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Comparative *In Vitro* Equivalence Evaluation of Some Loratadine Generic Tablets Marketed in Bangladesh

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Abstract: *Loratadine is a potent, rapidly effective and long-acting non-sedative, histamine H_1 receptor antagonist, with anti-allergic properties. The purpose of this research work was to evaluate the pharmaceutical equivalent of six different brands of loratadine 10 mg tablets using various pharmacopoeial and non-pharmacopoeial tests with special landmark on in vitro dissolution study and with different price ranges purchased from retail pharmacies of Bangladesh. All brands complied with the official specification for friability, uniformity of weight and disintegration time but four brands did not comply with the official specification for hardness. Assay of loratadine tablets revealed that all samples contained 86.65-95.02% of labeled potency. Drug release was satisfactory for all brands, since more than 96.76% of the loratadine was dissolved in the medium within an hour of the test. The dissolution profiles were compared with the use of model independent approaches of difference factor and similarity factor, showing that all brands are similar with brand L3 and can be used interchangeably.*

Keywords: *Loratadine, In vitro equivalence, Dissolution, Difference factor (f_1), Similarity factor (f_2)*

I. Introduction

The quantitative evaluation and assessment of a tablet's chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. These properties are important since chemical breakdown or interactions between tablet components may alter the physical tablet properties, and greatly affect the bioavailability of the tablet system. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, friability, disintegration and dissolution characters [1-2].

The most frequently used second-generation H_1 receptor antagonists are desloratadine, loratadine, fexofenadine, cetirizine and levocetirizine [3]. These are differentiated by organic structure into the piperazine class, consisting of cetirizine and levocetirizine and the piperadine class, which includes desloratadine, loratadine, fexofenadine [4]. However, the use of traditional antihistamines such as diphenhydramine, chlorpheniramine, triprolidine and promethazine is often associated with a number of unwanted side-effects of which sedation is the most pronounced [5-7].

Loratadine is a potent long-acting, long half-life, second generation nonsedating tricyclic antihistamine drug with selective peripheral H_1-receptor antagonist activity [8], which prevents and suppresses seasonal and perennial allergic rhinitis, allergic dermatitis, urticaria and occular allergy with no autonomic anticholinergic effects in humans [9-11]. In contrast to the first-generation antihistamines, loratadine does not cross the blood-brain barrier, shows selectivity when used at therapeutic concentrations and reveals high affinity to peripheral H_1 receptors, allowing avoiding induction of somnolence [12-15]. Loratadine is contraindicated on patients who have hypersensitivity or idiosyncrasy to its component. Less common side effects may include nervousness, wheezing, hyperkinesias, dysphonia, dizziness, dyspepsia, pharyngitis etc.

Loratadine ($C_{22}H_{23}ClN_2O_2$), chemically 4-(8-chloro-5,6-dihydro-11 H-benzo-[5,6] cyclohepta [1,2-b] pyridin-11-ylidene)-1-piperidinecarboxylic acid ethyl ester [16], is white crystalline powder with melting point of 131^oC to 137^oC, molecular weight of 382.89, virtually insoluble in water, poorly soluble in diethyl ether but well soluble in such organic solvents as ethanol (760 g/L), methanol, acetone, 2- propanol and chloroform [12, 17].

According to the Biopharmaceutical Classification System (BCS) drug substances are classified to four classes upon their solubility and permeability [18-19]. Loratadine is classified in the Biopharmaceutics Classification System (BCS) as a Class II drug i.e. low solubility and high permeability compound. Low solubility of the drug limits its bioavailability; despite having good absorption, only about 40% of the dose enters into the systemic circulation.

Generic substitution is the prescribing different brand or an unbranded drug which contains the same API at similar strength and dosage form [20]. 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 those [3].

The goal of this study was to investigate the physical quality control parameters of marketed loratadine 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.

II. Materials And Methods

2.1 Collection of sample products:

Standard of loratadine was a kind gift from ACI Pharmaceutical Ltd, Bangladesh. Loratadine tablets (10 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 L1, L2, L3, L4, L5 and L6 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" [21]. The reason behind poor patient compliance include poor availability, a lack of affordability, poor prescribing practices and a lack of patient adherence [22]. 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 loratadine tablets (10 mg) is represented in Table. 1.

Table. 1. Label information of six different brands of loratadine tablets

Brand code	Mfg. date	Exp. date	Pack size found	Price of pack found (BDT)	Price / 10 units (BDT)
L1	December 2015	December 2018	100	250	25
L2	November 2015	November 2018	100	300	30
L3	February 2016	February 2018	100	400	40
L4	February 2016	February 2018	30	90.60	30.2
L5	June 2016	June 2018	100	301	30.1
L6	January 2015	January 2018	50	125	25

2.3 Diameter and thickness inspection:

Ten 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). Ten tablets were randomly selected from each brand and the pressure required to crush were recorded.

2.5 Friability test:

Ten 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 ten 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 loratadine 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 (λ max) of loratadine of these concentrations using a UV-VIS spectrophotometer (UV-1700, Shimadzu, Japan). Maximum wavelength (λ max) was obtained by scanning samples at different wavelength ranging from 200 to 400 nm and it was found to be 280 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 [23]. 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 [24]. 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 280 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 loratadine. Standard solution was prepared accordingly. Absorbance was measured at 280 nm with 0.1 M sodium hydroxide in reference cell according to British Pharmacopeia, 2013 [25]. 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.

III. Results and Discussion

3.1 Price fluctuation:

Price, manufacturing and expiry date of loratadine were observed in the drug outlets on single visit during medicine collections. As the variation in the price has been observed from as much as 25 to 40 BDT per 10 units (Table 1), while there was no significant variation in the quality of the tested drugs. Hence it may be suggested that the pharmaceutical outcomes are promising too in terms of most economically available drug.

3.2 Diameter and thickness inspection:

By monitoring the diameter and thickness at regular intervals during the production may prevent potential problems related to tablet weight and to ensure uniformity in tablets appearance and fitting into the containers for packaging process at an early stage [26, 21]. Among six brands, the average diameter was found to be between the ranges of (6.06-8.03) mm and the average thickness was found to be between the ranges of (2.57-3.18) mm which makes it difficult for patient's points of view (Table. 2).

3.3 Hardness test:

Hardness has impact on disintegration and perhaps more significantly, to the drug release rate. Monitoring of tablet hardness is important for drug products that possess real or potential bioavailability problems or that are sensitive to altered drug release profile due to the compression force. 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. Hardness is referred to as non-compendial test. Among six brands, brand L4 had the highest percentage of hardness (46.1N) whereas brand L1 had the lowest percentage of hardness (15.4 N) (Table. 2). A force of about 40 N is the minimum requirement for a satisfactory tablet [27] but brands L1, L2, L3 and L5 did not comply with this requirement but their disintegration time was found satisfactory, therefore, the batches were considered as of good quality (Table. 2).

Table. 2. A summary of the quality control tests undertaken on different brands of loratadine tablets

Brand Code	Diameter* (mm)	Thickness* (mm)	Friability* (%)	Hardness* (N)	Weight Deviation* (gm)	DT* (min)	Potency* (%)
L1	6.11±0.02	2.91±0.05	0.44	15.4±5.80	0.09±0.27	2.25±0.03	86.65
L2	6.43±0.04	2.57±0.03	0.11	17.6±1.43	0.10±0.01	1.52±0.08	91.83
L3	7.08±0.13	2.80±0.02	0.08	28.5±2.80	0.13±0.01	2.33±0.03	90.87
L4	8.03±0.02	2.69±0.06	0.18	46.1±5.15	0.18±0.01	0.35±0.02	95.02
L5	7.08±0.05	3.18±0.05	0.15	28.9±2.56	0.14±0.01	6.53±0.01	92.95
L6	6.06±0.03	3.06±0.04	0.30	40.3±2.83	0.14±0.05	1.43±0.02	91.99

*Values are expressed as mean± SD

3.4 Friability test:

Friability test is now included in the United States Pharmacopeia, 1995 [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 loratadine tablet were in accordance with the stated USP guideline (Table. 2).

3.5 Weight variation:

Uniformity of weight serves as a monitor to good manufacturing practice as well as amount of the active pharmaceutical ingredient contained in the formulation [29]. 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 [2]. According to USP, the limit of deviation is ±10% for tablets weighing 130 mg or less and not more than two tablets should cross the single limit and none of them should cross the double of the limit. The weight variation for all the tablets used in this study showed compliance with the stated official specifications (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. 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. From table 2 it can be demonstrated that, all the brands of loratadine met the official criteria. Here, brand L5 took maximum time of 6.53 minute and brand L4 took the minimum time of 0.35 minute to disintegrate (Table. 2).

3.7 Potency:

Loratadine 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. Potency of all the brands was found within 86.65%- 95.02%. All the brands met this specification except brand L1, which released 86.65% of drug after an hour (Table. 2).

3.8 Dissolution test:

Inter-brand comparison showed that brand L3 had maximum drug release within the first 10 minutes (77.90%) of the *in vitro* dissolution test, while brand L1 released 74.96% of drug after this time. From the table 3, it can be demonstrated that tablets of all the six brands have more than 85 % of drug release after 60 minutes and tablets of brand L3 released 96.76% percent of drug which was the highest and tablets of brand L1 released 89.48% percent of drug which was the lowest of all six brands. Since the standard specification of percent of drug release is not less than 85%, 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 loratadine tablets

Time (min)	% Drug Release					
	Brand L1*	**Brand L2***	**Brand L3***	**Brand L4***	**Brand L5***	**Brand L6***
0	0±0	0±0	0±0	0±0	0±0	0±0
10	74.96±0.67	75.88±0.37	77.90±0.48	72.98±0.75	75.40±0.51	75.73±0.57
20	78.29±0.76	78.29±0.72	81.23±0.51	78.68±0.75	79.16±0.54	78.92±0.77
30	79.74±0.70	83.88±1.07	89.48±0.66	81.81±0.51	82.24±0.63	84.99±0.81
40	82.58±0.71	89.72±0.67	93.43±0.54	84.66±0.47	84.95±0.68	87.21±0.96
50	85.04±0.63	91.99±0.54	95.51±0.34	89.57±0.62	88.18±0.54	90.25±0.54
60	89.48±0.44	94.21±0.60	96.76±0.34	92.32±0.50	90.93±0.52	92.57±0.63

*Values are expressed as mean± SD

3.9 Comparison of dissolution data:

Difference factor (f_1) and similarity factor (f_2) 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 [30] 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 loratadine tablets tested

Pair Comparison	Difference Factor (f_1)	Similarity Factor (f_2)
L1 vs. L3	8.28	54.44
L2 vs. L3	3.81	71.51
L4 vs. L3	6.42	60.53
L5 vs. L3	6.26	60.48
L6 vs. L3	4.61	67.46

Table. 4 represent the f_1, f_2 values of different brands in respect of brand L3 as a reference brand. For all brands, f_1 was less than 15 and f_2 value was more than 50. So brands of all loratadine tablets are similar with brand L3 and can be used interchangeably.

IV. Conclusion

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. Implementation of these approaches can reduce the time and cost required for manufacturing, while improving quality control. *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 loratadine.

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