Kinetic Studies of Ranitidine Hydrochloride Film Coated Tablets Available in Bangladesh: *In vitro* Study Reflection on *in vivo*

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**Abstract**

**Background:** This study deals with the comparative *in vitro* dissolution and *in vitro* disintegration characteristics of different brands of ranitidine hydrochloride film coated tablets most commonly available in Bangladesh which reflects the *in vivo* study. The objective of this present study was to evaluate the *in vitro* kinetic studies of ranitidine hydrochloride film coated tablets available in Bangladesh. Ranitidine hydrochloride is a potent H₂ blocker recommended for hyperacidity related disorders and most common OTC drugs that frequently used by the common people in the world.

**Methods:** Twenty one brands of ranitidine hydrochloride film coated tablets available in Bangladesh drug market were assayed spectrophotometrically and their various kinetics (Zero Order, First Order, Higuchi and Hixson-Crowell) studies were performed to predict *in vivo* analysis.

**Results:** In Bangladesh, commercially available twenty one brands of ranitidine hydrochloride film coated tablets were studied. The media of the study was distilled water (pH 7.5) due to identify complete organoleptic properties of Ranitidine Hydrochloride. Nine brands (RH-3, RH-5, RH-6, RH-10, RH-11, RH-12, RH-13, RH-14 and RH-17) showed delayed disintegration time instead of quick release formulation, which often claimed by those manufacturer. Other twelve brands (RH-1, RH-2, RH-4, RH-7, RH-8, RH-9, RH-15, RH-16, RH-18, RH-19, RH-20 and RH-21) showed the moderate disintegration time. The tablets were studied for *in vitro* dissolution behavior for 1 h in distilled water using USP reference dissolution apparatus. The *in vitro* dissolution profiles of the thirteen brands (RH-1, RH-2, RH-4, RH-7, RH-8, RH-9, RH-13, RH-15, RH-16, RH-18, RH-19, RH-20 and RH-21) were fulfilled the USP *in vitro* dissolution specification of 80% drug release within 45 min. On the other hand, five of the total selected brands (RH-3, RH-5, RH-10, RH-12 and RH-17) showed failed to fulfill the USP *in vitro* dissolution specification. Rest three brands (RH-6, RH-11 and RH-14) exhibited very poor release pattern among the selected brands and their drug release rate were 23%, 11% and 19% respectively after one hour study. The drug potency, multiple coefficient (from zero order, first order, Higuchi and Hixson-Crowell cube root law), similarity and dissimilarity factors were determined in this study. The predicted steady state plasma concentration determined by comparing the *in vivo* pharmacokinetic data of reference brand (Zantac) using superposition principle of steady state plasma levels determination.

**Conclusion:** Most of the brands meet the official requirements, which are very essential parameters for the prediction of *in vivo* drug release by oral route. As a result the patients will get the proper therapeutic effect to combat against hyperacidity problems while they use those brands of ranitidine hydrochloride film coated tablets.

**Keywords:** Ranitidine hydrochloride; H₂ blocker; Hyperacidity; Kinetics studies; Bangladesh

**Abbreviations:** OTC: Over-The-Counter; GD: Gastrointestinal Disorder; NSAID: Non-Steroidal Anti-Inflammatory Drugs; GERD: Gastroesophageal Reflux Disease; USP: United States of Pharmacopoeia; DI: Dosage Form Index

**Introduction**

Ranitidine hydrochloride is a histamine H₂-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastro esophageal reflux disease (GERD) and erosive esophagitis. The effective treatment of erosive esophagitis requires administration of 150 mg of Ranitidine hydrochloride four times a day. A conventional dose of 150 mg can inhibit gastric acid secretion up to five hours, but not up to 10 h. An alternative dose of 300 mg leads to plasma fluctuations; thus a sustained release dosage form of Ranitidine hydrochloride is desirable. The short biological half-life of the drug (~2.5 3 h) also favors development of a sustained release formulation. Ranitidine is absorbed only in the initial part of the small intestine and has 50% absolute bioavailability. Moreover, colonic metabolism of Ranitidine is partly responsible for the poor bioavailability of ranitidine from the colon [1]. The gastro retentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability [2]. Hyperacidity is a serious health care problem and almost 67% of total global population suffered by gastrointestinal disorders (GD). Thus management of hyperacidity becomes very important to improve the human physiological system. A number of no systemic antacid drugs are used; however, their therapeutic potential is very ambiguous. On the other hand, H₂ blockers replaced the therapeutic discrepancies of non-systemic antacids and successfully managed the hyperacidity problems in pathological and NSAID induced condition [3].

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The process of in vitro disintegration and in vitro dissolution played vital roles in liberating a drug from the tablet matrix and marking whether it is available for subsequent gastrointestinal absorption. The in vitro dissolution of the drug from the tablet matrix depends on many factors, which include not only the physicochemical properties of drug, rather the nature of formulation and manufacturing process [4]. Hence in vitro dissolution analysis of pharmaceutical dosage form has emerged as a very important parameter that ensures product quality as well as for differentiating among formulations of the same therapeutic agent [5]. In vitro dissolution studies is an important tool in the evaluation of the best formulation and also in the understanding of possible risks related to specific gastrointestinal environment, dose dumping, food effects on bioavailability and interaction with other drugs [6]. In continuation of our research on different finished pharmaceutical dosage form [7] here we further focused on in vitro evaluations of different brands of ranitidine hydrochloride film coated tablets in Bangladesh.

Materials and Methods

Chemicals

USP references standard of ranitidine hydrochloride (Merk, Germany).

Reference brand

Zantac (Glaxo Smith Kline, Bangladesh).

Equipment

UV-visible Spectrometer (UV mini-1700, Shimadzu Corporation, Kyoto, Japan with 1 cm quartz cells), HANNA HI 2211 PH meter (Romania), Automated eight basket tablet dissolution tester UDP-80 USP Standard (Veego, India), Electronic balance AL 204 (Mettler Toledo, Japan), Hot air oven Labtech (Daihan, Korea), Sartorius electronic balance, Thickness gauge (Campbell Electronics, India), Monsanto hardness tester (Campbell Electronics, India), Roche friabilator (Campbell Electronics, India).

Dosages forms

Twenty one national brands of marketed (production date not more than four months ago from the time of purchase) ranitidine hydrochloride film coated tablets of the test drug were purchased from various stores. The samples were properly checked for their manufacturing license number, batch number and date of manufacture and expiry dates before collection. They were randomly coded (RH-1, RH-2, RH-3, RH-4, RH-5, RH-6, RH-7, RH-8, RH-9, RH-10, RH-11, RH-12, RH-13, RH-14, RH-15, RH-16, RH-17, RH-18, RH-19, RH-20, RH-21). The labeled active ingredient containing ranitidine hydrochloride was 150 mg and packaged in strip or in blister packing. The strip or blister packs were stored at 25 ± 2°C for four weeks before the dissolution study in order to evaluate any organoleptic changes.

In vitro dissolution study

The release rate of ranitidine hydrochloride film coated tablets was determined by United States Pharmacopoeia (USP) referred dissolution testing apparatus 2 (paddle method). The dissolution test was performed in distilled water (900 ml) at 37 ± 0.5°C and at 50 rpm paddle speed. The medium was preheated to 37°C and then added to the vessels. The paddle rotation was started after the medium was placed in the vessels and the system was allowed to equilibrate for 15 min. Each vessel, vessel position and corresponding tablet result were assigned the same number. Thus, for each sub sample of six tablets tested simultaneously, every individual tablet result was identified with a particular vessel and position. The in vitro release profile of those formulations were studied in distilled water (pH 7.5) continued for 1 h using USP reference dissolution apparatus. Six tablets from each formulation were weighed and placed in the baskets. At every ten minutes interval sample (10 ml) of the solution was withdrawn from the dissolution medium and immediately replaced with equal volumes of dissolution medium. The withdrawn sample (10 ml) was then filtered, diluted and analyzed at 314 nm for ranitidine hydrochloride by UV spectrophotometer (Shimadzu, Model UV-160A, Kyoto, Japan). The amount of drug present in the samples was calculated from calibration curves constructed from the standard solution of USP reference standard of the test drugs [8-10].

Drug release kinetics

The in vitro drug release kinetic data were tested with the following mathematical model:

**Zero order equation:** The equation assumes that the cumulative amount of drug release vs. time. The equation may be as follows [11]:

\[ C = K_0 t \]  

**First order equation:** The release behavior of first order equation expressed as log cumulative percentage of drug remaining vs. time. The equation may as follows [12]:

\[ \log C = \log C_0 - kt/2.303 \]  

**Higuchi square root law:** The Higuchi release models describe as cumulative percentage of drug release vs. square root of time. The equation may as follows [13]:

\[ Q = K't \]  

**Hixon-Crowell cube root law:** It is the law that presenting idea about the evaluation of drug release pattern changes with the surface area and the diameter of the particles/tablets. It is mentioned as the cube root of the percentage of drug remaining in the matrix vs. time. The equation may as follows [14]:

\[ Q_0^{1/3} - Q_{eq}^{1/3} = k_{HC} t \]  

**Distinguish the similarity and dissimilarity factors:** Dissolution profile were compared by fit factors (similarity and dissimilarity factor) using the dissolution profile of reference brand. In vitro drug release parameters (**R**= rate of input and **t**<sub>1/2</sub> = time of drug release) of similar release profile (based on **f**<sub>2</sub> value) to that of the reference product were fit to in vivo drug concentrations using reported pharmacokinetic properties. Method of superposition was used for steady state prediction concentration. The values of **C**<sub>max</sub> and **C**<sub>min</sub> obtained by comparing the actual plasma level of reference brand [15].

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The goodness of modified release formulations were evaluated from calculated dosage form index,

\[ DI = \frac{C_{\text{max}}}{C_{\text{min}}} \]  

(5)

And fluctuation (%): \[ \text{fluctuation} = \left( \frac{C_{\text{max}} - C_{\text{min}}}{C_{\text{av}}} \right) \times 100 \]  

(6)

Where \( C_{\text{max}} \) and \( C_{\text{min}} \) are maximum and minimum blood concentration. \( C_{\text{av}} \) = average blood concentration at steady state.

**Results and Discussion**

Commercially available twenty one brands (RH-1, RH-2, RH-3, RH-4, RH-5, RH-6, RH-7, RH-8, RH-9, RH-10, RH-11, RH-12, RH-13, RH-14, RH-15, RH-16, RH-17, RH-18, RH-19, RH-20 and RH-21) of ranitidine hydrochloride film coated tablet were thoroughly evaluated for their physical properties and found hardness (kg/cm²) 3.19 ± 0.01 to 4.35 ± 0.03, friability (%); 00 to 0.12 ± 0.02, thickness (mm); 2.51 ± 0.02 to 3.19 ± 0.12 and weight variation test (%); 1.132 ± 0.02 to 2.903 ± 0.23 parameters are in acceptable range. The potency of those selected brands was estimated and found four brands (RH-6, RH-11 and RH-14) did not meet the declared potency (Table 1).

The in vitro disintegration of the selected brands were studied and compared with reference brand (Zantak) as shown in Table 1.

**Table 1:** The amount of drug present in different commercial brands of ranitidine hydrochloride film coated tablets.

| Code | Potency (%) | Code | Potency (%) |
|------|-------------|------|-------------|
| RH-1 | 96.4        | RH-12| 99.7        |
| RH-2 | 94.8        | RH-13| 92.3        |
| RH-3 | 98.4        | RH-14| 69.7        |
| RH-4 | 96.6        | RH-15| 97.6        |
| RH-5 | 97.9        | RH-16| 93.2        |
| RH-6 | 72.8        | RH-17| 92.8        |
| RH-7 | 93.4        | RH-18| 99.1        |
| RH-8 | 94.8        | RH-19| 94.1        |
| RH-9 | 95.4        | RH-20| 96.7        |
| RH-10| 94.7        | RH-21| 98.2        |
| RH-11| 85.4        | Reference | 98.7 |

A: Code: RH-1 to RH-11

B: RH-12 to Reference

The declared disintegration time of brands (RH-3, RH-5, RH-6, RH-10, RH-11, RH-12, RH-13, RH-14 and RH-17) showed delayed disintegration time instead of exhibited quick release formulation that often claimed by those manufacturers. Moreover, other brands (RH-1, RH-2, RH-4, RH-7, RH-8, RH-9, RH-15, RH-16, RH-18, RH-19, RH-20 and RH-21) showed the moderate disintegration time which was similar to that of reference (9.8 min).

The tablets were studied for in vitro dissolution behavior for 1 h time period in distilled water using USP reference dissolution apparatus as shown in table and figure (Table 2, Figures 2 to 5).

The in vitro dissolution profile of the thirteen brands (RH-1, RH-2, RH-4, RH-7, RH-8, RH-9, RH-15, RH-16, RH-18, RH-19, RH-20 and RH-21) fulfill the USP in vitro dissolution specification of 80% drug release within 45 min. On the other hand, five of the brands (RH-3, RH-5, RH-10, RH-12 and RH-17) failed to fulfill the USP in vitro dissolution specification that was very much related with error in formulation. Rest three brands (RH-6, RH-11 and RH-14) exhibited very poor release pattern among the selected brands and their drug release rate were 23%, 11% and 19% respectively after 1 hour study.

In vitro dissolution studies of all the brands (RH-1 to RH-21) studied throughout the stipulated period and theoretical release profiles of the drug analyzed (Table 3) by multiple coefficients \( r^2 \), zero order release kinetics, first order release kinetics, Higuchi release kinetics and Hixson-Crowell release kinetics.

**Figure 1:** In vitro disintegration profile of different commercial brands of ranitidine hydrochloride film coated tablets.
Figure 2: Zero order release kinetic of different commercial brands of ranitidine hydrochloride.

Figure 3: First order release kinetic of different commercial brands of ranitidine hydrochloride film coated tablets.
Figure 4: Higuchi release kinetic of different commercial brands of ranitidine hydrochloride film coated tablets.

Figure 5: Hixson-Crowell release kinetic of different commercial brands of ranitidine hydrochloride film coated tablets.
The result obtained indicated the highest linearity of all analyzed formulations and the fit factors found ($f_1$ and $f_2$) discussed (Table 4). Considering the dissolution profile, similar value of $f_2$ should lie 50 to 100 and dissimilarity factor $f_2$ was also calculated to approximate the percentage error between different release profiles. The value of $f_2$ is zero when the test and reference formulation profiles are identical and increase proportionally with the dissimilarity between different profiles. If the value of $f_2$ is 50, 90% similarity in the profile was indicated and if it is 40 then 80% similarity may be indicated. Eight brands (Code: RH-1, RH-5, RH-9, RH-10, RH-16, RH-20 and RH-21) showed dissimilarity between their different release profiles (Table 4). On the other hand, eleven brands (Code: RH-2, RH-3, RH-4, RH-7, RH-11, RH-12, RH-13, RH-14, RH-15, RH-17 and RH-18) showed 80% similarity and two brands (Code: RH-8 and RH-19) showed 90% similarity between their different release profiles (Table 4).

Using superposition principle study, a steady state plasma level was calculated (Table 5). The predicted steady state plasma drug concentration of all brands showed some dissimilarity compared to reference brand (Zantac). The calculated plasma drug concentration of six brands (Code: RH-5, RH-6, RH-10, RH-11, RH-12 and RH-14) were in below therapeutic level and other fifteen brands (Code: RH-1, RH-2, RH-3, RH-4, RH-7, RH-8, RH-9, RH-13, RH-15, RH-16, RH-17, RH-18, RH-19, RH-20 and RH-21) lied within the therapeutically acceptable range compare to the reference brand. The dosage form index (DI) and fluctuation (%) determined by using zero order, first order and Higuchi release profile (Table 5).

Table 5 Predicted steady state plasma concentration level of different commercial brands of ranitidine hydrochloride film coated tablets determined from in vitro drug release profile by comparing with in vivo pharmacokinetic data of references brands available in Bangladesh.

Table 3: Drug release mechanism (Multiple coefficients [$r^2$]) of different commercial brands ranitidine hydrochloride film coated tablets.

| Code   | $f_1$   | $f_2$   |
|--------|---------|---------|
| RH-1   | 108.9   | 24.5    |
| RH-2   | 28.5    | 48.5    |
| RH-3   | 31.3    | 41.3    |
| RH-4   | 17.2    | 47.2    |
| RH-5   | 98.3    | 12.8    |
| RH-6   | 78.6    | 18.9    |
| RH-7   | 25.6    | 46.3    |
| RH-8   | 23.1    | 56.3    |
| RH-9   | 85.6    | 16.2    |
| RH-10  | 102     | 12.6    |
| RH-11  | 25.8    | 40.1    |
| RH-12  | 14.6    | 42.9    |
| RH-13  | 21.3    | 41.2    |
| RH-14  | 23.5    | 40.2    |
| RH-15  | 21.7    | 40.1    |
| RH-16  | 78.9    | 25.6    |
| RH-17  | 27.3    | 42.6    |
| RH-18  | 24.1    | 42.7    |
| RH-19  | 21      | 50.6    |
| RH-20  | 89.6    | 19.9    |
| RH-21  | 101.3   | 21.8    |
| Reference | 28.3 | 45.6 |

Table 4: Similarity and dissimilarity factor values for drug release profile of different commercial brands of ranitidine hydrochloride film coated tablets.

| Code   | Dose (mg) | $k$ | $C_{max}$ (mg/ml) | $C_{min}$ (mg/ml) | DI | Fluctuation (%) |
|--------|-----------|-----|------------------|------------------|----|-----------------|
| RH-1   | 100       | 0.345  | 435             | 418             | 1.04 | 3.82           |
| RH-2   | 100       | 1.976  | 427             | 411             | 1.04 | 3.596          |
| RH-3   | 100       | 1.356  | 408             | 201             | 2.03 | 46.52          |
| RH-4   | 100       | 0.894  | 445             | 412             | 1.08 | 7.416          |
| RH-5   | 100       | 1.458  | 324             | 86              | 3.77 | 53.48          |
| RH-6   | 100       | 24.210 | 368             | 314             | 1.17 | 12.13          |
| RH-7   | 100       | 1.147  | 418             | 392             | 1.07 | 5.843          |
| RH-8   | 100       | 0.387  | 432             | 411             | 1.05 | 4.719          |
| RH-9   | 100       | 1.156  | 441             | 410             | 1.08 | 6.966          |
| RH-10  | 100       | 0.142  | 389             | 100             | 3.89 | 64.94          |
| RH-11  | 100       | 1.261  | 359             | 130             | 2.76 | 51.46          |
| RH-12  | 100       | 1.487  | 289             | 40              | 7.23 | 55.96          |
| RH-13  | 100       | 18.341 | 426             | 405             | 1.05 | 4.719          |
| RH-14  | 100       | 1.132  | 289             | 240             | 1.2  | 11.01          |
| RH-15  | 100       | 1.325  | 415             | 395             | 1.05 | 4.494          |
| RH-16  | 100       | 0.621  | 422             | 398             | 1.06 | 5.393          |
| RH-17  | 100       | 1.213  | 389             | 165             | 2.36 | 50.34          |
| RH-18  | 100       | 1.712  | 440             | 422             | 1.04 | 4.045          |
| RH-19  | 100       | 1.167  | 429             | 410             | 1.05 | 4.27           |
| RH-20  | 100       | 0.371  | 421             | 390             | 1.08 | 6.966          |
| RH-21  | 100       | 0.154  | 425             | 410             | 1.04 | 3.371          |
| Reference | 1.214 | 445   | 412             | 1.08 | 7.416          |

$C_{max}$: Maximum Plasma Concentration; $C_{min}$: Minimum Plasma Concentration; DI: Dosage Form Index; $k$: Release Rate Constant (a: first order release order, b: zero order release order and c: Higuchi Release)

Table 5: Predicted steady state plasma concentration level of different commercial brands of ranitidine hydrochloride film coated tablets determined from in vitro drug release profile by comparing with in vivo pharmacokinetic data of references brands available in Bangladesh.
Conclusion

The present study indicated that most of the brands meet the official requirements, which are very essential parameters for the prediction of in vivo drug release by oral route. As a result the patients will get the proper therapeutic effect to combat against hyperacidity problems while they use those brands of ranitidine hydrochloride film coated tablets. This investigation was performed to evaluate quality of drug products, ensure patient’s health at home and promote export of medication from Bangladesh.

Authors’ Contributions

MKI, MDS and MHK designed the concept of the study. MKI, MDS and RH performed the laboratory works. MDS and TS drafted the manuscript. MHK critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interests

The authors declare that they have no conflict of interest.

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