ORIGINAL ARTICLE

Assessment of quality control parameters of aceclofenac sustained release tablets marketed in Nepal

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ABSTRACT

Introduction: Aceclofenac has low solubility and high permeability; its dissolution is rate-limiting step for its absorption. Different brand products of same drug require analysis for their biopharmaceutical equivalence to ensure their safety and efficacy.

Methods: It was a cross-sectional study. Eight brands of Aceclofenac SR tablets were collected from various retailerstoassess for their shape, size, weight and color and also were tested for their biopharmaceuticaland physicochemical equivalence. Descriptive statistics were calculated.

Results: The weight variation of all brands ranged within the maximum limit of ±5% except brand H.All of the brands had the recommended hardness (≥4Kg/cm^2). The friability values of all products were within the recommended specification (≤1%). All tablets passed the test for assay as the amount of drug in each tablet was in the range of 85% - 115%. The % drug release of all brands were in the range of 50-80% except brand E and H at 8thhrs that showed 63.88% drug release. The brand A, B and H followed Pappes release model whereas brand C followed zero order model, brand D and G followed first order model and brand E & F followed Higuchi model.

Conclusions: All brands except one were interchangeable in terms of biopharmaceutical equivalence and sustained release formulation. Further, more in-vivo bioequivalent studies in human should be conducted to correlate the findings.

Keywords: Aceclofenac, Quality Assessment, Sustained Release

INTRODUCTION

Aceclofenac is a non-steroidal anti-inflammatory cytokine inhibitor which is broadly used for the symptomatic treatment of pain and inflammation specifically in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis with the recommended dose of 100 mg twice daily.[1,2]For the same but prolonged action Aceclofenacsustained release (SR) tablet is administered with the recommended dose of 200 mg. This drug works by inhibiting the action of cyclooxygenase that is involved in the production of prostaglandins which is accountable for pain, swelling, inflammation and fever.[3-5] Use of SR formulation of Aceclofenac leads to reduction in frequency of dosing, uniform drug release over time and better patient compliance.[6-8]Increased cost, toxicity due to dose

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dumping and unpredictable and often poor in vitro-in vivo correlation are the some disadvantages of Aceclofenac SR.[9,10]

Aceclofenac is a poorly water-soluble drug according to the biopharmaceutical classification system (class II, low solubility and high permeability); its dissolution is rate-limiting step for its absorption.[11,12] The factors that determines drug absorption from solid dosage forms after oral administration are i) the release of the drug substance from the drug product, ii) the dissolution of the drug under physiological conditions and iii) its permeability across the membranes of gastrointestinal tract.[13]Therefore, in-vitro dissolution test of tablets might be relevant to the prediction of their in-vivo bioequivalence.[14]

The safety and efficacy of a pharmaceutical dosage form can be guaranteed when its quality is reliable.[15]The brand products of Aceclofenac SR available in the market are from both Nepalese companies and Indian companies. Products of different brand with the same amount of active pharmaceutical ingredients (API) may have distinct differences in their therapeutics effect due to differences in their bioequivalence.[16] Therefore,these brands might not be used interchangeabledue to difference in biopharmaceutical equivalence. Availability of numerous brands also places health practitioners in a dilemma of generic substitution. Variation in clinical response to these brands have been reported due to availability of substandard fortified and counterfeit drugs also.[17] Thus, different brand products of same drugs require analysis for their biopharmaceutical equivalence to ensure their safety and efficacy.It is essential to have a constant surveillance on marketed Aceclofenac SR tablets by the government, manufactures and independent research groups. Quality assessment of locally available Aceclofenac tablets are also lacking. Therefore,the present study aimed toevaluate biopharmaceutical and physicochemical equivalence of different brands of Aceclofenac SR tablets available in the Nepalese market.

MATERIALS AND METHODS

Study design and setting: A cross-sectional study was conducted in the Department of Pharmacy, Shree Medical and Technical College, Bharatpur, Chitwan, Nepal for three months (May-June 2020).

Reagents and Chemicals: All reagents used were of analytical grade. Necessary chemicals and Aceclofenac SR tablets of various brands were purchased from the local market. Freshly prepared distilled water was used throughout our work.Potassium dihydrogen orthophosphate, Sodium Hydroxide and Methanol were obtained from Qualikeme Fine Chem Pvt. Ltd. Aceclofenac reference standard powder was obtained from Time Pharmaceutical Pvt. Ltd, Mukundapur, Nawalparasi, Nepal as a gift sample for our research work. Eight different brands of Aceclofenac SR tablets, having label strength of 200mg were selected and purchased from registered retail pharmacies and these products were coded as A, B, C, D, E, F, G, and H.The tablets were properly checked for their batch number, manufacturing and expiry dates before purchasing (**Table 1)**.

Table 1. List of different brands of Aceclofenac SRtablets used in the study

Code	Brand name	MFG date	EXP date
A	Brand 1	Oct 2019	Sep 2021
B	Brand 2	Oct 2018	Sep 2020
C	Brand 3	Apr 2019	Mar 2021
D	Brand 4	Aug 2018	July 2020
E	Brand 5	Apr 2019	Mar 2021
F	Brand 6	Sep 2018	Aug 2020
G	Brand 7	Mar 2019	Feb 2021
H	Brand 8	Sep 2018	Aug 2020

The different brands of Aceclofenac SR tablets were subjected to thefollowing assessments to assess their biopharmaceutical equivalence.[18-20]

(i) Physical Inspection: The shape, size, thickness and color of these brands of tablets were examined visually. The thickness and diameter of five tablets from each brand were measured using digital vernier Caliper and the average were taken and standard deviation were calculated.

(ii) Uniformity of weight: Twenty sample tablets of each brand were weighed individually using a digital analytical balance. The average weight was determined

and then the percentage (%) deviation of each tablet was calculated using the formula below:

As per Indian Pharmacopoeia (IP), if mean weight of tablets is 250mg or more, the maximum percentage differences allowed should be ±5%.

(iii) Hardness: The crushing strength of the tablets was evaluatedindividually using the Monsanto hardness tester. Five tablets for each brand were tested of the breaking strength with applied pressure and the machine simply read and record the value to break. The average tablet hardness and standard deviation were calculated. To withstand mechanical shocks during handling in manufacture, packing, shipping and handling by retailers, a good tablet should have a hardness of at least 4 kg/cm^2.[21]

(iv) Friability Test: This test is conductedto evaluate the ability of the tablets to withstand abrasion.Twenty sample tablets of each brand were taken and then weighed. They were then subjected to abrasion using a Roche friabilator test apparatus at 25 revolutions per minute. After 100 revolutions, the tablets were de-dusted and re-weighed. The friability of the tablets was then calculated as the percentage (%) weight lost using the following expression;

(v) Assay (Drug Content): Twenty tablets were weighed and crushed to obtain a fine powder. An accurately weighed tablet powder equivalent to about 100 mg of Aceclofenac were transferred to 100 ml volumetric flask and dissolved in 50 ml of methanol. The volume were made up to the mark using methanol as solvent. The resulting solution were filtered through Whatmann filter paper and 10 ml of this filtrate were appropriately diluted to get concentration of 100 µg/ml of Aceclofenac. This solution were further diluted to get concentration of 20 µg/ml of Aceclofenac. Absorbance of sample solution were measured at 276 nm using UV spectrophotometer. The percentage content were determined using standard graph and calculations. The test tablets comply with the assay test if not more than one of the individual values thus obtained is outside the limits90 to 110% of the average value[22].

(vi)In-vitro Dissolution Rate Determination: The in-vitro dissolution study was carried out using USP type II dissolution apparatus. The study was carried out in 900 ml phosphate buffer (pH 7.5)upto 16thhrs. The dissolution medium were kept in thermostatically controlled water bath, maintained at 37±0.5°c. Paddle rotation were adjusted to 50 rpm. At different intervals of 1st, 4th 8th and 16th hours, 5 ml of sample were withdrawn and analyzed spectrophotometrically at 274nm for the drug release. At each time of withdrawal, 5 ml of fresh corresponding medium were replaced into the dissolution flask.The amount dissolved should be within prescribed limit for the tablets to comply with the test (**Table 2**).

Table 2. Percentage of Aceclofenac release in time[22]

Times (hrs)	Amount dissolved (%)
1	NMT 25
4	20-50
8	50-80
16	NLT 80 of the stated amount

(vii) Preparation of Calibration Curve: UVvisible Spectrophotometric method of analysis at λ_{max} 273nm was developed with the help of calibration curve. First of all, a stock solution of concentration 20µg/ml Aceclofenacwas prepared in a phosphate buffer of pH 7.5. From this solution, other solutions of concentration (4, 8, 12,16 and 10 µg/ml) were prepared with appropriate dilutions. Finally, absorbance of these solutions was determined by UV spectrophotometry at the λ_{max} 274nm. A calibration curve showing the relationship between concentration and absorbance was plotted.[23]

Statistical analysis: The date were entered into Microsoft Excel 2016 and checked for its correctness and completeness. Descriptive statistics mean, standard deviation, frequency and percentage were calculated using Microsoft Excel 2016. The data were presented as tables and graphs.

RESULTS

All of the brands of Aceclofenac SR tablets had all the information which is required on a pharmaceutical product including batch number, manufacturing

and expiry dates. The calibration curve was also obtained by plotting the values of concentration verses respective absorbance for each of the concentration of 4, 8, 12, 16 and 20µg/ml of standard Aceclofenac. This analysis for linearity showed that the solvent used for testing Aceclofenac SR tablet and in-vitro drug release were suitable and had no interference while obtaining absorbance in UV visible spectrophotometer. From the curve, the value for correlation coefficient (R^2) was found to be 0.998 in phosphate buffer pH 7.5. The plotted calibration curve for Aceclofenac in phosphate buffer as solvent is given in Figure 1.

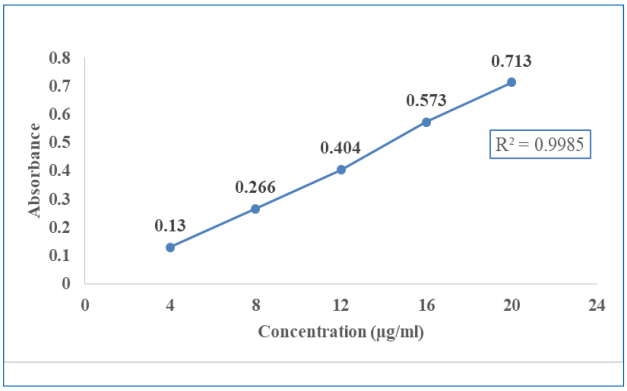

Figure 1. Standard calibration curve of absorbance of Aceclofenac in 7.5 pH phosphate buffer

On physical inspection, all tablets were white in color and oval in shape and three brands (code A, C and H) were uncoated (**Table 3)**.

Table 3. Physical aspects examination of the different brands of Aceclofenac SR tablets

Brand code	Colour	Shape	Coating
A	White	Round	Uncoated
B	White	Round	Film coated
C	White	Round	Uncoated
D	White	Round	Film coated
E	White	Round	Film coated
F	White	Round	Film coated
G	White	Round	Film coated
H	White	Round	Uncoated

The mean weight of different brands of Aceclofenac SR tablets is shown in **Table 4**. The brand F had minimum average weight (301±1.70mg) whereas brand H had maximum average weight (428±12.91mg). The maximum standard deviation was seen in brand H and minimum in brand E.The weight variation of all brands ranged within the maximum limit of ±5% except brand H.

Physiochemical Parameters of different brands of Aceclofenac SR tablets is shown in **Table 5**.

Table 4. Weight variation of different brands of Aceclofenac SR tablets

Variables	Weight of different brand of Aceclofenac SR tablets (mg)							
	A	B	C	D	E	F	G	H
Mean	422	426	333	319	405	301	395	428
SD	3.57	4.4	3.38	6.16	1.34	1.700	4.73	12.91
Minimum	417	417	331	310	402	297	384	407
Maximum	429	413	340	332	407	303	400	466

Table 5. Physiochemical Parameters of different brands of Aceclofenac SR tablets

Brand Code	Thickness (mm) (n=5)	Diameter (mm) (n=5)	Hardness (Kg/cm^2) (n=5)	Friability(%)	Content of active ingredient (%)(n=3)
A	4.34±0.012	111.074±0.008	9.6±0.82	0.011	105.51±6.93
B	4.27±0.018	11.27±0.0083	17.7±0.44	0	93.22±1.89
C	4.002±0.004	11.128±0.008	15.6±0.96	0.105	96.06±3.72
D	4.04±0.039	11.9±3.008	11.9±3.008	0	99.31±2.17
E	4.52±0.037	11.30±0.046	16.4±0.22	0	94.75±13.50
F	4.52±0.016	10.9±1.41	10.9±1.41	0	90.10±1.46
G	5.42±0.016	12.7±0.41	12.7±0.44	0	92.73±0.42
H	4.87±0.111	9.76±2.22	9.76±2.22	0.035	92.23±1.09

The thickness of different Aceclofenac SR tablets varied with brands ranging from 4.002±0.0044 mm to 5.42±0.016 mm.All of the brand tablets had the recommended hardness (≥4Kg/cm^2). The Brand B had a maximum hardness (17.7±0.44 kg/cm^2) while brand A had minimum hardness (9.6±0.82 kg/cm^2). Brand D had larger deviation of 3.008 and brand E had a smaller deviation of 0.22. Brand C had maximum friability (0.105%) and brand A had a minimum friability (0.011%). The friability values of all products were within the recommended specification (≤1%).All tablets passed the test for assay as the amount of drug in each tablet was in the range of 85% - 115%. The brand A had maximum assay value (105.51±6.93%) and brand F had a minimum value (90.10±1.46%) (**Table 5)**.

The cumulative amount of Aceclofenac released from the product at different time interval (1st, 4th, 8th and 16thhrs) is shown in **Figure 2**.Brand C has maximum released drug of 109.55±3.09 % and brand H had lowest drug released of 63.88±3.71% at 16 hrs. The % drug release of all brands were in the range of 50 – 80% except brand E & H at 8thhrsthat showed 63.88% drug release.

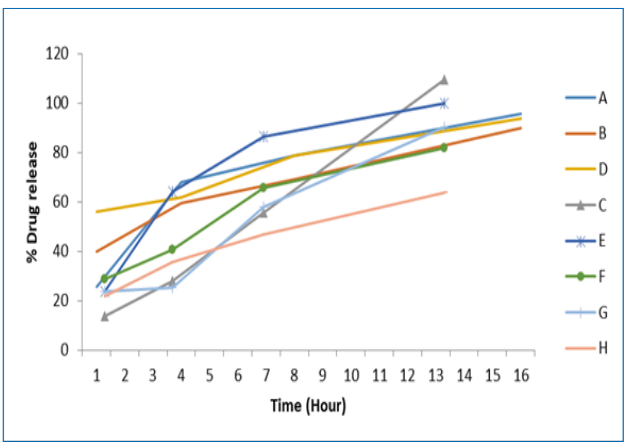

Figure 2. Dissolution Profile of the eight tested different brands of Aceclofenac SR Tablets

Release kinetics of Aceclofenac SR tablets is shown in **Table 6**. The brand A, B and H followedPappes release model whereas brand C followed zero order model, brand D andG followed first order model and brand E & F followed Higuchi model.

Table 6. Release kinetics of Aceclofenac SR tablets

Brand code	R^2 value			
	Zero order	First order	Higuchi	Pappas
A	-0.00	0.648	0.871	0.934
B	-1.08	0.887	0.684	0.993
C	0.990	0.943	0.849	0.968
D	-4.02	0.950	-0.27	0.901
E	0.247	0.666	0.918	0.915
F	0.227	0.883	0.939	0.457
G	0.850	0.916	0.890	0.803
H	0.158	0.890	0.956	0.996

The price of different brand of Aceclofneac SR tablets per strip (one strip=10 tablets) is shown in **Figure 3**. The brand E was the most expensive.

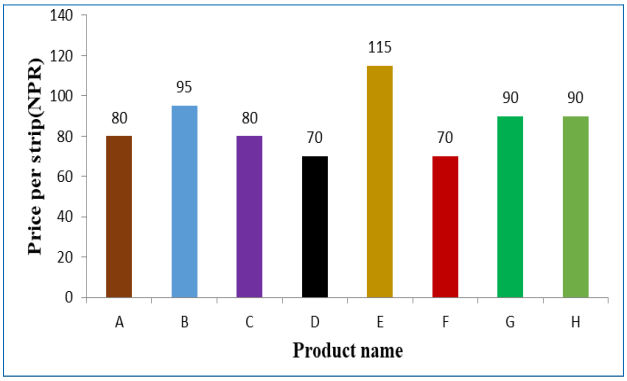

Figure 3. Price variation among different brand of ACF SR tablets in Nrs

DISCUSSION

All of the brands of Aceclofenac SR tablets had all the information which is required on a pharmaceutical product including batch number, manufacturing and expiry dates. All the brands passed the weight uniformity test since they all complied with the international standard as the weight variation of all brands ranged within the maximum limit of ±5% except brand H. Hence, only seven brands of Aceclofenac tablets conformed to the specifications. All of the brand tablets had the recommended hardness (≥4Kg/cm^2). A friability value of less than 1% is desirable for the good quality of the tablet.[24] The results of the tablet friability

test of Aceclofenac tablets showed that virtually all the brands tested had impressive friability values as it were within the recommended specification (≤1%). Therefore, all brands of Aceclofenac tablets were mechanically stable as all met the recommended standard.[24]

It was interesting to find out that all eight brand of Aceclofenac SR tablet had the values of drug content assay within the standard specification limit of 90-110%.[22] Most of the brands showed drug release more than 80% at 16thhrs except brands H that showed 63.88% drug release.The data shows that only brand C showed zero order kinetics.

Our study showed thatall eight brands of Aceclofenac tablets passed the standard specifications for the dissolution rate test. According to the data it has been found that price doesnot causes to make the product better. Drug release kinetics showed more or less same release kinetics of expensive and cheap products of Aceclofenac. Hence low priced drugs can be used interchangeable with the expensive drugs. The study had some limitations. The sample size was small.

CONCLUSION

All of the brands of Aceclofenac SR tablets passed the physical inspection test, uniformity of weight test, hardness test, friability test, content uniformity assay. Only seven brands of Aceclofenac passed dissolution taste and hence they can be substituted with one another. The study findings highlights that one brand products of Aceclofenac available in the market did not meet up to the required biopharmaceutical specifications; post marketing product assessment should be carried out regularly in order to ascertain the quality of drug products being sold in the market. All healthcare professional should also have adequate information on inter-changeability for the brand substitution of Aceclofenac SR and other drugs as well. Further, more in-vivo bioequivalent studies in human should be conducted to confirm the quality of the brands of Aceclofenac SR tablets.

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REFERENCES

1. Chandrasekaran AR, Han CY, Alex CYC, Cheang LW and Ping LS. Post–market in vitro Equivalency Evaluation of Paracetamol Tablets in Kedah, Malaysia.Int J Pharm SciNanotechnol. 2011;4(2):1403-07.
2. 2Karmaker Palash, KibriaMd G. In vitro comparative evaluation of quality controlparameters between Aceclofenac and Aceclofenac/caffeine tablets in Bangladesh. IntCurr Pharm J. 2012;1(5):103-9.
3. Kwakye KO, Yeboah FO, and Kipo SL. Formulation and quality evaluation of two conventional release tablet formulations. Int J Pharm Sci Res. 2010;4(1):94-99.
4. Kalakuntla R, Veerlapati U, Chepuri M, Raparla R. Effect of various superdisintegrantsonhardness, disintegration anddissolution of drug from dosage form; Journal of advance Sci Res. 2010;1(1):15-19.
5. Moffat A, Osselton M, Widdop B. Clarke's analysis of drugs and poisons. 4thed. the pharmaceutical press. 2011.
6. Lachman Leon, Lieberman Herbert A. Compression coatedand layer tablets. In: Pharmaceutical Dosage Forms: Tablets.Marcel Dekker, Inc., New York, 2002; vol 1; 2ndedition: 24784.
7. Chein YW. Oral Drug delivery and delivery systems. In: Noveldrug delivery systems. Marcel Dekker, Inc., New York, 2002;50; 3rdedition: 139-96.
8. Vyas SP, KharRK.Controlled Drug delivery: Concepts andAdvances.1sted.vallabhprakashan,2002,p:156189.
9. ShargelL,Yu ABC. Modified release drug products. In: AppliedBiopharmaceutics and Pharmacokinetics.4th ed.McGrawHill.1999;169-171.
10. Welling P G and Dobrinska M R, Dosing considerationand bioavailability assessment of controlled drug deliverysystem, Chapter 7, Controlled drug delivery; fundamentalsand applications, 2nd edition, Robinson J.R. and Lee V. H. L.(Eds.), Marcel Dekker Inc., New

York, 1978, 29,p. 254, 373.

11. Kumar Maheshwari R, Indurkhya A. Formulation and evaluation of aceclofenac injection made by mixed hydrotropic solubilization technique. Iran J Pharm Res. 2010;9(3):233-42.

12. Papich MG, Martinez MN. Applying biopharmaceutical classification system (BCS) criteria to predict oral absorption of drugs in dogs: Challenges and Pitfalls. AAPS J. 2015;17(4):948-64.

13. Alagga AA, Gupta V. Drug Absorption. [Updated 2022 Jun 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557405/

14. Soni T, Chotai N. Assessment of Dissolution Profile of Marketed Aceclofenac Formulations. J Young Pharm. 2010;2(1):21-26.

15. Shrestha J , Shrestha A , Shrestha B , Gamal K , Manandhar S , Koju S , et al . Oral solid dosage form modification in community pharmacies of Kavrepalanchok and Bhaktapur districts of Nepal. Kathmandu Univ Med J. 2022;20(77):29-37.

16. Karmoker JR, Sarkar S,Joydhar P, Chowdhury SF. Comparative in vitro equivalence evaluation of some Aceclofenac generic tablets marketed in Bangladesh. The Pharma Innovation Journal. 2016; 5(3):3–7.

17. Nemati M, valizadeh H. In-vitro Bioequivalance Studies of 8 Brands of Marketed Tablets in Iranamarket. J Appl PharmSci. 2012;2(8):194-7.

18. Wadher KJ, Kakde RB, Umekar MJ. Formulation and evaluation of a sustained-release tablets of metformin hydrochloride using hydrophilic synthetic and hydrophobic natural polymers. Indian J Pharm Sci. 2011;73(2):208-15.

19. Ukweuze S, Uzochukwu I, Ngonebu EJ. Comparative quality assessment and In-vitro dissolution profile of paracetamol tablet generics marketed in Nigeria. Port Harcourt Med J. 2008;3(1):85-90.

20. Khan S, Naimi R. Comparative In-vitro Pharmaceutical evaluation of four brands of metronidazole tablets marketed in gulf region. Jordan J Pharm Sci. 2014;7(2):144-51.

21. Ibezim EC, Attama AA, Obitte NC, Onyishi VI, Brown SA. In vitro prediction of in vivo bioavailability and bioequivalence of brands of metronidazole tablets in Eastern Nigerian drug market. Sci Res Essay. 2008; 3(11):552-8.

22. Department of Drug Administration, National Medicines Laboratory, Analytical method validation committee for non pharmacopoeial product /aceclofeenacSR tablet. Available at https://www.dda.gov.np/content/method-validation.

23. Arpit Sharma, Manish Kumar, Anuj Malik, VipinSaini, APandurang. Comparative quality evaluation of aceclofenac marketed tablet. SD Int jPharm Sci. 2018;1(1):50-57.

24. Gupta MM, Khoorban A, Ali A, Ramlogan O, Talukdar D. Comparative quality control study of different brands of diclofenac sodium tablet available in local and government pharmacies by in-vitro testing. Cureus. 2020;12(11):e11348.