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In-vitro comparative dissolution study of different brands of Ranitidine hydrochloride tablets available in Bangladesh

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Abstract

Branded drug products are normally expensive than the locally marketed drug products of regional pharmaceutical companies. Generic substitution is very common in under-developed and developing countries including Bangladesh. The aim of the present study was to evaluate and compare dissolution pattern of locally branded drug products of Ranitidine HCl available in Bangladesh with the innovator brand of Ranitidine HCl (Zantac®) marketed by GSK pharmaceutical company. Tablets of six brands of Ranitidine available in Bangladesh as well as Zantac® were collected from a reputed pharmacy store in Dhaka, Bangladesh. Six tablets from each of the brands were used for the *in-vitro* dissolution study. Cumulative drug release was measured up to 50 minutes for all the brands. All the brands were compared with the innovator brand. Differential factor, f1 and similarity factor, f2 were determined. No significant difference was observed during *in-vitro* drug release pattern of brand A, B, D and F with the innovator brand, whereas brand C and E were significantly different from Zantac®. The drug release pattern is not an indicator of drug efficacy in the body. Nevertheless, it is a need to compare drug release pattern of generic brand with the innovator brand. Manufacturer of brand C and E are advised to revise their drug release pattern to be more similar with Zantac®.

Keywords: Ranitidine HCl, Generic brand, Innovator drug product, Comparative dissolution, *In-vitro* drug dissolution study

Introduction

Ranitidine is a H_2 blocker, which is used to reduce the excessive acid secretion in the stomach. It inhibits the action of histamine at the histamine H2 receptor competitively and reversibly which are found in the gastric parietal cells. This inhibition results in decreased acid secretion. Hence, this popular class of drug is being used to treat ulcer and Zollinger-Ellison syndrome (Bradshaw et al., 1979; Cappola 2001; Drugs.com, 2016).

Tablets are mostly used solid dosage form, which comprises the large portion of pharmaceutical markets. The advantages of tablets include ease of dosing; good physical, chemical and microbiological stability; patient compliance and acceptability etc (Aulton 2002; Lieberman et al. 1989). Anyway, the drug availability 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 very important that ensures the optimum release of the drug from the drug product (Shah et al. 1989a; Shah et al. 1998b).

Generic substitution is the prescribing different brand or an unbranded drug which contains the same API at similar strength and dosage form (Posner and Griffin 2011). 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, which are in the ability of general mass. However, this approach should not exceed the need for a bioequivalence testing. One brand can be replaced by another brand if they are bioequivalent only (Meredith 1996).

In Bangladesh, there are more than 200 pharmaceutical companies. It is needless to mention that ranitidine is one of the widely prescribed medication all over the world for the treatment of acidity and ulceration (Park et al. 2016; Chopra et al. 2014). Almost all the pharmaceutical companies manufacture ranitidine HCl tablet and market them under their own brand name. It is obvious that drug release from the drug product should be optimum for the availability at the absorption site. The *in vitro* drug dissolution test is used for the assessment of drug release.

This experiment was aimed to evaluate and compare dissolution pattern of commercially available different ranitidine tablets available in Bangladesh with the innovator brand Zantac® which is manufactured by GSK pharmaceutical company.

Materials and methods

Ranitidine HCl USP (Potency 88.68% w/w), Zantac tablets, Six brands of ranitidine HCl from Bangladesh (Table 1), Dissolution test USP apparatus II, UV visible spectrophotometer, conical flasks, measuring cylinders, distilled water pumps, pipette fillers, filter papers, aluminum foils etc.

Preparation of Standard Curve

Stock solution A of 500µg/mL was prepared by dissolving 25 mg equivalent of ranitidine HCl USP in 50mL distilled water. Then it was diluted 10 times to make stock solution B of 50µg/mL. From the stock solution B five solutions of 5, 10, 15, 20 and 25 µg/mL were prepared using freshly prepared distilled water. 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 (Hoegy et al. 2014).

Table 1: Different brands with their code.

Code	Mfg. Date	Exp. Date	Price (BDT)
Zantac®	March-2015	March-2017	4.00
A	March-2015	March-2018	1.50
B	April-2015	April-2017	2.00
C	February-2016	February-2019	2.00
D	January-2016	January-2017	2.00
E	March-2015	March-2017	2.00
F	February-2016	February-2018	2.50

Table 2: Dissolution test conditions for ranitidine HCl USP.

Dissolution Apparatus Type	USP Apparatus II
Dissolution Media	Distilled Water of pH 7.0
Agitation	100 rpm
Temperature	37.5±0.5°C
UV Detection Wavelength	314 nm

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 100. The machine was preheated to reach the temperature. 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, 30, 40 and 50 minutes and the loss of the solvent was minimized 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 314 nm.

Statistical Analysis

Difference Factor, *f1*

The difference factor f1 is the average difference between all the points of sampling between two brands e.g. reference brand and one of the six test brands. The equation of f1 is given below:

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

Rt 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 (Lokhandwala et al. 2013; Parakh and Patil 2014; Patel et al. 2015; Qazi et al. 2013).

Similarity Factor, *f2*

Similarity factor is calculated to determine significant similarity between two brands. The equation of f2 is given below:

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

The range of the f2 value is between 0 to 100. If the value remains between 50 to 100, it is acceptable(Lokhandwala et al. 2013; Parakh and Patil 2014; Patel et al. 2015; Qazi et al. 2013).

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:

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

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 (Anderson et al. 1998; Parakh and Patil 2014).

Results

For the calculation of drug release from the innovator brand as well as test brands, a standard curve was prepared within the concentration range of 0-25 microgram/mL. The curve displayed sufficient linearity with a correlation coefficient (R^2) value of 0.9992 and provided an equation y=0.0455x+0.0125. The standard curve is shown in figure 1.

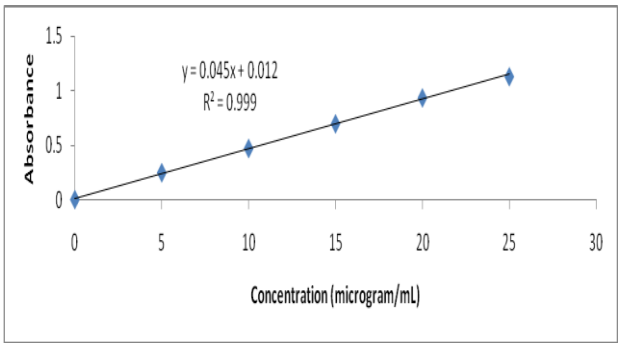

Fig. 1: Standard curve of ranitidine HCl.

In the recent experiment, six commercially available brands and innovator brand Zantac were undertaken for dissolution study. Dissolution was allowed to continue upto 50 minutes. According to the USP specifications for ranitidine HCl tablets, more than 80% drug should be released from the tablets within 45 minutes. Almost all of the brands satisfy this criteria except brand A. The average drug release pattern for six tablets of all of the formulations are displayed in figure 2.

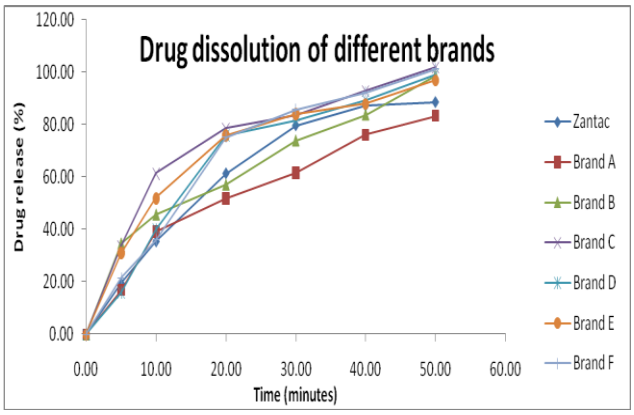

Fig. 2: Drug release from different brands of Ranitidine HCl tablets.

For the assessment of comparative dissolution, difference factor f1 and similarity factor f2 were calculated between Zantac 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 Zantac and each of the other brands were calculated. Then the differences in dissolution efficiency of different brands with Zantac were measured.

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

Comparison	f1	Justification	f2	Justification
Zantac & Brand A	13.42	No significant difference between two brands	51.87	Significant similarity
Zantac & Brand B	13.19	No significant difference between two brands	53.50	Significant similarity
Zantac & Brand C	21.55	Significant difference between two brands	42..49	No significant similarity
Zantac & Brand D	10.01	No significant difference between two brands	56.92	Significant similarity
Zantac & Brand E	15.19	Significant difference between two brands	49.71	No Significant similarity
Zantac & Brand F	10.92	No significant difference between two brands	55.23	Significant similarity

Table 4: Average weight and mean hardness of tablets of different brands.

Formulations	Weight (mg)	Hardness (Pa)
Zantac	305.00	11.00
Brand A	234.00	11.00
Brand B	255.00	9.00
Brand C	277.00	12.00
Brand D	301.00	14.00
Brand E	295.00	12.00
Brand F	324.00	10.00

Table 5: Disintegration time of all the brands.

	Minimum	Maximum	Average
Zantac	13:12	14:10	14:00
Brand A	9:00	9:50	9:36
Brand B	4:10	5:00	4:41
Brand C	10:00	11.00	10:47
Brand D	13:00	14:00	13:50
Brand E	10:15	10:50	10.30
Brand F	11:15	11:43	11:31

Table 6: Dissolution efficiency of different brands.

Brand	Dissolution Efficiency	Difference with Zantac
Zantac	61.76%	00.00%
Brand A	53.84%	07.92%
Brand B	63.10%	01.34%
Brand C	73.75%	11.99%
Brand D	66.82%	05.06%
Brand E	70.22%	08.46%
Brand F	68.36%	06.60%

Discussion

The innovator brand Zantac in this study was found with very low dissolution efficiency (DE) i.e. 61.76%. All the brands satisfied the USP requirements of drug release except Brand A. Although brand A did not meet USP criteria, but it passed the f1 and f2 analysis when comparing with Zantac®. Nevertheless, the main objective of this study was to compare the dissolution pattern of 6 brands (A, B, C, D, E and F) with the innovator brand Zantac®. In this regard, the results are quite satisfactory in spite of having different weight, hardness and disintegration time (Table 4 and 5).

All the brands had acceptable f1 and f2 values except Brand C and Brand E (Table 3). The probable reason they deviated from Zantac® highly might be because of their very higher dissolution rate from the beginning. It was mentioned earlier that the acceptable f1 range is 0-15 and f2 range is 50-100. Brand C was far away from these f1 and f2 ranges i.e. by 6.55 and by 7.51 respectively. On the other hand, Brand E was just close to these ranges. It scored 15.19 in f1 and 49.71 in f2 analysis which was only 0.19 and 0.29 away from the ranges respectively. Brand D gave the lowest f1 value and highest f2 value. We can conclude, brand D is most similar to the innovator brand in dissolution pattern. The difference in mean DE should be within ±10% to be significantly similar in dissolution pattern (Kassaye and Genete 2013). In this regard, all the brands were similar to Zantac except brand C. However, DE of brand B was most close to that of Zantac®.

As we know that several process variables such as excipients, hardness, coating materials, process variables as well as disintegration time may affect the dissolution efficiencies (Gabbott et al. 2016; Jaya et al. 2012; Kitazawa et al. 1975; Okor et al. 2007; Rahman et al. 2015; Zimmer et al. 2015). In this study, the hardness and disintegration tests were carried out to understand the unacceptable f1 and f2 values. Interestingly no significant correlation was found in these regards (Table 3,4,5 and 6). Therefore, the excipients used might be the cause of unacceptable f1 and f2 values of Brand C and Brand E.

Conclusion

This study was an *in-vitro* study and we know that the *in-vivo* results could be different (Lawrence 2016). Nevertheless, Brand A,B,C,D,E and F are the most widely used ranitidine brands available in Bangladesh. These brands may probably be accepted because of their dissolution similarities with the innovator brand Zantac®. Moreover, this study also recommends the manufacturers to reevaluate their formulations for maintaining or improving dissolution efficiency.

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