IJPSR (2017), Volume 8, Issue 12 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 18 June, 2017; received in revised form, 22 November, 2017; accepted, 26 November, 2017; published 01 December, 2017

COMPARATIVE QUALITY EVALUATION OF SIX BRANDS OF ENTERIC COATED DICLOFENAC SODIUM TABLETS MARKETED IN ADDIS ABABA

Nisha Mary Joseph[*1], Meklit Degu[1] and S. Palani [2]

School of Pharmacy [1], College of Health Sciences, Addis Ababa University, Ethiopia.
College of Medicine and Health Sciences [2], Jijiga University, Ethiopia.

Keywords:

Generic, Dissolution, Anti-inflammatory, Diclofenacsodium

Correspondence to Author:
Dr. Nisha Mary Joseph

School of Pharmacy,
College of Health Sciences,
Addis Ababa University, Ethiopia.

E-mail: nisha_pharma@yahoo.com

ABSTRACT: Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAIDs) with analgesic and antipyretic properties. Because of widespread use of this drug, quality control testing should be done for diclofenac marketed products to ensure safety; efficacy; accepted quality; rationality of use to protect public health. Quality of pharmaceuticals has been great concern of WHO. Drug cost needs to be reduced as health care costs continue to rise. Generic products need to be therapeutically equivalent to the brand innovator products. This can be achieved only when bioequivalent study is conducted to show whether a generic product is interchangeable with brand product or another generic product. In this study focus is given to evaluate and compare the quality of six different brands of enteric coated diclofenac sodium tablets marketed in Addis Ababa and also to study the different physicochemical properties of diclofenac sodium enteric coated tablets and to compare in vitro dissolution profile of six brands of diclofenac sodium delayed release tablets.

INTRODUCTION: The oral route of delivery is the most preferred administration route as it offers one of the safest and most convenient methods of drug administration. Tablet Dosage form is one of a most preferred dosage form all over the world. Almost all drug molecules can be formulated in a tablet and process of manufacturing of tablets is very simple, and is very flexible [1]. In tablet formulation there are active ingredients and the excipients. The excipients can include glidants (flow aids), diluents, binders or granulating agents and lubricants to ensure efficient tableting; disintegrates to promote tablet break-up in the digestive tract; sweeteners or flavors to enhance taste; and pigments to make the tablets visually attractive.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(12).5386-91

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8(12).5386-91

A polymer coating is often applied to enhance the tablet's appearance or to make the tablet smoother and easier to swallow and to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life) [2]. Enteric-coated tablets are compressed tablets coated with an inert substance which resists dissolution in gastric juices, but freely dissolves and liberates the drug in the intestine [3].

Materials used for enteric coatings include cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP) and hydroxypropyl methyl cellulose phthalate HPMCP, fatty acids, waxes, shellac, plastics and plant fibers [4]. The choice of the polymer and the thickness of the coated layer are critical to control the pH solubility profile of the enteric coated dosage form. The most common drugs which cause stomach ulcers like aspirin, diclofenac and naproxen are frequently available with enteric coatings. Inflammation is a defensive response that begins after cellular injury, which may be caused by microbes, physical agents (burns, radiation, and trauma), chemicals (toxins, caustic

substances), necrotic tissue and/or immunological reactions. Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAIDs) with analgesic and antipyretic properties (**Fig. 1**).

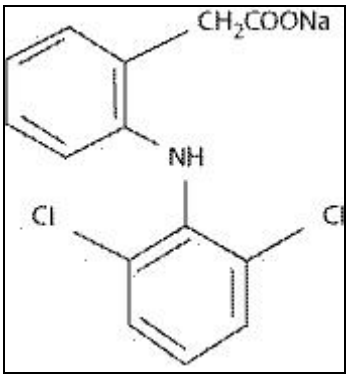

FIG. 1: MOLECULAR STRUCTURE OF DICLOFENAC SODIUM

It is widely used in management of mild to moderate pain particularly when inflammation is also present as in cases of rheumatoid arthritis, osteoarthritis, musculoskeletal injuries and some post operative conditions [5 - 7]. Diclofenac sodium delayed - release tablet 2-[(2,6-dichlorophenyl) amino] benzene acetic acid, mono sodium salt is a benzene-acetic acid derivative. It is nonselective cyclo-oxygenase inhibitor.

It inhibits the prostaglandin synthesis [8]. It is well absorbed orally, 99% protein bound, metabolized and excreted both in urine and bile. The plasma $t_{½}$ is 2 hours. However it has good tissue penetrability and concentration in synovial fluid which is maintained for 3 times longer period than in plasma, exerting extended therapeutic effect within joints.

It is poorly soluble in simulated gastric fluid and highly soluble in simulated intestinal fluid suggesting that the pH affects the solubility and absorption of diclofenac. So it required a delayed release mechanism, most often accomplished with stable coating that prevents the drug in stomach and there by delayed release. The formulation is in more favourable environment of the small intestine; this technology commonly referred as enteric coating system [9].

In-vitro testing or quality control of drugs is a set of studies or experiments undertaken during production in process and occasionally ought to be undertaken post production by regulatory agencies and researchers. Routine laboratory testing of drugs in the market is a crucial to protect public health especially in developing countries where counter-feit and substandard drugs have become a major challenge to health care services. The objective of this work was to evaluate and compare the quality of six different brands of 50 mg enteric coated diclofenac sodium tablets marketed in Addis Ababa.

METHODS:

Preparation of Standard Calibration Curve: 20 mg of diclofenac sodium was taken in a 50 ml volumetric flask and volume was made up to the mark by adding the buffer solution (pH 6.8). The solution was used as a stock solution having a concentration of 0.4 mg/ml. The stock solution was further diluted with phosphate buffer to obtain concentrations ranging from 2 µg/ml- 20µg/ml. Absorbance of the samples was taken at 276 nm in a UV spectrophotometer using phosphate buffer pH 6.8 as blank. Plot between the concentrations versus absorbance was obtained [10].

Marketed Brands of Enteric Coated Tablets of Diclofenac Sodium: Six different brands of diclofenac sodium tablets were compared for their dissolution profile and physic-chemical properties. List of six marketed brands of enteric coated diclofenac sodium tablet (**Table 1**).

Evaluation of Different Marketed Brands of Diclofenac Sodium:

Analysis of Drug Content: Twenty tablets from each brands were finely powdered and a quantity of powder equivalent to 100mg of Diclofenac sodium were accurately weighed and dissolved in phosphate buffer pH 6.8 and the volume was made up to 50 ml with the same buffer and analyzed for the drug content using UV spectrophotometer [10].

Determination of Hardness of the Tablets: Ten tablets from each Brand were selected and hardness was measured using hardness tester (CALEVA). The tablets were placed between the two jaws of the hardness tester and the hardness was measured as the strength needed to crush the tablets. That crush the tablet then the average crushing strength was calculated along with the standard deviation. This was triplicate.

TABLE 1: MARKETED BRANDS OF ENTERIC COATED TABLETS OF DICLOFENAC SODIUM

Code	Name	Dosage	Manufacturer	Mfg. date	Exp. date
A	Almiral	50 mg	Medochemie LTD Limassol-cyprus	April 2013	April 2018
B	Dicloas	50 mg	Astra Life Care Pvt. Ltd-India	Oct. 2013	Sep. 2016
C	Diclo-denk	50 mg	Denk pharma Gmbh & Co.KG- Germany	March 2013	Feb. 2016
D	Dicloran	50 mg	Unique Pharmaceutical Labs. India	March 2012	Feb. 2015
E	Retilon	50 mg	Daehwa-republic of Korea	April 2013	Mar. 2016
F	Voveran	50 mg	Novartis India Ltd. Baddi	July 2012	June 2015

Determination of Friability of the Tablet: Twenty tablets from each brand were randomly selected and carefully de dusted prior to testing then accurately weighed and placed in the friability tester (ERWEKA). The friabililator was rotated 25 rpm per min for 4 min so that the tablets were subjected to 100 revolutions.

Tablets were removed, de-dusted and weighed again. The friability of the tablets was calculated from the difference between the initial and final weight of the tablets and the percentage friability was calculated using the formula. This was triplicate. The percentage of friability is given by

$$\% F = (w_{initial} - w_{final} / w_{initial}) \times 100 \quad \text{.....1}$$

The percentage of Friability should not be more than 1%. (USP, 2007).

Determination of Weight Variation of the Tablet: Twenty tablets from each batch were collected randomly and weight of individual tablet was determined. The average weight of the twenty tablets was calculated. Percentage deviation in the weight of each tablet from the average weight was determined by using this equation

$$\text{Weight variation} = \frac{\text{Weight of tablet} - \text{average weight}}{\text{Average weight of tablet}} \times 100 \quad \text{...2}$$

Determination of Disintegration Time of the Tablet: One tablet was placed in each of the 6 tubes of disintegration apparatus USP (ERWEKA). The assembly was suspended in the beaker containing 0.1N HCl for two hours. At the end of two hours, the medium was replaced with phosphate buffer pH 6.8 followed by operation of the disintegration tester for 45 minutes. The time taken for all the tablets to disintegrate was noted [11]. The test was repeated three times and the average disintegration time was calculated.

Dissolution Test of Enteric Coated Diclofenac Sodium Tablets: A comparative *in-vitro* dissolution study was conducted in USP Type I, basket model according to the procedure described in the US Pharmacopeia (USP 2007). The test was carried out using 900 ml of 0.1 N HCl for 2 hours followed by phosphate buffer pH 6.8 for the next 1 hour as dissolution media and at 37 ± 0.5°C at 100 rotations per minute.

Samples of 10 ml were withdrawn at predetermined time intervals (5, 10, 20, 30, 45, 60 min and replaced with the same volume of fresh buffer. Each sample solution was filtered, diluted and the absorbance determined at 276 nm by UV spectrophotometer with phosphate buffer as blank. The percentage releases of the drug at different time intervals were calculated.

The mean dissolution values at each time interval were used to calculate similarity factor (f_2) using the standard mathematical equations

$$f_2 = 50.\text{Log}\ \{[1 + (1/n)\Sigma^{n}_{t=1}\ (Rt - T_t)^2]^{-0.5} \times 100 \quad \text{...3}$$

Where n is the number of dissolution sample times, Rt is percentage drug dissolved from reference formulation, T_t is percent drug dissolved from test formulation.

RESULTS AND DISCUSSION: Six brands of diclofenac sodium enteric coated tablet having label strength of 50 mg and manufactured from four different countries were purchased from a community pharmacy in Addis Ababa. These products are Indian, Korean, Germany and Cyprus products were mostly marketed in and around Addis Ababa due to their low price. All the products tested were within their expiry date. The tablets were analysed for their drug content, hardness, friability, weight variation, dissolution and disintegration in accordance to USP limit.

Calibration Curve of Pure Diclofenac Sodium: The values of absorbance were plotted against respective concentrations (**Fig. 2**). The concentrations ranging from 2 to 20 µg/ml showed linearity when the curve was plotted indicating it obeyed beers law. The regression coefficient R^2 was 0.999.

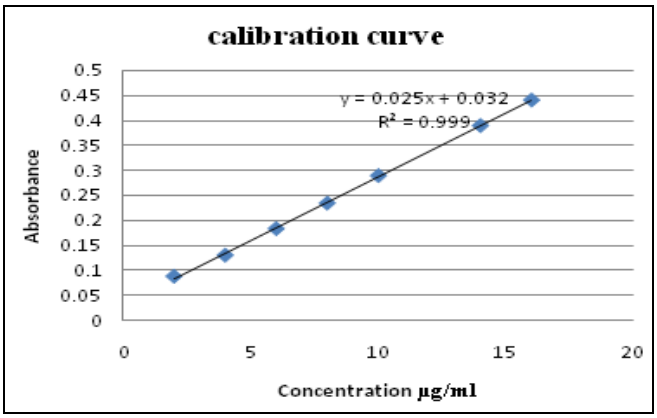

FIG. 2: UV ABSORPTION CALIBRATION CURVE OF PURE DICLOFENAC SODIUM IN PHOSPHATE BUFFER (pH 6.8) AT 276 nm

Drug Content of Different Brands of Diclofenac Sodium 50 mg Tablets: Determination of the drug content was performed according to USP method. The drug content value was found to be between 92.8 % - 99.9 % (**Table 2**) which is within the USP limit (90-110%). It ascertains the presence of diclofenac sodium in all the brands and so could not be judged as counterfeits without active pharmaceutical ingredient. The result was similar to the study reported in India **(**Giri TK *et al.*, 2012). Where the drug contents were between 95.90 - 99.42 %.

Friability, Hardness and Diameters of Different Brands of Diclofenac Sodium Tablets: The friability of the tablets which is determined using Friabilator was found between 0.02 - 0.05 % (**Table 3**) this indicates an acceptable result because Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable as specified in USP. The study conducted by **(**Giri *et al*., 2012) focusing on the comparison of four brands of diclofenac determines the friability of the tablets between 0.012 - 0.102 % which is more or less similar to the result obtained in this study. This value indicates sufficient mechanical integrity and strength of the tablets after abrasion and shock.

The hardness of the tablets is an essential criterion in the determination of the ability of the tablets to resist chipping, abrasion or breakage under conditions of storage, transportation and handling. Too hard tablets may result in decrease in the release of the drug. The hardness of the tablet was found to be 46.7N-48.3N (**Table 3**). This shows all the tablets required highest pressure to crush the tablet. The results obtained from other study was in a similar range [12]. Results from weight variation study (**Table 3**) all brands showed percentage of weight variation ranging from 0.012 to 0.039. It is evident that the deviations from the average weight are below the permissible value 5%. The result obtained from other study show approximate value (0.005- 0.010) [12].

TABLE 2: DRUG CONTENT OF DIFFERENT BRANDS OF DICLOFENAC SODIUM 50 mg TABLETS

Brand	A	B	C	D	E	F
Drug content %	97.2 %	96.6 %	94.3 %	99.9 %	92.8 %	99.42 %

TABLE 6: FRIABILITY, HARDNESS, WEIGHT VARIATION AND DIAMETERS OF DIFFERENT BRANDS OF DICLOFENAC SODIUM TABLETS

Brands	Friability (%) ± SD n=20	Hardness (N) ± SD n=10	Diameter(mm) ± SD n=10	Weight variation (%) n=20
A	0.03 ± 0.016	48.3 ± 0.03	1.95 ± 0.047	0.0299
B	0.02 ± 0.015	48.2 ± 0.025	1.99 ± 0.029	0.018
C	0.05 ± 0.021	48.3 ± 0.036	1..96 ± 0.040	0.039
D	0.02 ± 0.014	48.1 ± 0.02	1.95 ± 0.049	0.012
E	0.04 ± 0.017	48.3 ± 0.04	1.95 ± 0.030	0.1124
F	0.020 ± 0.070	46.7 ± 0.05	1.95 ± 0.049	0.010

Disintegration Time of Diclofenac Tablet: Disintegration time is a necessary condition and could be the rate determining step in the process of drug absorption. The type and amount of excipients used in the tablet formulation as well as the manufacturing process are all known to affect the disintegration time of all tablets. The disintegration time of enteric coated diclofenac sodium 50 mg

tablets were determined according to the procedure mentioned in USP [10]. To determine the disintegration time of a tablet the tablets was placed in the tubes of the apparatus with 0.1N HCl as an immersion fluid, the tablet does not show signs of either disintegration or cracks that would allow the contents to escape. At the end of two hour the tablets were transferred to phosphate buffer (pH 6.8) which simulate the intestinal fluid and the tablets start to disintegrate. The disintegration time of these six brands (**Table 4**) ranges between 14min-23min. Brand A, D and E disintegrates below the time taken by brand B and C but all the brands passed the disintegration test within the time limit of 23 minutes because all fulfills the requirements stated in the USP for enteric coated tablet not to disintegrate in HCl. Study conducted in India [12] shows the disintegration time between 15 -22 min which is closer to the results in this study. The importance of studying the disintegration time of the tablet is because to be absorbed the tablet needs to disintegrate.

Dissolution Profile of Six Brands of Diclofenac Sodium Tablet in Both Hydrochloric Acid (0.1N) and Phosphate Buffer pH (6.8): From the dissolution profiles(**Fig. 3** and **Fig. 4**), it is clear that there was almost no drug release from all enteric coated formulations in the acidic medium as expected for an enteric coated tablet. However, in the phosphate buffer medium (pH 6.8), more than 80 % of drug was released. Diclofenac sodium is a salt of a weak acid (2-[(2,6-dichlorophenyl) amino] benzene-acetic acid). Therefore, the solubility strongly depends on the pH of the dissolution medium. The dissolution profiles were statistically compared by calculating the similarity factor (f_2).

$$f_2 = 50.\text{Log}\ \{[1 + (1/n)\Sigma^{n}_{t=1}\ (Rt - T_t)^2]^{-0.5} \times 100$$

(f_2= 50) is border line value for similarity of considered as the conversion factor which takes into account variability between samples at each time point. The similarity factor (f_2) of 83% (acceptable limit 50-100) [13] were calculated. A comparative *in-vitro* dissolution study provides a basis for predicting the likelihood of achieving a successful *in-vivo* bioequivalence performance.

This *in vitro* dissolution study showed that the test brands (brand A, B, C, E, F) and reference brand (D) were comparable, here the reference was selected as brand D based on the results of the other evaluation tests performed in which it showed good result compared to the other brands. Further the *in - vitro* dissolution tests of the six brands showed comparable results.

TABLE 4: DISINTEGRATION TIME OF DICLOFENAC TABLET

Code	Disintegration time in simulated gastric fluid	Disintegration time in simulated intestinal fluid
A	No disintegration after 120 min	16 min
B	No disintegration after 120 min	20 min
C	No disintegration after 120 min	22:35 min
D	No disintegration after 120 min	14 min
E	No disintegration after 120 min	15:14 min
F	No disintegration after 120 min	22 min

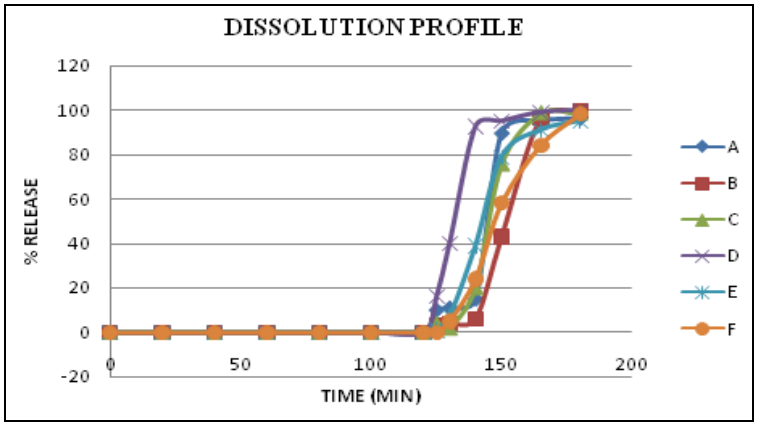

FIG. 3: DISSOLUTION PROFILE OF SIX BRANDS OF DICLOFENAC SODIUM TABLET IN BOTH HYDRO-CHLORIC ACID (0.1N) AND PHOSPHATE BUFFER pH (6.8)

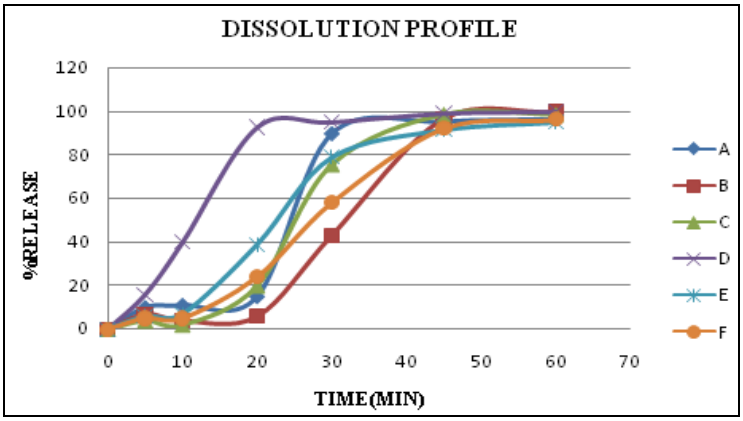

FIG. 4: DISSOLUTION PROFILE OF SIX BRANDS OF DICLOFENAC SODIUM TABLET IN PHOSPHATE BUFFER pH (6.8)

CONCLUSION: The six brands of diclofenac sodium enteric coated tablets analyzed in this study could be regarded as being pharmaceutically and chemically equivalent and can therefore be freely interchanged. Drug content, hardness, friability, disintegration time and dissolution profiles of all enteric coated products used in the study were within USP specified limits.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

REFERENCES:

1. Kamble ND, Chaudhari1 PS, Oswal RJ, Kshirsagar SS and Antre RV: Innovations in tablet coating technology: International Journal of Applied Biology and Pharmaceutical Technology. 2011; 2(1): 214-218.
2. Hussan SD, Santanu R, Verma P and Bhandari V: A review on recent advances of enteric coating: IOSR Journal of Pharmacy. 2012; 3(6): 05-11. http://dailymed.nlm.nih.gov/
3. Zaid AN and Qaddomi A: Development and stability evaluation of enteric coated diclofenac sodium tablets using sureteric. Pakistan Journal of Pharmaceutical Sciences 2012; 25(1): 59-64.
4. Gwozdz R: Polymers for Solid Oral Dosage Forms: Drug Development and Delivery. 2012; 12(2): 34-37.
5. Lavand'homme PM, Roelants F, Waterloos H and De Kock MF. Postoperative analgesic effects of continuous wound infiltration with diclofenac after elective cesarean delivery. Anesthesiology. 2007; 106: 1220-1225.
6. Raja SN, Meyer RA and Campbell JN: Peripheral mechanism of somatic pain. Anesthesiology. 1988; 68: 571-590.
7. Aulter JO, Espada EB, Crivelli E, Quintavalle TBG, Kurata A, Stolf NAG *et al*., Diclofenac plasma protein binding: PKPD modeling in cardiac patients submitted to cardiopulmonary bypass. Braz J Med Biol Res. 1997; 30: 369-374.
8. Yadav L, Chandel D, Mishra SS and Bajpai D: Formulation and evaluation of aqueous based enteric coated tablet of diclofenac sodium: Asian Journal of Pharmaceutical Education and Research. 2012; 1(1): 42-49.
9. Jain R, Pandey A and Pandeya SS: Mechanism of dissolution of delayed release formulation of diclofenac sodium: Journal of Chemistry. 2009; 18(4): 132-138.
10. United States Pharmacopoeia. 2007; 31(3): 751
11. European Pharmacopoeia 7.0: 201 and European Pharmacopoeia 5.0 :175
12. Giri TK, Parveen N, Thakur D, Alexander A, Ajazuddin, Badwaik H and Tripathi DK: *In-vitro* evaluation of commercially available enteric coated tablet containing diclofenac sodium: International Journal of Research in Pharmaceutical and Biomedical Sciences. 2012; 3(2): 875-881.
13. Prior A, Frutos P and Correa C: Comparision of Disoution Profiles. Conference on control drug release abstract. 2002; 159-160.

How to cite this article:
Joseph NM, Degu M and Palani S: Alzheimer's disease: Comparative quality evaluation of six brands of enteric coated diclofenac sodium tablets marketed in Addis Ababa. Int J Pharm Sci Res 2017: 8(12): 5386-91.doi: 10.13040/IJPSR.0975-8232.8(12).5386-91.