, similarity factor.

1. Introduction

Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product. A medicine should be of adequate quality such that its contents and its pharmaceutical performance should conform to acceptable standards. The risk of using a medicine should be acceptable and reasonable, taking into account that the use of any medicine carries a risk which should be considered in the light of the likely benefit. The overall quality of a medicine has dimensional parameters such as safety, potency, efficacy, stability, bioavailability, volume of distribution, clearance time, absorbance, acceptability, regulatory compliance and etc.

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 [1]. Aceclofenac is a potent non-steroidal anti-inflammatory drug which is a commonly prescribed drug for the treatment of patients suffering with pain, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Aceclofenac is a relatively new phenylacetic acid that is an analog of diclofenac [2]. The compound is stable to oxidative stress, heat, and photolytic stress (in solid form). It is a white crystalline solid, practically insoluble in water, freely soluble in acetone and soluble in ethanol (96%). It is well absorbed orally (60-70% of bioavailability following oral administration) and undergoes hepatic first pass metabolism. It is 99% bound to plasma protein extensively with albumin. The elimination half-life is 4 hrs and volume of distribution is 25 liters. The pharmacodynamic profile is similar to indometacin and diclofenac and, being superior to naproxen and phenylbutazone. Aceclofenac is available as oral, rectal and injectable formulations [3].

Aceclofenac works by blocking the effect of chemicals called cyclo-oxygenase (COX) enzymes. These enzymes help to make other chemicals in the body, called prostaglandins. Some prostaglandins are produced at sites of injury or damage and cause pain and inflammation. By blocking the effect of COX enzymes, fewer prostaglandins are produced which means pain and inflammations are eased. Aceclofenac belongs to biopharmaceutics classification system (BCS) class II drug and its dissolution is rate-limiting step for its absorption [4, 5]. The drug demonstrates better gastric tolerance than other non-steroidal

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anti-inflammatory drugs (NSAIDs) such as indomethacin and diclofenac [6]. However, cases of indigestion [7] and pancreatitis [8] have been reported.

The present study has been designed with a view to identify the difference in physicochemical properties of the manufactured aceclofenac tablets, to differentiate visual uniqueness and assure the best quality level of these products of well-known pharmaceutical companies in Bangladesh.

2. MATERIALS AND METHODS

2.1 Collection of sample products:

Standard of aceclofenac was collected from a reputed pharmaceutical company in Bangladesh. Aceclofenac tablets (100 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 etc. and for ethical concerns, the tablets were coded as A1, A2, A3, A4, A5, A6, A7, A8 and A9 so that the identity of the manufacturer can be blinded. The nine different brands of aceclofenac tablets had the following label information (Table 1)-

Table 1: Label information of nine different brands of aceclofenac tablets

Brand code	Mfg. date	Exp. date	Pack size found	Price of pack found (BDT)	Price / unit (BDT)
A1	June 2016	June 2018	100	250	2.5
A2	May 2016	May 2018	50	150	3
A3	April 2016	April 2018	50	100	2
A4	June 2016	June 2018	100	300	3
A5	June 2016	June 2018	50	150	3
A6	October 2016	October 2018	50	150	3
A7	July 2016	July 2018	100	300	3
A8	March 2016	March 2018	100	300	3
A9	April 2016	April 2018	50	150	3

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 Friability test:

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

2.4 Hardness test:

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

2.5 Weight variation:

For weight variation twenty tablets from each brand were weighed individually using an analytical balance (TE214S, Sartorious Germany). Average weight and the percent deviations were determined.

2.6 Standard assay preparation:

For preparing standard solution, 10 mg of aceclofenac was accurately weighed and dissolved in 100 ml Phosphate buffer (p^H = 6.8). This was then properly diluted to get a concentration of 10 µg/ml and was used as standard. 0 ml, 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 7 ml, 8 ml, 9 ml standard solution were withdrawn and diluted up to 10 ml with the media and thus the concentrations of 0µg/ml, 1 µg/ml, 2 µg/ml, 3 µg/ml, 4 µg/ml, 5 µg/ml, 6 µg/ml, 7 µg/ml, 8 µg/ml and 9 µg/ml were got respectively. Absorbance values were measured at the maximum wavelength (λ max) of aceclofenac 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 273 nm.

2.7 Measurement of potency:

Sample was prepared by weighing and crushing 10 tablets, transferring amount of drug powder equivalent to 10 mg in Phosphate buffer (p^H = 6.8) solution and placing it in sonicator. The portion of solution was filtered and the filtrate was suitably diluted to give concentrations of 10 µg/ml. Absorbance was taken at 273 nm by using UV-visible spectrophotometer. Finally, the potency of different tablets was determined.

2.8 Disintegration test:

By definition, disintegration time is the time taken for the entire tablet to disintegrate completely. A product which fails to disintegrate properly will presumably fail dissolution criteria [9]. Six tablets from each brand were employed for the test using distilled water at 37 °C and 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 for each tablet and then average disintegration time for each brand was calculated.

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 Phosphate buffer (p^H = 6.8) 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 as per the method described in the standard assay. Absorbance was measured at 275 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 aceclofenac tablets were observed in the pharmacy stores during medicine collections. All the brands had similar unit price (3 BDT/ tablet) and A3 had the lowest unit price among them.

3.2 Diameter and thickness test:

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 A8 had the highest average diameter (11.19 mm) whereas brand A1 had the lowest average diameter (7.22 mm). The average thickness was found to be between the ranges of 3.42 mm- 4.84 mm (Table 2).

Table 2: Summary of quality control tests performed on different brands of aceclofenac tablets

Brands	Diameter (mm)	Thickness (mm)	Friability (%)	Hardness (N)	Average Weight (gm)	DT (min)	Potency (%)
A1	7.22±0.01	4.84±0.06	0.17	40.33±0.73	165±1.75	1.68±0.52	95.44
A2	8.14±0.02	3.79±0.03	0.07	55.67±0.79	204±1.22	1.03±0.66	97.88
A3	10.23±0.02	3.78±0.02	0.09	41.33±0.88	307.45±1.34	0.47±0.49	101.88
A4	9.188±0.01	3.74±0.02	0.18	41.2±0.63	230.4±1.12	0.87±0.55	97.19
A5	9.182±0.01	4.72±0.06	0.05	67.67±0.71	257.2±1.70	1.04±0.68	102.4
A6	9.087±0.01	3.42±0.06	0.13	69.33±0.70	224.3±1.88	1.37±0.39	103.3
A7	9.228±0.04	3.79±0.06	0.05	36.67±0.55	264.6±2.06	0.9±0.57	95.8
A8	11.19±0.01	4.10±0.01	0.03	68±0.67	366.1±1.59	1.13±0.52	97.47
A9	11.16±0.01	3.68±0.05	0.05	82±0.76	246.2±1.09	1.29±0.57	105

*Values are expressed as mean± SD

3.3 Friability test:

Friability is often measured 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. 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 [12]. Friability test is included in the United States Pharmacopeia as a compendial test [13]. The USP specification for friability is 1%. Usually harder the tablets less will be the percentage friability [14]. It was found that nine different brands of aceclofenac tablets were in accordance with the stated USP guideline (Table 2).

3.4 Hardness 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 [15]. Hardness is a non-compendial test. High hardness values may result in increased disintegration time and decreased dissolution rate. In contrast, high friability values may be observed in tablets having 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 [16]. Tablet hardness was found between 36.67-82 N. A force of about 40 N is the minimum requirement for a satisfactory tablet [17]. So, the tablets of all the brands complied with this requirement except brand A7.

3.5 Uniformity of weight test:

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 [12].

The average weight of tablets of different brands was between 130 mg-324 mg except for brand A8 and USP specification for weight variation of tablets is ±7.5% for this average weight range. Brand A8 tablets had average weight of 366.1 mg. For tablets having average weight greater than 324 mg, USP specification of weight variation is ±5%. From the results, it can be said that, the percent deviations of all the brands of aceclofenac tablets are within specification.

3.6 Disintegration test:

Disintegration time is one of the determination factors for release of drug content from its dosage form. The disintegration tests do serve as a component in the overall quality control of tablets manufacturing [9]. Disintegration time depends on the product, the stirring speed etc [12]. According to BP specification, film coated tablets should disintegrate within 30 minutes, while the USP specifies that both uncoated and film coated tablets should disintegrate within 30 minutes. Here all brands of aceclofenac tablets were film coated and disintegration observed was very fast for each of them. Maximum time for disintegration was found 1.68 min in case of brand A1 (Table 2).

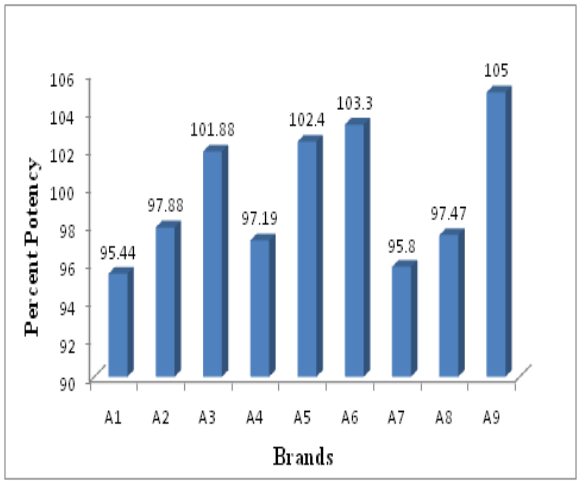

Figure 1: Percent Potency of nine brands of aceclofenac tablets

3.7 Potency test:

Potency of all the brands was found within 95.44-105%. No official specification for aceclofenac's potency in tablet 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 aceclofenac tablets (100 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 A3 showed maximum drug release (99.55%) and brand A9 exhibited minimum drug release (83.75%). Since all the brands released more than 80% drug in the first 30 minutes except for brand A9, it can be assumed that all the brands possessed good dissolution profile (Table 3).

Table 3: Dissolution profile of nine brands of aceclofenac tablets

Time (min)	% Drug Release								
	A1	A2	A3	A4	A5	A6	A7	A8	A9
0	0	0	0	0	0	0	0	0	0
5	66.97	67.77	68.47	79.13	79.03	40.02	65.24	65.17	69.49
15	71.04	71.79	72.66	85.24	84.03	80.05	79.12	80.05	78.51
30	80.19	83.18	85.19	88.12	88.75	90.04	80.57	81.23	79.04
45	85.20	87.28	89.29	90.00	90.55	92.04	81.17	85.08	82.86
60	97.15	99.29	99.55	91.06	92.36	95.08	88.47	87.02	83.75

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 [18]. Table 4 shows the f1, f2 values of different brands in respect of brand A3 as a reference brand. Brand A3 was chosen as reference brand because A3 showed highest percent release of drug after 60 minutes.

Table 4: f1 and f2 of nine brands of aceclofenac tablets tested

Pair Comparison	Difference Factor (f1)	Similarity Factor (f2)
A1 vs A3	3.52	75.25
A2 vs A3	1.41	89.61
A4 vs A3	8.52	55.69
A5 vs A3	8.18	57.30
A6 vs A3	11.54	45.15
A7 vs A3	8.07	57.30
A8 vs A3	7.56	58.80
A9 vs A3	8.49	62.76

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

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

It can be seen from the Table 4 that, all the brands have difference factor between 0 and 15, and similarity factor between 50 and 100 except for brand A6. So, all the brands except brand A6 can be used interchangeably with brand A3.

4. CONCLUSION

In vitro tests play a remarkable role while comparing the quality of different branded products. Patient's wellbeing depends upon the safety and efficacy of the drug product. In our study, aceclofenac tablets of different brands showed satisfactory drug release pattern and potency. Other compendial and non-compendial tests for the products also met specification criteria. As a consequence, we can reach a conclusion that, pharmaceutical companies in Bangladesh are playing notable role in developing quality products and patients can use these products interchangeably.

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