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In-vitro Comparative Dissolution Study of Different Brands of Levocetirizine Dihydrochloride Available in Bangladesh

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ABSTRACT: Branded drugs are more expensive than locally marketed drugs. The aim of this present study was to evaluate and compare dissolution pattern of locally branded drug products of Levocetirizine dihydrochloride of regional pharmaceutical companies available in Bangladesh with the reputed brand of Levocetirizine 2HCl (Purotrol®) marketed by Square pharmaceuticals Ltd. Four different brands of Levocetirizine 2HCl tablets and Purotrol® were collected from a reputed pharmacy store, then evaluated and compared subsequently. Five tablets from each of the brands were used for the *in-vitro* dissolution study. Cumulative drug release was measured up to 30 minutes for all the brands. Differential factor, f1 and similarity factor, f2 were determined. Significant difference was observed for *in-vitro* drug release pattern of local brands with respect to Purotrol®. Here it was found that the values of *f*1 are 25.11, 26.08 and 15.52 for brand B, C, and D respectively so it is not acceptable. Only brand A has f1 value less than 15 (13.7) therefore that is accepted. In case of similarity factor it was seen that the values of *f*2 are 44.79, 37.54, 30.77 and 16.27 for brand A, B, C, and D respectively, so it is also not acceptable. Significant difference was observed during *in-vitro* drug release pattern of B, C and D with from Purotrol®. Manufacturer of brand B, C, and D are advised to revise their drug release pattern to be more similar with Purotrol®.

KEYWORDS: Levocetirizine 2HCl, Comparative dissolution, Differential factor, Similarity factor, *In- vitro* drug dissolution study.

1 INTRODUCTION

Levocetirizine is a non-sedative third-generation antihistamine indicated for the relief of symptoms affiliated with seasonal and perennial allergic rhinitis along with uncomplicated chronic idiopathic urticarial skin manifestations. It was developed from the second-generation antihistamine cetirizine. Levocetirizine is the r- enantiomer (isolated levorotatory enantiomer) of the cetirizine racemate. Levocetirizine is an inverse agonist which decreases activity at histamine H1 receptors. In vitro binding experiments revealed that levocetirizine has 2 fold higher affinities for the human H1-receptor as compared with cetirizine. This in turn prevents the release of other allergenic and inflammatory mediators together with increased blood supply to the area and provides relief from the typical symptoms of hay fever. It does not prevent the actual release of histamine from mast cells. Levocetirizine was approved by the United States Food and Drug Administration on May 25, 2007 and is marketed under the Purotrol®YZAL® by Sanofi-Aventis U.S. LLC [1]. Levocetirizine dihydrochloride is classified in class II as it has high solubility and low permeability by the biopharmaceutical classification system (BCS). Dissolution tests are essential for the prognosis of solid dosage form oral absorption and bioequivalence parameter of drugs. In this study we have compared the dissolution profile of local brands B, C, D, E etc. with respect to a reference Purotrol®. Tablets are holding the peak market value as solid dosage form, which comprises the large portion of pharmaceutical markets. The advantages of tablets include good physical ease of dosing, chemical and microbiological stability; patient compliance and acceptability etc. [2]. Anyway, the drug bioavailability into the systemic circulation from the tablets includes the steps of disintegration, dissolution and absorption. The co-ordination between these three steps ensures the bioavailability of a drug from tablets. Therefore, dissolution tests are

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very important that ensures the optimum release of the drug from the drug product [3]. Generic substitution is prescribing different brand or an unbranded drug which contains the same API at similar strength and dosage form [4]. Branded drug products are costly that are hardly affordable to the poor people of under-developed and developing countries. Many health authorities including WHO suggest the replacement of patent brands with generic brands for general mass. However, this approach must not exceed the need for a bioequivalence testing. One brand can be replaced by another brand if they are bioequivalent only [5].One of the most significant concerns of this experiment is to study whether there are any impacts on the efficacy of the products that can raise further concerns about the sub therapeutic outcomes and repercussions of treatment failures especially due to levocetirizine.

This experiment was performed to evaluate and compare the dissolution pattern of commercially available different local brands of levocetirizine 2HCL tablets available in Bangladesh with the Purotrol®.

2 MATERIALS AND METHODS

2.1 DRUGS AND APPARATUS

Levocetirizine Dihydrochloride(Initial U.S. Approval: 1995),Five brands of Levocetirizine Dihydrochloride from Bangladesh (Table 1), USP Apparatus II– Paddle (37°C), UV visible spectrophotometer, conical flasks, measuring cylinders, distilled water pumps, pipette fillers, filter papers, aluminum foils, Pipette (1 ml &10 ml), Beaker, Mortar and pestle, volumetric flasks , test tubes etc.

Table 1. Different brands with their codes and prices

Code	Price (BDT)
X	3.50
A	2.00
B	2.00
C	2.00
D	2.52
E	2.00

2.2 PREPARATION OF STANDARD CURVE

Stock solution A of 10µg/mL was prepared by dissolving 10 mg equivalent of Levocetirizine Dihydrochloride USP in 100mL distilled water. Then it was diluted 10 times to make stock solution B of 10µg/mL. From the stock solution B five solutions of different concentrations (2, 4, 6, 8, 10) µg/ml of levocetirizine dihydrochloride was prepared. Then spectrophotometer is turned on and 231 nm wave length was set up. The solutions were placed on spectrophotometer to measure the absorbance. These concentrations were selected by trial and error method to keep the absorbance between 0.1 to 1 for the satisfaction of Beer-Lambert law [6].

2.3 DISSOLUTION TEST

USP apparatus II (Paddle) was used in the experiment for the dissolution test. Six vessels were used simultaneously. In each of the vessel 900mL of distilled water was poured. The temperature was set to 37.5±0.5°C. The RPM was set at 50. The machine was preheated to reach the temperature (Table 2). One tablet was placed in each of the vessel when time started. 5 mL of sample was withdrawn from each of the vessels at time interval 10, 20 and 30minutes and the loss of the solvent was compensated by the addition of fresh distilled water. Each of the samples was filtered and diluted 10 times before taking absorbances. At the end of the dissolution test, absorbances were taken at 231nm.

Table 2. Dissolution test conditions for Levocetirizine dihydrochloride USP

Dissolution Apparatus Type	USP Apparatus II
Dissolution media	Distilled water
Temperature	37°C ± 0.5°C
RPM	50
Time	30 minutes
Wavelength	231 nm

2.4 STATISTICAL ANALYSIS DIFFERENCE FACTOR, F1

The difference factor *f*1 is the average difference between all the points of sampling between two brands e.g. reference brand and one of the four test brands. The equation of *f*1 is given below:

$$f1 = \frac{\sum_{t=1}^{n} Rt - Tt}{\sum_{t=1}^{n} Rt} \times 100$$

R_t is the percentage of drug release from the reference drug product and Tt is the percentage of drug release from the test drug product at t time. Acceptable range of f1 is between 0-15. *f1* value greater than 15 means significant difference between two brands which is not accepted [7-10].

2.5 STATISTICAL ANALYSIS SIMILARITY FACTOR, F2

Similarity factor is calculated to determine significant similarity between two brands. The equation of *f*2 is given below:

$$f2 = 50\ log[1/\sqrt{\{1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2\}} \times 100]$$

The range of the f2 value is between 0 to100. If the value remains between 50 to100, it is acceptable [7-10].

2.6 DISSOLUTION EFFICIENCY

The dissolution efficiency is not a parameter to compare dissolution pattern between two brands. It is just a parameter to indicate drug release. It is calculated by the following equation:

$$DE = \frac{\int_{t2}^{t2} \mathrm{y.dt}}{\mathrm{y100} \times (\mathrm{t2} - \mathrm{t1})} \times 100$$

In the above equation, y is the percentage of drug release. The numerator of the equation indicates the area under within the time frame. The denominator indicates the rectangle of 100% drug release from 0 time throughout the time frame. The area under the curve is calculated by the help of Microsoft Excel software [11].

3 RESULT

For the calculation of drug release from the reference brand as well as test brands, a standard curve was prepared within the concentration range of 0-10 µg/mL. The curve displayed sufficient linearity with a correlation coefficient (R^2) value of 0.991 and provided an equation y = 0.033x - 0.009. The standard curve is shown in figure 1.

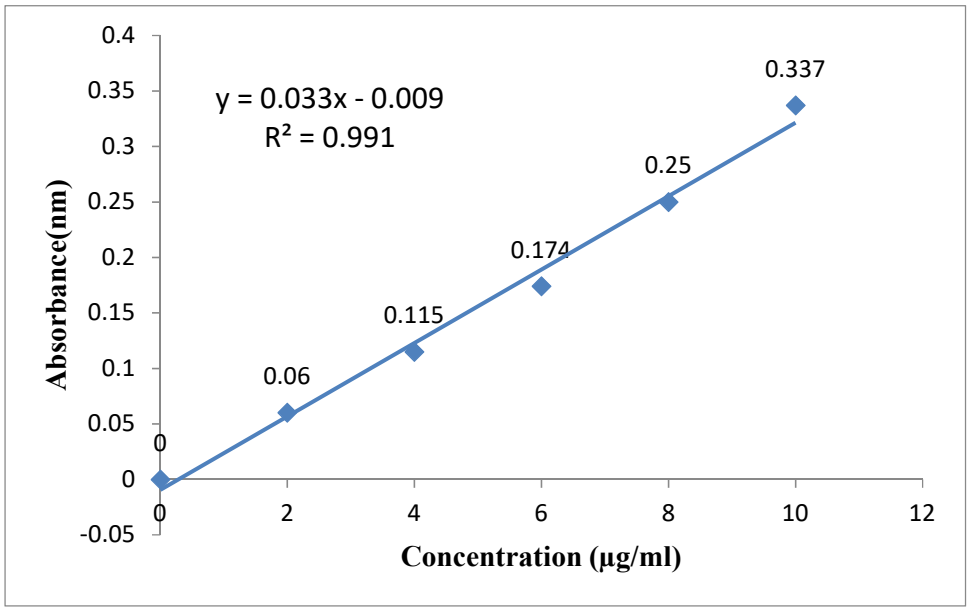

Fig. 1. Standard curve of the reference brand

In the recent experiment, four commercially available brands and reference brand Purotrol® were undertaken for dissolution study. The Dissolution tests were allowed to continue upto 30 minutes. According to the USP specifications for Levocetirizine dihydrochloride tablets, more than 80% drug should be released from the tablets within 45 minutes. Almost all of the brands satisfy this criterion except brand C which is below 80%. The average cumulative drug release pattern for four different brands of Levocetirizine tablets along with that of the reference brand Purotrol® have been illustrated below in the figure 2.

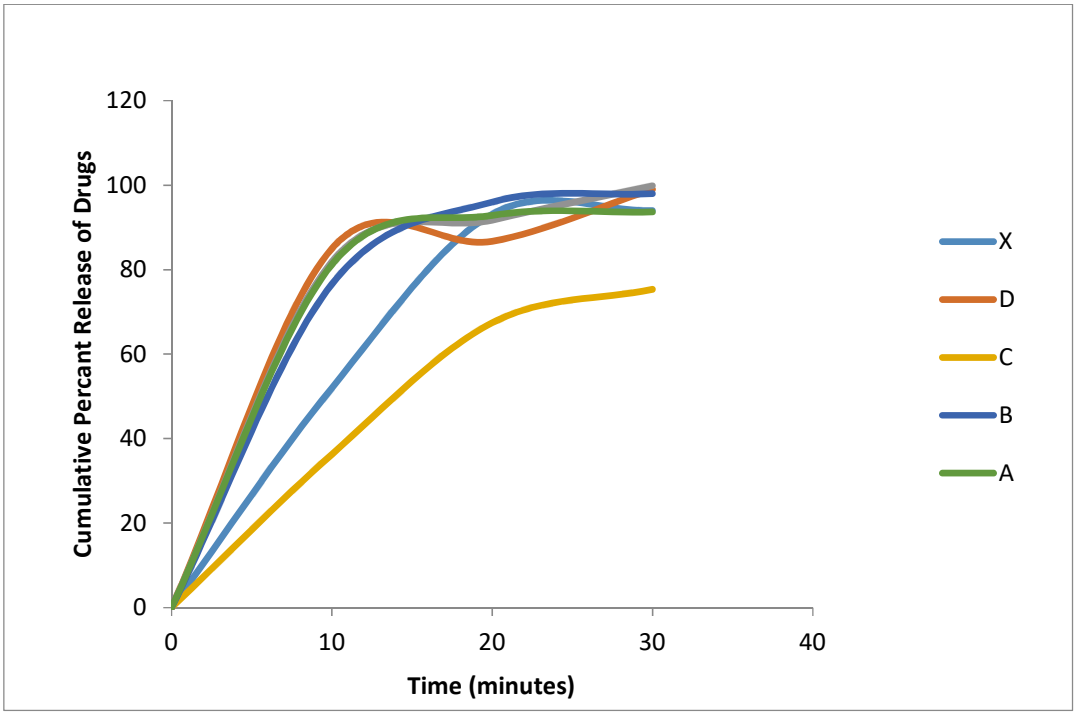

Fig. 2. Cumulative percent drug releases of different brands of Levocetirizine, their comparisons with Purotrol (X)

For the assessment of comparative dissolution, difference factor f1 and similarity factor f2 were calculated between Purotrol and each of the brands, because these two factors are most widely used for the comparison between different brands. The values of f1 and f2 are given in table 3 with justification. Dissolution efficiency was determined to evaluate the percentage dissolved from each of the formulations and difference between dissolution efficiency of Purotrol and each of the other brands were calculated. Then the differences in dissolution efficiency of different brands with Purotrol were measured.

Table 3. f1 and f2 values for the comparison between Purotrol and other brands

Comparison	*f1*	Justification	*f2*	Justification
Purotrol® & A	13.7	No significant difference between two brands	44.79	No significant similarity
Purotrol® & B	25.11	Significant difference between two brands	37.54	No significant similarity
Purotrol® & C	26.08	Significant difference between two brands	30.77	No significant similarity
Purotrol® & D	15.52	A little but having a difference between two brands	16.27	No significant similarity

4 DISCUSSION

In this study from the above figure 2, comparisons of dissolution profiles of Levocetirizine tablets were done to see the release pattern of Levocetirizine Dihydrochloride with different time intervals. Purotrol® was used as a reference brand and other brands like A, B, C and D were used to see the release pattern with different time intervals with respect to Purotrol®. It is acknowledged that, *f1*(difference factor) and *f2* (similarity factor) are used widely to find out both the average difference in between the reference brand and one of the four brands as well the similarity factor to detect the possible similarities amongst those brands with respect to the reference brand. From table 3, we observed Brand B, C, D had *f1* values greater than 15 i.e. 25.11, 26.08, and 15.52 deviating from the range of the values 10.11, 11.08 and 0.52 (almost closer to the range) respectively and so, therefore they are not acceptable. Only Brand A has *f1* value less than 15, i.e.13.7 and as a result that was accepted since it complied with the given range. It is stated that the similarity factor (*f2*) is inversely proportional to the average squared difference between the two profiles. From the table 3, we observed that the *f2* values of Brand A, B, C and D are 44.79, 37.54, 30.77 and 16.27 and thus deviated from the range of values 5.21, 12.46, 19.23 and 33.73 respectively. The probable reason they deviated from Purotrol® highly might be because of their very higher dissolution rate from the beginning. Therefore they were not acceptable at all. To sum up, it is clearly observed that these have impacts on efficacy of the products raising further concerns about the sub therapeutic outcomes and repercussions of treatment failures especially for Levocetirizine.

Overall, it can be concluded that, the brand A having the lowest *f1* value of 13.7(within the range) and highest *f2* value of 44.79 (closer to the range) is most similar to the reference brand in dissolution pattern apart from other brands.

The study was carried out in deionized water media and the values were calculated. The extreme variations in the API release profiles for Levocetirizine tablets reflect significant differences in the manufacturing quality which could be due to different sources, quality of coating process, relative comparison of content of polymers and other effects of excipients used in the formulation [12-15].

5 CONCLUSION

This study was an *in-vitro* study and we know that the *in-vivo* results could be different [16]. Levocetirizine dihydrochloride is classified in Class II as it has high solubility and low permeability by the BCS [17]. Dissolution tests are essential for the prognosis of dosage form oral absorption and bioequivalence of drugs. In this study we have compared the dissolution profile of local brands with respect to reference brand. The similarity factors (*f2*) and Difference factors (*f1*) of the local brands B, C, D was not in the acceptable range except Brand A because it scored an *f*1 value less than 15 which complying within the range and therefore is accepted. In conclusion, further investigations are needed to find out the better dissolution profile for these brands that were undergone dissolution study. Moreover, this study also recommends the manufacturers to reevaluate their formulations for maintaining or improving dissolution efficiency.

CONFLICT OF INTEREST

The authors declare they have no competing interests.

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