ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2017; 3(2): 288-293
www.allresearchjournal.com
Received: 15-12-2016
Accepted: 16-01-2017

Sumaiya Huque
Pharmaceutical Technology Research Laboratory, Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh

Nadia Rouf Brishti
Pharmaceutical Technology Research Laboratory, Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh

Musarrat Noor
Pharmaceutical Technology Research Laboratory, Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh

Sajan Das
Pharmaceutical Technology Research Laboratory, Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh

Rumana Akhter
Pharmaceutical Technology Research Laboratory, Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh

Md. Zobayer Hossain Gorapi
Pharmaceutical Technology Research Laboratory, Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh

Kaniz Afroz Tanni
Pharmaceutical Technology Research Laboratory, Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh

Mohammad Shahriar
Pharmaceutical Technology Research Laboratory, Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh

Correspondence
Mohammad Shahriar
Associate Professor, Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh

Comparative *in vitro* equivalence evaluation of some Desloratadine generic tablets marketed in Bangladesh

Sumaiya Huque, Nadia Rouf Brishti, Musarrat Noor, Sajan Das, Rumana Akhter, Md. Zobayer Hossain Gorapi, Kaniz Afroz Tanni and Mohammad Shahriar

Abstract
Desloratadine is a potent, rapidly effective, long-acting, non-sedative antihistamine with selective H_1 receptor histamine antagonist activity. The purpose of this research work was to evaluate the pharmaceutical equivalent of six different brands of desloratadine 5 mg tablets using *in vitro* dissolution study and with different price ranges purchased from retail pharmacies of Bangladesh. Some other evaluations of desloratadine tablets were done using various pharmacopoeial and non-pharmacopoeial tests with an aim to assess whether these selected brands are pharmaceutically equivalent or not. The tested brand products had a satisfactory hardness except brand (D1, D5 and D6), average weight except brand D4, friability, disintegration and potency except brand D6 results. Drug release was satisfactory for all brands, since more than 75% of the desloratadine was dissolved in the medium within 40 min of the test. The dissolution profiles were compared with the use of model independent approaches of difference factor and similarity factor, showing that brand D4 is similar with brand D1 and can be used interchangeably.

Keywords: Desloratadine, *in vitro* equivalence, dissolution, difference factor (f_1), similarity factor (f_2)

1. Introduction
A major advance in antihistamine development occurred in the 1980s with the introduction of second-generation H_1 antihistamines [1] which are minimally sedating or nonsedating because of their limited penetration through the blood brain barrier. In addition, these drugs are highly selective for the histamine H_1 receptor and have no anticholinergic effects [2]. Allergic rhinitis is a common illness, which affects approximately 15% of the population [3] and has a large impact on the quality of life of the patients. Antihistamines are important medications in the treatment of allergic rhinitis (AR) including Seasonal AR, intermittent AR, persistent AR, perennial RA, and chronic idiopathic urticaria. One should expect that the effect of an antihistamine is best near or shortly after peak serum level is attained. If this also coincides with the peak in allergy symptoms, an optimal treatment effect should be expected [4].

The most frequently used second-generation H_1 receptor antagonists are desloratadine, loratadine, fexofenadine, cetirizine and levocetirizine. These are differentiated by organic structure into the piperazine class, consisting of cetirizine and levocetirizine and the piperidine class, which includes desloratadine, loratadine, fexofenadine [5].

According to the Biopharmaceutical Classification System (BCS) drug substances are classified to four classes upon their solubility and permeability [6, 7]. Desloratadine is classified in the Biopharmaceutics Classification System (BCS) as a Class I drug i.e. highly soluble and highly permeable compound. Desloratadine (descarboethoxyloratadine) is a selective, non-sedating, second-generation tricyclic antihistamine which has a selective and peripheral antagonistic action. Desloratadine is the most potent antihistamine as compared to the other second-generation H_1 antihistamines and is the major biologically active metabolite of loratadine [8]. Histamine is an endogenous chemical, which, upon release, may lead to inflammatory responses. Desloratadine can be used for treatment of allergic asthma and allergic rhinitis conditions [9]. Desloratadine is an International Nonproprietary Name(INN) drug, approved by the Food and Drug Administration on December 21, 2001 [10].

Desloratadine is well absorbed into the systemic circulation following oral administration and has high plasma binding affinity. Desloratadine has >60 times higher affinity for H_1 receptors than it has for H_2 receptors [11]. The apparent volume of distribution is particularly large for desloratadine (~49 L/kg) [12] due to its extensive intracellular uptake. The speed of onset of action [2] and the duration of action of desloratadine is higher [13]. Desloratadine undergoes extensive metabolism in the liver but no significant interactions have been observed by Devillier *et al*., (2008) [5] although this gives the potential for drug-drug interactions. Desloratadine does not impair cognitive or psychomotor performance [14] or potentiate the deleterious effects of alcohol (ethanol) on psychomotor performance [15] and is also non sedating, even at nine times its standard dose [16, 17].
Generic substitution is the prescribing different brand or an unbranded drug which contains the same API at similar strength and dosage form [18]. Branded drug products of top pharmaceutical companies are better in terms of efficacy as well as they are costly. As a consequence, patients from low-income countries can hardly afford them.
The goal of this study was to investigate the physical quality control parameters of marketed desloratadine tablets in Bangladesh. These parameters included diameter, thickness, weight variation, hardness, friability with special landmark on disintegration and dissolution study due to their mountainous significance in predicting bioavailability and product quality.

2. Materials and methods

2.1 Collection of sample products

Standard of desloratadine was a kind gift from ACI Pharmaceutical Ltd, Bangladesh. Desloratadine tablets (5 mg) of six different brands were purchased from registered pharmacy stores of Dhaka, Bangladesh. The samples were properly checked for their manufacturing license numbers, batch numbers, manufacturing, expiry dates and for ethical concerns, the tablets were randomly coded as D1, D2, D3, D4, D5 and D6 so that the identity of the manufacturer can be blinded (Table 1). The shape, size and color of different branded tablets were subjected to visual inspection at the very beginning of research work.

2.2 Physiochemical parameters

Rational use of medicines requires that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" [19]. The reason behind poor patient compliance include poor availability, a lack of affordability, poor prescribing practices and a lack of patient adherence [20]. The purchase of medicines contributes significantly to the health care budget of developing countries. Due the resources of the National Health Services are limited which can be considered as the tip of iceberg, so it is the need of time to keep eye on the quality and cost of the drugs that are available in the markets. The label information of six different brands of desloratadine tablets (5 mg) is represented in (Table 1).

Table 1: Label information of six different brands of Desloratadine tablets (5 mg)

Brand code	Mfg. date	Exp. date	Pack size found	Price of pack found (BDT)	Price / 5 units (BDT)
D1	April 2016	April 2018	100	251.37	12.57
D2	March 2016	March 2018	100	250	12.5
D3	October 2015	October 2017	50	150	15
D4	February 2016	February 2018	50	125	12.5
D5	July 2016	July 2018	100	251	12.55
D6	December 2015	December 2017	50	100	10

2.3 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.

2.4 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 were recorded.

2.5 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 and then all tablets were weighted after 100 revolutions.

2.6 Weight variation

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

2.7 Standard assay preparation

The powder equivalent to 100 mg of desloratadine was taken and dissolved in phosphate buffer (PH 6.8). Then it was diluted to produce a final concentration of 0.016mg/ml (16µg/ml) for working solution. Absorbance values were then measured at the maximum wavelength (λmax) of desloratadine of these concentrations using a UV-VIS spectrophotometer (UV-1700, Shimadzu, Japan). Maximum wavelength (λmax) was obtained by scanning samples at different wavelength ranging from 200 to 400 nm and it was found to be 273 nm.

2.8 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 [21]. 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 [22]. The disintegration time (DT) was noted down and by definition,

it's the time taken for the entire tablet to disintegrate completely.

2.9 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. The standard was prepared in the same concentration as for the dissolution testing. Sample was prepared by weighing and crushing 10 tablets, transferring amount of drug powder equivalent to 20 mg in pH 1.2 buffer solutions and placing it in sonicator. The portion of solution was filtered and the filtrate was suitably diluted. Absorbance was taken at 242 nm by using UV-visible spectrophotometer. Finally the potency of different tablets was determined by using the following equation:

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

2.10. Dissolution test

The dissolution test was undertaken for six randomly selected tablets using dissolution apparatus paddle (VEEGO, India). The dissolution medium was 900 ml of phosphate buffer (PH 6.8) which was maintained at 37±0.5 °C. Rotations were 50 revolutions per minute. 10 ml sample was withdrawn after 45 minutes, and was diluted to 200 ml by using 0.1 M sodium hydroxide to obtain a solution containing 0.00075% w/v of desloratadine. Standard solution was prepared accordingly. Absorbance was measured at 257 nm with 0.1 M sodium hydroxide in reference cell according to British Pharmacopeia, 2013 [23]. To determine the concentration of sample, 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 desloratadine were observed in the drug outlets on single visit during medicine collections. The highest price variation was for brand D3 with a maximum price of 3 taka per tablet and minimum of 2 taka per tablet for brand D6 (Fig 1) while there was no major variation in the quality of the tested drugs.

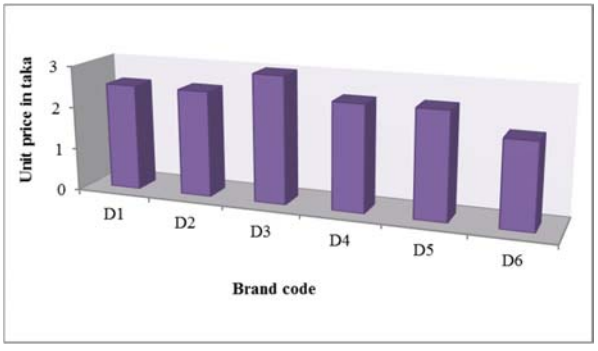

Fig 1: Price fluctuation among different brands of Desloratadine available in local market of Bangladesh

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 [24]. Among six brands, brand D1 had the highest average diameter (7.66 mm) whereas brand D6 had the lowest average diameter (5.62 mm) which makes it difficult for patient's points of view. The average thickness was found to be between the ranges of (2.75-3.61) mm (Table 2).

3.3 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 [25]. 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 times and decreased dissolution times. 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 [26, 21]. Hardness is referred to as non-compendial test. Tablet hardness was found between 24.65-56.85 N. A force of about 40 N is the minimum requirement for a satisfactory tablet [27]. Hence the tablets of brands D2, D3 and D4 were satisfactory for hardness but brands D1, D5 and D6 did not comply with this requirement but their disintegration time was found satisfactory, therefore, the batches were considered as of good quality.

3.4 Friability test

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 [28] as a compendial test. The compendial specification for friability is 1%. Usually harder the tablets less will be the percentage friability and vice versa [29]. It was found that 6 different brand of desloratadine tablet were in accordance with the stated B.P/U.S.P 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 which the tablets were made were perfect [30]. Brand D1 has average weight of 145.29 mg and is within the acceptable range of ± 7.5% with maximum deviation of 4.06% and minimum deviation of 1.45%. All of the other 5 brands have average weight less than 130 mg. Among them, brand D4 did not meet the specification of ± 10% because of its minimum deviation of 10.03%, but the other brands have average weight within the acceptable limit (Table 2).

3.6 Disintegration test

Tablets is expected to break down into smaller particles or granules inside the stomach within a reasonable time to release the active ingredient into the body as the process will

facilitate further dissolution in the biological fluids before gastrointestinal absorption followed by distribution, metabolism and excretion, which is the fate of drug. It has to be pointed out that a product which fails disintegration will presumably fail dissolution criteria [21] because the disintegration tests do serve as a component in the overall quality control of tablets manufacturing. 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 desloratadine were film coated and maximum time for disintegration was found 98 sec in case of brand D3 (Table 2).

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

Brand Code	Diameter* (mm)	Thickness* (mm)	Friability* (%)	Hardness* (N)	Weight Deviation* (Gm)	DT* (sec)	Potency* (%)
D1	7.66±0.01	2.89±0.03	0.34	24.65±0.93	145.29±2.13	35.67±0.82	101.12
D2	6.64±0.03	3.61±0.04	0.08	56.85±0.88	125.59±1.49	71.83±0.98	96.54
D3	6.62±0.03	3.00±0.04	0.29	51.35±0.88	116.8±1.82	98.83±0.75	98.95
D4	6.13±0.03	3.30±0.07	0.29	40.6±0.82	104.73±4.54	44.50±0.55	98.28
D5	6.56±0.02	2.92±0.03	0.14	35.85±0.99	97.33±0.93	85.33±0.52	95.24
D6	5.62±0.04	2.75±0.07	0.19	27.95±0.83	62.55±1.89	92.00±0.63	86.36

*Values are expressed as mean± SD

3.7 Potency test

Potency of all the brands were found within 86.36%-101.12%. Desloratadine is an INN drug; no official specification 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 low dose desloratadine tablets (5mg), percent potency should be within 90-110% [22]. All the brands met this specification except brand D6 which released only 86.36% of drug after an hour (Table 2).

3.8 Dissolution test

Inter-brand comparison showed that brand A and D had maximum drug release within the first 10 minutes (72.53%) of the *in vitro* dissolution test, while brand D6 released only 48.97% of drug after this time. After the 60 minutes interval, brand D1 and D5 showed maximum drug release (97.15%) and brand D exhibited minimum drug release (90%). Intra-brand comparison of the drug release profile of all the brands indicated increase in drug release after every 10 minutes although this increase varied from brand to brand. Since all the brands released more than 75% drug in the first 40 minutes, 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 six brands of Desloratadine tablets

Time (min)	% Drug Release					
	Brand D1*	Brand D2*	Brand D3*	Brand D4*	Brand D5*	Brand D6*
0	0±0	0±0	0±0	0±0	0±0	0±0
10	72.53±0.67	52.59±0.64	52.59±0.64	72.53±0.82	54.18±0.86	48.97±0.80
20	80.29±0.93	60.61±0.87	65.56±0.97	76.90±0.57	63.18±0.64	60.79±0.85
30	84.00±0.55	70.59±1.85	69.79±0.91	80.53±0.80	72.18±0.64	64.41±0.80
40	86.21±0.78	78.18±0.93	77.38±0.78	84.97±0.99	81.26±0,93	76.32±0.85
50	89.65±0.93	82.76±0.64	83.03±0.97	88.24±0.93	86.12±1.24	82.59±0.89
60	97.15±0.99	90.97±0.78	92.74±0.62	92.38±0.99	97.15±0.87	93.09±0.97

*Values are expressed as mean± SD

3.9 Comparison of dissolution data

Difference factor (f_1), similarity factor (f_2) and dissolution efficiency (%DE) were calculated to compare the dissolution profile. The following equations were used to calculate f_1 and f_2. 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 (f_2) 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 [31], dissolution profiles are similar if f_1 values are between 0 and 15 and f_2 values are between 50 and 100.

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

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

Table 4: f_1 and f_2 of six brands of Desloratadine tablets tested

Pair Comparison	Difference Factor (f_1)	Similarity Factor (f_2)
D2 vs. D1	14.54	43.21
D3 vs. D1	13.48	44.85
D4 vs. D1	2.80	75.79
D5 vs. D1	10.94	46.71
D6 vs. D1	16.41	40.13

Table 4 shows the f_1, f_2 values of different brands in respect of brand D1 as a reference brand. Factors f_1 and f_2 were different and below the requirements for products D2, D3, D5 and D6 when compared to brand D1. For brand D4, f_1 was less than 15 and f_2 value was more than 50. So brand D4 is similar with brand D1 and can be used interchangeably.

4. Conclusion

The pharmaceutical industries manufacture a variety of medicinal and other health related products that save us from various diseases but poor quality medicines might result in treatment failure. During the formulation and manufacturing of a drug product it is very important to keep a check on each and every step. *In vitro* tests must be done in order to compare the multi brand generic molecules for having good therapeutic activity. Drug release was satisfactory for all brands, whereas only one brand can be used interchangeably. However, *in vitro* dissolution test in three pH levels and probably *in vivo* test may be required for final comments regarding the quality of marketed brands of desloratadine.

5. References

1. Holgate ST, Canonica GW, Simons FE, Taglialatela M, Tharp M, Timmerman H *et al*. Consensus Group on New-Generation Antihistamines (CONGA): present status and recommendations. Clinical & Experimental Allergy. 2003; 33(9):1305-1324.
2. Diana S, Martin K. Pharmacology of Antihistamines. World Allergy Organization Journal. 2011; 4(3):S22-S27.
3. Nathan RA, Meltzer EO, Seiner JC, Storms W. Prevalence of allergic rhinitis in the United States. Journal of Allergy and Clinical Immunology. 1997; 99(6):S808-S814.
4. Haye R, Høye K, Berg O, Frønes S, Ødegård T. Morning versus evening dosing of desloratadine in seasonal allergic rhinitis: a randomized controlled study [ISRCTN23032971]. Clinical and Molecular Allergy. 2005; 3(3):1-6.
5. Devillier P, Roche N, Faisy C. Clinical pharmacokinetics and pharmacodynamics of desloratadine, fexofenadine and levocetirizine: a comparative review. Clinical Pharmacokinetics. 2008; 47(4):217-230.
6. Yasir M, Asif M, Kumar A, Aggarval A. Biopharmaceutical Classification System: An Account. International Journal Pharm Tech, Research. 2010; 2(3):1681-1690.
7. Dahan A, Miller JM, Amidon GL. Prediction of solubility and permeability class membership: Provisional BCS classification of the world's top oral drugs. American Association of Pharmaceutical Scientists Journal. 2009; 11(4):740-746.
8. Etman MA, Gamal M, Nada AH, Shams-Eldeen MA. Formulation of Desloratadine Oral Disintegrating Tablets. Journal of Applied Pharmaceutical Science. 2014; 4(11):054-061.
9. Hibaezzathamed, Kamal BA. Preparation and *in vitro* evaluation of desloratadine floating tablets. International Journal of Pharmacy and Pharmaceutical Sciences. 2014; 6(9):154-159.
10. Buck ML. Loratadine and desloratadine use in children. Pediatric Pharmacotherapy. 2011; 17(5):1-4.
11. Kreutner W, Hey JA, Anthes J, Barnett A, Young S, Tozzi S. Preclinical pharmacology of desloratadine, a selective and nonsedating histamine H_1 receptor antagonist. 1st communication: receptor selectivity, antihistaminic activity, and antiallergenic effects. Arzneimittelforschung. 2000; 50(4):345-352.
12. Molimard M, Diquet B, Benedetti MS. Comparison of pharmacokinetics and metabolism of desloratadine, fexofenadine, levocetirizine and mizolastine in humans. Fundamental & Clinical Pharmacology. 2004; 18(4):399-411.
13. Purohit A, Melac M, Pauli G, Frossard N. Twenty-four-hour activity and consistency of activity of levocetirizine and desloratadine in the skin. 2003; 56(4):388-394.
14. Vuurman EFPM, Rikken GH, Muntjewerff ND, Halleux FDe, Ramaekers JG. Effects of desloratadine, diphenhydramine and placebo on driving performance and psychomotor performance measurements. European Journal of Clinical Pharmacology. 2004; 60(5):307-313.
15. Simons FER, Fraser TG, Maher J, Pillay N, Simons KJ. Central nervous system effects of H_1- receptor antagonists in the elderly. Annals of Allergy, Asthma, & Immunology. 1999; 82(2):157-60.
16. Kreutner W, Hey JA, Chiu P, Barnett A. Preclinical pharmacology of desloratadine, a selective and nonsedating histamine H_1 receptor antagonist. 2nd communication: lack of central nervous system effects. Arzneimittelforschung. 2000: 50(5):441-448.
17. Banfield C, Padhi D, Glue P, Herron JM, Statkevich P, Affrime MB. Electrocardiographic effects of multiple high doses of desloratadine. Journal of Allergy and Clinical Immunology. 2000; 104(1):S383.
18. Posner J, Griffin JP. Generic substitution. British Journal of Clinical Pharmacology. 2011; 72(5):731-732.
19. Bano R, Gauhar S, Naqvi SBS, Mahmood S. Pharmaceutical evaluation of different brands of levofloxacin tablets (250 mg) available in local market of Karachi (Pakistan). International Journal of Current Pharmaceutical Research. 2011; 3:15-22.
20. Mendis S, Abegunde D, Yusuf S, Ebrahim S, Shaper G, Ghannem H, Shengelia B. WHO study on Prevention of REcurrences of Myocardial Infarction and StrokE (WHO-PREMISE). Bulletin World Health Organization. 2005; 83(11):820-828.
21. Du J, Hoag SW. Characterization of excipient and tableting factors that influence folic acid dissolution, friability, and breaking strength of oil- and water-soluble multivitamin with mineral tablets. Drug Development and Industrial Pharmacy. 2003; 29:1134-1147.
22. United State Pharmacopoeia. United States Pharmacopoeial Convention. Rockville, Maryland, 2014.
23. British Pharmacopeia (BP), Her Majesty's Stationary Office, London, 2013.
24. Akgeyik E, Kaynak MS, Çelebier M, Altınöz S, Şahin S. Evaluation of pharmaceutical quality of conventional dosage forms containing paracetamol and caffeine available in the Turkish drug market. Dissolution Technology. 2016; 23(2):36-41.

25. Banker GS, Anderson NR. In The Theory and Practice of Industrial Pharmacy; Lachman L, Lieberman HA, Kanig JL., Eds.; Philadelphia, USA: Varghese Publishing house, 2011, 293-345.
26. Pisek R, Korselj V, Vrecer F. Comparison of direct rotor pelletization (fluid bed) and hign shear pelletization method for pellet production. Pharm and Biopharm. 2002; 53:327-333.
27. Allen LV, Popovich NG, Ansel HC. Ansel's pharmaceutical dosage forms and drug delivery systems. Edn. 8th, Lippincott Williams & Wilkins, Philadelphia, 2011, 225-256.
28. US Pharmacopeia National Formulary USP 23/NF 18. United States Pharmacopeial Convention. Inc., Rockville, MD, 1995.
29. Oishi TS, Nimmi I, Islam SMA. Comparative *in vitro* Bioequivalence Analysis of Some Generic Tablets of Atorvastatin, a BCS Class II Compound. Bangladesh Pharmaceutical Journal. 2011; 14(1):61-66.
30. Lachman L, Lieberman H, Kanig J. The theory and practice of industrial pharmacy. Edn, 3rd, Varghese publication house, 1987, 293-345.
31. Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system; guidance for industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office: Washington, DC, 2000.