Life Science Journal

Websites:
http://www.lifesciencesite.com
http://www.sciencepub.net

Emails:
editor@sciencepub.net
sciencepub@gmail.com

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

Physical Evaluation and *In Vitro* Bioequivalence Study of Marketed Aspirin Enteric Coated Tablets in KSA

Muhammad Hadi Sultan*, Md Sarfaraz Alam, Osama A. Madkhali, Md Sajid Ali., Muaid Ahmed Aqeel, Ryan Ibrahim Gaderi, Abdullah Muhammad Khardali

College of Pharmacy, Jazan University, Jazan, Saudi Arabia, KSA, Zip Code: 45142
Mobile No.- +966-557119488; E-mails: mhsultan@jazanu.edu.sa, msultan151@gmail.com

Abstract: Purpose: The main objective of this study is to evaluate the *in-vitro* bio equivalency of enteric coated Aspirin tablets in the Kingdom of Saudi Arabia (KSA). **Methods:** Two available brands of Aspirin enteric coated tablets were randomly collected from various pharmacies, and were then coded as A (DISPRIN) and B (JUSPRIN). An innovator Aspirin enteric coated tablet was also procured fromalocal community pharmacy. Pure Aspirin drug was procured from Sigma-Aldrich. General quality assessment such as weight variation, hardness, friability, disintegration test, and a dissolution study were performed as per USP guidelines. **Results:** All A and B brands passed the weight variation test, as no more than two tablets failed, in all cases. The hardness test results for the innovator, and brands A and B, were recorded as 4.91, 5.25 and 4.58 kg, respectively. The friability test was also carried out for the innovator and brands A and B, whereby all experienced weight loss of 0.086%, 0.030% and 0.077%, respectively. Although the results of the disintegration test made it clear that the innovator, as well as brands A and B, did not disintegrate in an acidic medium, all tablets disintegrated in a pH 6.8 buffer solution in 19.36, 21.58 and 15.13 minutes, respectively. There were no significant variations in the dissolution profiles or in the release profiles of the innovator, nor in brands A and B. There was a release of drug in a basic medium within one hour (90.19%, 82.04% and 87.64%, respectively). Finally similarity factors (f_2) were calculated for brands A and B, which were 72.12% and 88.72%, respectively. **Conclusion**: On the basis of *in-vitro* tests, brands A and B are considered bioequivalent and interchangeable, while brand B is closer to the innovator in terms of hardness, disintegration and dissolution profile.

[Muhammad Hadi Sultan, Md Sarfaraz Alam, Osama A. Madkhali, Md Sajid Ali., Muaid Ahmed Aqeel, Ryan Ibrahim Gaderi, Abdullah Muhammad Khardali. **Physical Evaluation and *In Vitro* Bioequivalence Study of Marketed Aspirin Enteric Coated Tablets in KSA.** *Life Sci J* 2020;17(9):1-7]. ISSN: 1097-8135 (Print) / ISSN: 2372-613X (Online). http://www.lifesciencesite.com. 1. doi:10.7537/marslsj170920.01.

Key words: Aspirin, Enteric coated tablet, *In-vitro* bioequivalence, and Dissolution study

1. Introduction

Generic drugs can be characterized as chemically identical to their branded counterparts; generally available on the market at a lower price (FDA, 2016 and Joshi, 2019). The increased availability of generic drug products has tasked health care professionals with selecting the right option among various equivalent products. In 1975, nearly 9% of all dispensed prescription drugs in the United States were a generic version. Over the next decades, generic versions increased by up to 40%. Our study revealed that clinical research varied with respect to the innovator, which was supplied by two or more drug manufacturers (Davit, 2009). These variable responses were due mainly to formulation, packaging, storage, and even rigors in quality control processes. All categories of dosage forms are the research product of multinational drug manufacturing firms (Khan, 2011), who claim that their products are not at all inferior to the products of innovator (Al-Jazairi, 2008). For that reason, W.H.O. issued guidelines to meet global standards and requirements for registration, assessment, marketing, authorization, and quality control of generic pharmaceutical products (WHO, 1990). It is mandatory to submit an abbreviated new drug application (ANDA) for approval to commercialize a generic product or dosage form by any generic dosage form manufacturing company. With the ANDA process, it is not necessary to perform costly animal and clinical research on dosage forms or drugs. Each ingredient or dosage form was previously tested to assure its safety and efficacy in all aspects (Chow, 2014). In order to obtain FDA approval, the generic dosage forms must have the same active moiety as the innovator or brand drug, be equal in strength (dosage), have an identical dosage form, have the same bioequivalency, have the same route of application of a drug, meet the same batch requirements for recognition, purity, strength (dose), and quality, and be formulated under similar standards

and guidelines of the FDA's "Good Manufacturing Practice" (GMP) regulations required for innovator products (Caudron, 2008 and FDA, 1997). Basically, the physical and chemical evaluations of the dosage forms are very important. *In-vitro* dissolution, or *in-vitro* bioequivalence testing, provides a small indication of the *in vivo* bioavailability and *in vivo* bioequivalence of dosage forms (Basmenji, 2011). The objective of our present work is to compare the *in-vitro* bioequivalency of different Aspirin tablets that are commercially available in KSA with respect to the innovator. The significance of our research project may be helpful for healthcare professionals to choose efficacious, safe and economical generic Aspirin tablets that are commercially available in KSA for the management of pain and inflammation caused by various diseases and medical conditions.

2. Experimental

2.1. Materials

Sodium hydroxide and tribasic sodium phosphate were purchased from Merck Laboratory in Stockholm, Sweden. Hydrochloric acid (37% pure) was procured from Sigma-Aldrich, Saudi Arabia. The innovator and generic Aspirin tablets were purchased at a local market, where by the generic tablets were coded as A and B. Only two generic tablets were obtained from a community pharmacy, each at strength of 81 mg.

The following testing equipment was used for this study: A double beam UV-visible spectrometer (UV mini-1700, Labomed, USA with 1 cm quartz cells), a Martini PH meter MI-150, a Copley tablet dissolution tester, an electronic digital scale (Adam PW124), a hot air oven JSR- JSOF-150, a Copley friability tester FR-200, and a Monsanto hardness tester.

2.2. Determination of λ max in an acidic medium of 0.1 N HCL, and a pH 6.8 phosphate buffer solution

A pure drug solution was prepared and scanned using a UV Spectrophotometer from Labomed; model UVD-3200, from 200 to 400 nm, in order to determine λ *max* (Abu-Alhassan, 2017).

2.3. Preparation of calibration curve of Aspirin in 0.1N HCL

100 mg of pure Aspirin (99.94% pure) was dissolved in 2 mL of methanol to obtain a clear solution. Then, 0.1 N HCL was added to the 100 mL-mark in a volumetric flask.0.2mLto 1 mL was then removed and placed in a 10 ml volumetric flask, and 0.1 N HCL was added to the 10 ml mark in each volumetric flask. The concentration of this solution achieved 20 to 100 µg/mL (Vikas, 2017).

2.4. Preparation of calibration curve of Aspirin in pH 6.8 buffer solution

100 mg of pure Aspirin (99.94% pure) was dissolved in 2mLof methanol to obtain a clear solution. A pH 6.8 buffer solution was then added to the 100 mL-mark in a volumetric flask. 0.2 mL to 1 mL was then removed and placed in a 10 ml volumetric flask, and pH 6.8 buffer solutions was added to the 10 mL mark in each volumetric flask. The concentration of this solution achieved 20 to 100 µg/mL (Wang, 2012).

2.5. Preparation of simulated buffer solution medium

Phosphate buffer solution (pH 6.8) was prepared as follow: 11.45 g of NaH_2PO4 and 28.8g of Na_2HPO4 were dissolved in water; the volume was then adjusted by 1000 mL (Jantratid, 2008). 0.20 M of tribasic sodium phosphate was also prepared.

The evaluation was done according to USP standards.

2.6. Physical appearance

The physical characterizations such as shape, surface and color of the different brands of tablets, as well as that of the innovator, were examined (FDA, 2014).

2.7. Weight variation test

A weight variation test confirmed the accurate dosage of the drug. It is determined according to USP guidelines.

Weigh 20 tablets individually. Calculate the average weight; compare the individual tablet weights to the range obtained from the percentage limit allowance provided in Table 1. According to USP, the tablets pass the test if no more than two tablets fall outside the range, which was calculated as mentioned above. None of the tablets differed by more than two times their percentage limit (Uddin, 2015).

Table 1: Percentage limit allowance for weight variation test as per USP

S. No.	Average weight	Percent difference
1.	130 mg or less	±10
2.	More than 130 mg, and upto 324 mg	±7.5
3.	325 mg and more	±5

2.8. Hardness Test

A hardness test is conducted to ensure that the tablet is hard enough so as not to break during handling. However, it should break into small pieces as soon as it reaches the stomach in order to facilitate absorption (units expressed in kg). Although the hardness range for oral tablets is usually between4 kgand8 kg, hypodermic and chewable tablets can have

a value of 3 kg, whereas certain sustained release tablets may have a hardness value of 10-20 kg.

Place the tablet diagonally in the Monsanto tester, and tighten the screw only to the point where it touches the tablet's edge. The scale should read zero (if not, record the reading as the initial reading). Until unless tablet break tighten the screw and record the final reading displayed on the scale, and calculate the actual hardness by subtracting the initial value (Giri, 2012 and Swardrick, 2006).

2.9. Friability test of tablets

A friability test is performed to check for medication loss during transportation, packaging and other means of handling. A Roche friability tester is used to estimate the weight loss of 6tablets after 100 rotations at 25 rpm, allowing the tablets to fall from a height of six inches. Weight loss should be less than 1%.

Weigh 6 tablets together. Place all 6 tablets in a disc in only one of the two partition chambers. Revolve for 4 minutes at 25 rpm. Weigh the 6 tablets together, once again. Calculate the percentage of weight loss according to the following formula (Uddin, 2017):

% Friability:

$$\frac{\text{Initial weight of 6 tablets} - \text{final weight of 6 tablets after rotation}}{\text{Initial weight of 6 tablets}} \times 100$$

2.10. Disintegration test for tablets

A disintegration test is conducted to ensure that the tablet breaks into very small pieces, up to a granular level, to liberate the drug to the surrounding medium within a specified time and given conditions. Tablet disintegration tests were performed according to USP. Copley disintegration tester was used for this test. Initially, six tablets were tested, but only one tablet was placed in each of the six tubes inside the basket assembly. The disintegrator was operated using0.1 N HCl and temperature was kept at 37± 2°C, for one hour. For the enteric coated tablet, conditions were slightly modified as per USP. If one or two tablets failed to disintegrate within the specified timeframe and condition, the test was repeated on twelve additional tablets. At this point, no less than 16 of the 18 tablets must disintegrate in order to pass the test (Almukainzi, 2010).

2.11. In-vitro bioequivalence studies

An *in-vitro* drug release profile was performed for the tablets as per USP" Dissolution Test". The rotational speed of 100 rpm was kept for the basket type apparatus and temperature maintained at 37°C, as described in USP Chapter 711. Initially, dissolution volume 750 mL (pH value of 1.2) of 0.1 M HCl was placed into a vessel for the first two hours. Between the 120-minutesandthe 210-minutes marks, the dissolution medium was a pH 6.8phosphate buffer solution with the addition of 250 mL of 0.20 M tribasic sodium phosphate (total vessel fills 1000 mL at a pH value of 6.8). Sampling was performed at a single time point from the acidic dissolution media after120 minutes, followed by sampling every 15 minutes after the media pH changed to basic. All standards were prepared in acidic and basic dissolution media prior to dissolution testing due to the sensitivity of Aspirin in extreme pH media. Absorbance was measured using a UV apparatus for the acidic and basic media. Dissolution profiles were assessed individually for the generic products, which were compared to the innovator. The f_2 similarity factor, i.e., dissolution similarity, was assessed using the FDA-approved approach (*f2* similarity factor). The similarity factor f_2 was calculated using the formula below (Diaz, 2016 and Stevens, 2015):

$f_2 = 50 \times \log \{100/ [1+ (\Sigma (a-b)^2/n)]^{½}\}$

Where

n= number of dissolution sample time points

The similarity factor should be between 50 and 100 (Kassaye, 2013 and WHO, 2006).

It is indicated as a measure of the similarity between two respective dissolution profiles if the f_2 value registers under the given range. Dissolution testing is the most important parameter related to quality control testing among different batches of the same formulation and different branded products. The dissolution parameter must be similar for both the innovator and test products with respect to strength of dosage form, test time intervals, temperature, rpm, and total test time. f_1 (dissimilarity or difference factor) and f_2 (similarity factor) were used for investigating dissolution profile comparison. Dissimilarity or difference factor reveals the difference in percent dissolved between the innovator and the generic products, tested at various time points. It can be mathematically calculated by applying:

$f_1 = \{\Sigma (a-b)/\Sigma a\} \times 100$

Where A and B are cumulative, the percentage of drug dissolved at each of the selected n time points of the two brands, respectively, (e.g., dissimilarity or difference factor) ranged between 0 and15, a range which signifies a minor difference between the two products. Moreover, the similarity factor was used for the comparison of the likeness of the generic products with respect to the innovator [Table 2].

Table 2: Comparison of dissolution profile

Dissimilarity factor (f_1) value	Similarity factor (f_2) value	Inference
0 to ≤ 15	≥ 50 to 100	Dissolution profiles are identical

3. Results and Discussion

3.1. Determination of λ max at acidic medium, and pH 6.8 phosphate buffer solution:

Using the UV method, λ *max* was determined to be230 nm and 265nm, respectively; in an acidic medium and pH 6.8. It was further utilized to create a calibration curve and Aspirin estimation.

The calibration curve of Aspirin pure drug was developed in an acidic medium and a pH 6.8 buffer solution, as shown in Figures 1 and Figure 2 for the determination of drug content released during different stages of the dissolution study.

3.2. Physical appearance of the tablet:

While all tablets looked good, brand B was more attractive due to its orange color, as described in Table 3.

3.3. Weight Variation Test

Weight variation testing was carried out as per USP specifications. All brands, as well as the standard, passed the test. This type of testing confirms that tablet weight is within the range, and that therapeutic effects will not vary after consumption by patients, as shown in Table 4.

Table 3: Physical appearance of different brands of tablets (A & B), and the innovator

Items	Color	Surface	Shape	
Innovator (81 mg)	white	Smooth and slippery	round and oval	All types of tablets were enteric coated
A (81 mg)	orange	slightly rougher than the other tablets B	round and oval	
B (81 mg)	white	Smoot hand slippery	round and oval	

Table 4: Weight variation test of different tablet brands (A & B), and the innovator

Item	Average weight of 20 tablets	%variation allow as per USP	Number of tablets that failed (out of 20)
Innovator	135.42	± 7.5	1
A	104.65	± 10	2
B	127.41	± 10	1

3.4. Hardness Test

Tablet hardness tests were carried out as per specifications. All brands, as well as the standard, passed the test, as shown in Figure 3. All tablets broke within the 4-6 kg weight. A hardness test confirms that the tablet is hard enough so as not to break during handling and transportation, or before ingestion by patients. Six tablets were tested from each group.

3.5. Friability Test:

Disintegration tests were carried out as per USP specifications. The percentage weight loss of the different tablet brands (A & B), and the innovator, was calculated to be 0.1% or less, in all cases, as illustrated in Figure 4. As a result, all tablets successfully passed the friability test. This test confirms that no further loss of weight of a tablet will occur during packaging, handling, or transportation.

3.6. Disintegration Test

Disintegration testing was conducted as per USP specifications. None of the six tablets disintegrated in acidic medium within one hour. However, all tablets disintegrate Dina pH 6.8 buffer solution within 30 minutes. Brand B experienced color loss in the acidic medium. Disintegration testing confirms that a tablet disintegrates within the specified time, and that all granules pass through sieve number 10 in the disintegration apparatus, as outlined in Table 5.

Table 5: Disintegration test of different tablet brands (A & B), and the innovator

Items	Number of tablets (out of 6) disintegrate in acidic medium within one hour	Length of time taken (in minutes) to disintegrate all 6 tablets in a pH 6.8 buffer solution after one hour
innovator	00	19. 36
A	00	21.58
B	00	15.13

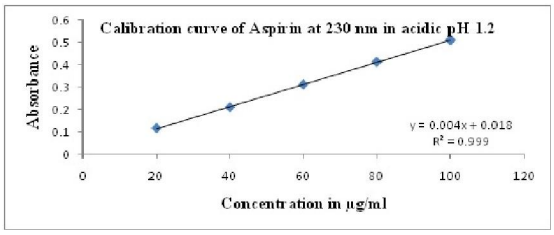

Figure 1: Calibration curve of Aspirin pure drug in acidic medium at 230 nm

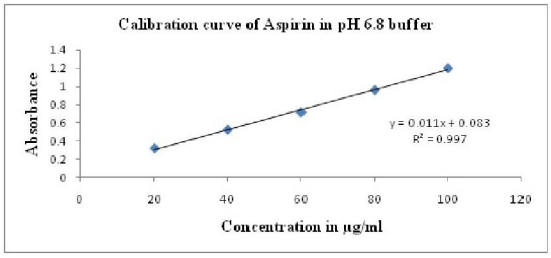

Figure 2: Calibration curve of Aspirin pure drug in pH 6.8 buffer solution at 265 nm

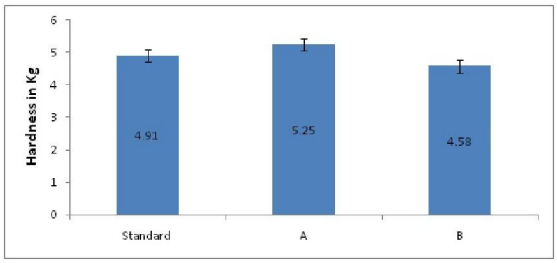

Figure 3: Hardness test of different brands tablet (A & B), and innovator

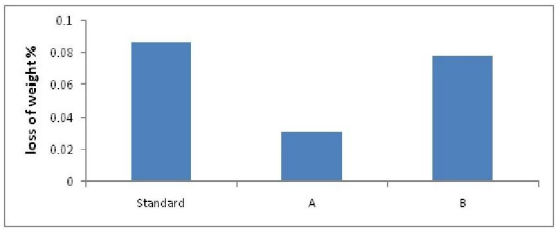

Figure 4: Percent of weight loss of different brands tablet (A & B), and the innovator

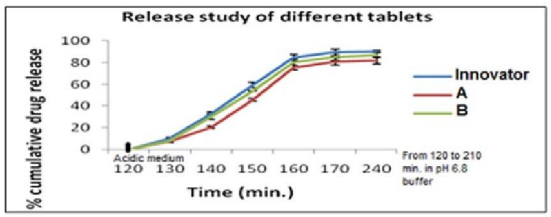

Figure 5: % cumulative release of Aspirin from the innovator, and brands A & B

3.7. In-vitro bioequivalence studies:

In-vitro drug dissolution studies are vital, and are used as a quality control tool to monitor batch-to-batch consistency of the drug released in dosage form (Qureshi, 1999). In *in-vitro* dissolution testing, the dissolution process is a rate-limiting step. As a result, the reliability and discriminatory capabilities of the dissolution tests for Aspirin-marketed products have attracted much attention in recent years. USP dissolution apparatus Type I (basket) is the most widely used dissolution test for Aspirin products, at stirring rates of 100 or 50 rpm, respectively. The stirring rate is proportional to the dissolution rate: the higher the rate, the thinner the surface diffusion layer becomes (Banakar, 1992). Dissolution profiles were produced and compared at a stirring rate of 50 rpm, using the basket method. *In-vitro* dissolution was performed for each brand of Aspirin according to the USP dissolution apparatus (basket) for enteric coated dosage forms. An *in-vitro* dissolution study was carried out in an acidic medium, as well as in a pH 6.8phosphate buffer solution. The amount of Aspirin released from each tablet in the dissolution samples were measured by a UV-visible spectrophotometer (Graffner, 2006). Dissolution profiles for each product were compared with the innovator to determine the efficacy of each generic product. The dissolution of a drug from an oral solid dosage form is an important aspect for drug bio-availability. Accordingly, dissolution testing of solid oral drug products has emerged as one of the most important control tests for assuring product uniformity and batch-to-batch equivalence. In order to judge whether these differences in dissolution profiles were significant, all dissolution profiles were compared to that of the innovator. *In-vitro* dissolution methods were developed to assess the potential *in-vitro* performance of a solid oral dosage form. There was no significant variation in the dissolution profiles or release profiles of the innovator, or of brands A and B. There was 90.19%, 82.04% and 87.64% release of drug, respectively, in a basic medium within 1 hour. Finally, the similarity factor (f_2) was calculated for brands A and B: with reported values of 72.12% and 88.72%.

The results obtained from this study exhibit different dissolution profiles are graphed in Figure 5.

4. Conclusion

The traditional official and non-official tests carried out in this study revealed that all selected generic brands of Aspirin from the Saudi market are chemically and pharmaceutically comparable to the innovator. Hence, it can be concluded that they are bioequivalent, and likely to deliver a similar therapeutic result as that of the innovator. This means

that all generic Aspirin tablets are alternatives to the innovator. *In-vitro* tests are less complex, as well as time-saving and cost-efficient, and can work as advantageous quality control indicators for evaluating generic brands. This method can be used to scrutinize substandard drug products before conducting tedious *in-vivo* bioequivalence studies.

Conflicts of Interest:

There are no conflicts of interest.

Acknowledgments:

The authors wish to thank the Dean of Scientific Research, and the Dean of the College of Pharmacy, Jazan University, Jazan, KSA, for providing the funding and facilities necessary to complete this project.

Corresponding Author:
Dr. Muhammad Hadi Sultan
Assistant Professor,
Department of Pharmaceutics
College of Pharmacy, Jazan University
Jazan, KSA, Saudi Arabia. Zip Code: 45142
Mobile No.- +966-557119488
E-mail – mhsultan@jazanu.edu.sa, msultan151@gmail.com

References

1. US FDA Generic Drug Approval [21CFR314.92 and 314.105(c)] [Last accessed on 2016 Sep 25]. Available from: http://www.fda.gov/cder/regulatory/applications/anda.htm.
2. Joshi SS, Shetty YC, Karande S. Generic drugs - The Indian scenario. J Postgrad Med 2019; 65(2):67–69.
3. Davit BM, Nwakama PE, Buehler GJ, Conner DP, Haidar SH, Patel DT, et al. Comparing Generic and Innovator Drugs: A Review of 12 Years of Bioequivalence Data from the United States Food and Drug Administration. Ann Pharmacother 2009; 43: 1583-97.
4. Khan MA, Khan J, Razvi N. Physicochemical equivalence of different brands of diclofenic sodium SR tablets available at local market. IRJP. 2011; 2(11): 81-84.
5. Al-Jazairi AS, Bhareth S, Eqtefan IS, Al-Suwayeh SA. Brand and generic medications: are they interchangeable? Ann Saudi Med. 2008; 28(1):33–41.
6. WHO Expert Committee on Specifi cations for Pharmaceutical Preparations. Guiding principles for small national drug regulatory authorities (Annex to TRS790); 1990. https://apps.who.int/medicinedocs/en/d/Jh1792e/24.4.html
7. Chow, Shein-Chung. "Bioavailability and Bioequivalence in Drug Development." Wiley interdisciplinary reviews. Computational statistics 2014; 6(4) 304-312.
8. Caudron JM., Ford N, Henkens M, Mace C, Kiddle-Monroe R, Pinel J. Substandard medicines in resource-poor settings: a problem that can no longer be ignored. Trop Med Int Health 2008; 13(8):1062-72.
9. Food and Drug Administration, Department of Health and Human Services. 21CFR 210, 211. Washington: Office of the Federal Register National Archives and Records Administration, 1997.
10. Basmenji S, Valizadeh H, Zakeri-Milani P. Comparative in-vitro dissolution and in vivo bioequivalence of two diclofenac enteric coated formulations. Arzneimittel-forschung 2011; 61(10):566-70.
11. Abualhasan MN, Mansour J, Jaradat N, Zaid AN, Khadra I. Formulation and Development of a Validated UV-Spectrophotometric Analytical Method of Rutin Tablet. IntSch Res Notices 2017;262494:7.
12. Vikash Sharma V, Bhowmick M, Rathi V, Rathi J. Preformulation, recompression and post-compression evaluation of bilayer tablet of aspirin as immediate release and nicotinic acid as sustained release. IJPCBS 2017; 7(1): 55-70.
13. Wang Y, Ping Xu P, Xia Li X, Nie K, Tuo M, Kong B, Chen J. Monitoring the hydrolyzation of aspirin during the dissolution testing for aspirin delayed-release tablets with a fiber-optic. Journal of Pharmaceutical Analysis 2012; 2(5): 386-389.
14. Jantratid E, Janssen N, Reppas C, Dressman JB. Dissolution media simulating conditions in the proximal human gastrointestinal tract: an update. Pharm Res 2008; 25(7):1663-76.
15. FDA. New Guidance for Industry: Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules, 2014.
16. Uddin MS, Mamun AA, Tasnu T, Asaduzzaman M. In-process and finished products quality control tests for pharmaceutical tablets according to pharmacopoeias. J Chem Pharm Res 2015;7(9):180–5.
17. Giri TK, Parveen N, Thakur D, Tripathi DK. In-vitro Evaluation of Commercially Available Enteric Coated Tablet Containing Diclofenac Sodium. IJRPBS 2012; 3: 875-881.
18. Swarbrick JS, Encyclopedia of Pharmaceutical Technology, Third Edition - 6 Volume Set, Taylor & Francis, 2006.

19. Uddin MS, Mamun AA, Hossain MS, Asaduzzaman M, Sarwar MS, Rashid M, et al. In vitro quality evaluation of leading brands of ciprofloxacin tablets available in Bangladesh. BMC Res Notes 2017; 10(1):185.
20. Almukainzi M, Salehi M, Bou-Chacra NA, Löbenberg R. Investigation of the performance of the disintegration test for dietary supplements. AAPS J. 2010; 12(4):602-7.
21. Diaz DA, Colgan ST, Langer CS, Bandi NT, Likar MD, Van Alstine L. Dissolution Similarity Requirements: How Similar or Dissimilar Are the Global Regulatory Expectations? AAPS J. 2016; 18(1):15-22.
22. Stevens RE, Gray V, Dorantes A, Gold L, Pham L. Scientific and regulatory standards for assessing product performance using the similarity factor, *f2*. AAPS J. 2015; 17(2):301-6.
23. Kassaye L, Genete, G. Evaluation and comparison of *in-vitro* dissolution profiles for different brands of amoxicillin capsules. Afr. Health Sci 2013;13: 369–375.
24. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability; WHO Technical Report Series, No. 937, Annex 7; World Health Organization: Geneva, 2006; pp 347–438. http://apps. who.int/prequal/info_general/documents/TRS937 /.pdf WHO_TRS_937_eng #page=359 (assessed Jan 12, 2015).
25. Qureshi SA, McGilveray IJ. Typical variability in drug dissolution testing: study with USP and FDA calibrators tablets and marketed drug (glibenclamide) product. Eur J Pharm Sci1999; 7:249-58.
26. Banakar UV. Pharmaceutical dissolution testing. New York: Marcel Dekker; 1992. 437.
27. Graffner C. Regulatory aspects of drug dissolution from a European perspective. Eur J Pharm Sci2006; 29(3-4):288-93.

8/20/2020