

Research Article

Impact of Calcium-Vitamin D Supplements on the Dissolution Pattern of Ranitidine Hydrochloride Tablets: An *in vitro* Dissolution Study using UV Spectroscopy

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ABSTRACT

The objective of this study was to evaluate the impact of Calcium-Vitamin D supplement formulations on the dissolution pattern of different Ranitidine Hydrochloride tablet formulations. This was an *in-vitro* dissolution study using USP apparatus II and UV spectroscopy. Three different brands of Ranitidine hydrochloride i.e. Brand A, Brand B and the innovator brand 'Zantac[®]', were chosen. Besides CS1, CS2 and CS3 were the three Calcium-Vitamin D tablet brands used to carry out the experiments. In our study, all the brands of Ranitidine HCl tablets satisfied the USP requirements by showing dissolution of more than 80% within 60 minutes when tested alone. The dissolution patterns were 98%, 96% and 94% respectively for Brand A, Brand B and 'Zantac[®]'. However, their dissolution rates were significantly reduced when they were tested with the Calcium-Vitamin D tablets. With the Brands CS1, CS2 and CS3, the percent drug releases were 50%, 46% and 75% for Brand A, 48%, 49% and 73% for Brand B and 49%, 48% and 72% for 'Zantac[®]'. These results may be due to the common ion effects and/or the altered dissolution medium environment. Therefore, this study suggests separate intake of Ranitidine and Calcium supplements to ensure a better therapeutic efficacy.

Keywords: Dissolution, Ranitidine Hydrochloride, Calcium, Vitamin D, UV spectroscopy.

Introduction:

Ranitidine, a H₂ receptor blocking antihistamine [1], which is used to treat intestinal and stomach ulcers and gastrointestinal reflux disorders (GERDs) including treatment of the rare Zollinger-Ellison syndrome. Ranitidine is found as tablet, capsule, or syrup and the available with different brand names like Zantac. Ranitidine can interact with other medications like vitamins and foods or herbs that we often use. [2,3]. Ranitidine is more prescribed than other H₂ Blockers like Cimetidine, as Ranitidine doesn't exhibit anti-androgen side effects, which is found in Cimetidine therapy [4], except this Ranitidine has prolonged clinical response with eight folds greater potency than the Cimetidine [1].

Calcium is the most abundant mineral in body and most studied mineral, found in many foods like available as a dietary supplement, and present in some medicines. Calcium plays very significant role in vascular contraction and vasodilatation, nerve transmission, hormonal secretion, muscle function and intracellular signaling though less than 1% of total calcium in body is required to support these

critical metabolic functions [5,6]. Except these calcium mineral is important to develop and build strong bones with supporting the function of heart, muscle also with nerves [7,8]. Excluding the other factors, a healthy man with age of 70 or younger, or a healthy woman with age of 50 or younger needs 1000mg of Calcium per day, whereas about 99 percent of the total Calcium is important to support the bones and teeth [9,10].

In adults calcium deficiency can result the mobilization of bones that leads to osteoporosis and in human. This disease is very common symptom of ageing [11]. Though people of all races and genders can be affected by osteoporosis but Asian and White women are at highest risk of this disease [12]. In ideal care for osteoporosis should encompass adequate calcium and vitamin D intake and the most available Calcium supplements in recent time are Calcium Carbonate and Calcium Citrate which are well absorbed with normal foods [13]. Medicines used to reduce pain from fractures are normally acetaminophen and other non-steroidal anti-inflammatory drugs (NSAIDs) like Ibuprofen and Naproxen with an anti-ulcerant to protect the digestive system

[14,15,16]. Ranitidine is a popular anti-ulcerant which is prescribed frequently due to its cheap price and wide availability [17]. Ranitidine is a water soluble drug and it is easily dissolved in the stomach with a satisfactory dissolution profile. [18]

The aim of the study was to evaluate if there is any effect of calcium supplements on dissolution profile of Ranitidine. Different Ranitidine tablets are available in Bangladesh including the innovator brand Zantac® manufactured by GSK pharmaceutical. Three different calcium supplements were used to examine the impact of calcium on drug release pattern from three different Ranitidine tablets including Zantac.

Materials and Methods:

Ranitidine HCl USP (Potency 88.68% w/w), Zantac tablets, two brands of Ranitidine HCl from Bangladesh (Table 1) and three brands of calcium supplements from Bangladesh (Table 2), 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 X of 500µg/mL was prepared by dissolving 25 mg equivalent of Ranitidine HCl USP in 50mL of distilled water. 10 times dilution was done to make stock solution Y of 50µg/mL. 5, 10, 15, 20 and 25 µg/mL solutions were prepared from the stock solution Y using prepared distilled water. To satisfy Beer-Lambert law these concentrations were selected by trial and error method to keep the absorbance between 0.1 and 1. [19]

Table 1: Different brands of Ranitidine with their code.

Code	Mfg. Date	Expire Date	Price (BDT)
Zantac®	March-2015	March-2017	4.00
A	March-2015	March-2017	2.00
B	April-2015	April-2018	2.00

Table 2: Different brands of Calcium supplements with their code.

Code	Ingredients	Mfg. Date	Expire Date	Price (BDT)
CS1	Calcium (600mg) +Vitamin D (200 IU) +Minerals	June-2015	April-2017	3.33
CS2	Calcium (500 mg) + Vitamin D (200 IU)	April-2015	March-2017	4.00
CS3	Calcium (500 mg) + Vitamin D (200 IU)	July-2015	June-2018	5.00

Table 3: Dissolution test conditions for Ranitidine HCl USP and Calcium supplements

Dissolution Apparatus	Type USP Apparatus II
Dissolution Media	Distilled Water of pH 7.0
Agitation	50 rpm
Temperature	37.5±0.5°C
UV Detection	Wavelength 314 nm

Dissolution Test:

For the dissolution test, USP apparatus II (Paddle) was used. Six vessels were used simultaneously. Each of the vessel contained 900mL of distilled water with fixed temperature of $37.5 \pm 0.5^\circ\text{C}$. The RPM was set 50. Machine was preheated to reach the temperature. One Ranitidine tablet was placed in each of the vessel when time started. 5mL of sample was withdrawn from each of the vessels at time interval 20, 40 and 60 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 absorbance in 314 nm. Same procedure was done for Ranitidine and calcium supplement tablets together.

Results:

For the calculation of drug release from the Ranitidine tablets, a standard curve was prepared within the concentration range of 0-25 microgram/mL. The curve provided 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.

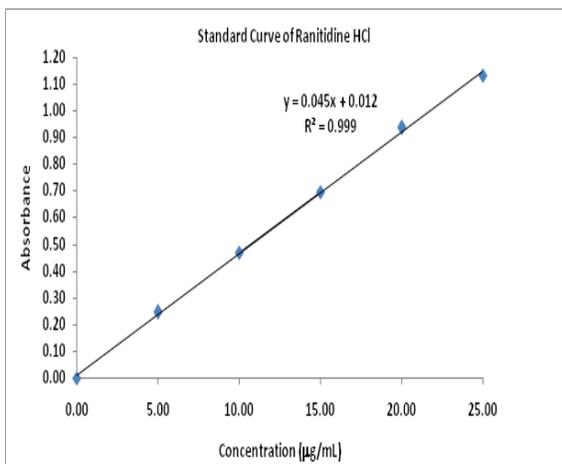


Figure 1: Standard curve of Ranitidine HCl

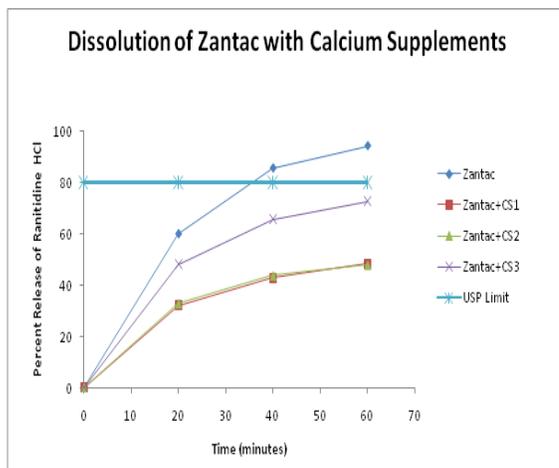


Figure 2: Percent of drug release of Ranitidine HCl with time from Zantac with calcium supplements

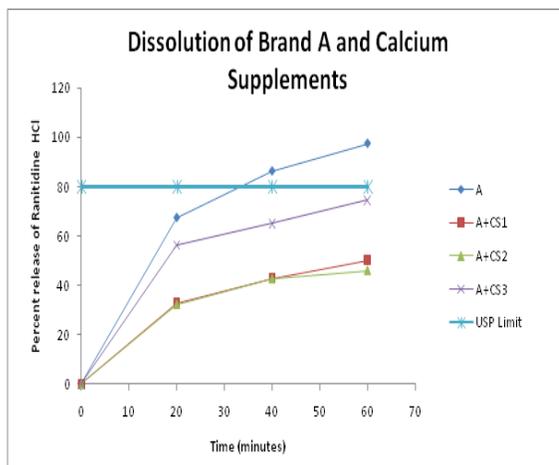


Figure 3: Percent of drug release of Ranitidine HCl with time from Brand A with calcium supplements

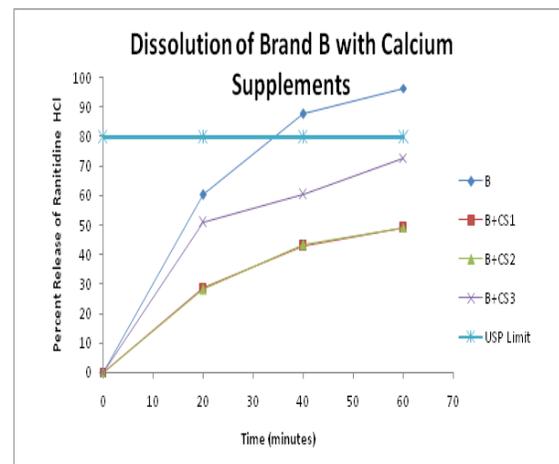


Figure 4: Percent of drug release of Ranitidine HCl with time from Zantac with calcium supplements

Discussion:

According to USP 29, when Ranitidine tablets are subjected to dissolution test, at least 80% drug must be released within 45 minutes [20]. In the recent study, when Zantac was tested alone for dissolution, it satisfied the USP requirement. After 60 minutes dissolution, average drug release from all the six tablets of Zantac was 94%. However, when Zantac was subjected to dissolution in presence of calcium supplements, there was considerable reduction in drug dissolution rate for all three different calcium supplements (Figure 2). CS1 and CS2 both provided significant decrease (49% and 48% respectively) in drug dissolution of Ranitidine HCl from Zantac. CS3 also displayed reduction in total drug release of Ranitidine HCl but its impact was less than those of CS1 and CS2 (72%). These findings may be attributed to the common ion effect, change of dissolution environment for Ranitidine HCl etc. [21, 22, 23]. In presence of these calcium supplements, the drug release of Ranitidine HCl was reduced below the limit provided by the USP 29.

In the figure 3 and 4, impact of calcium supplements on drug dissolution rate of Ranitidine HCl from Brand A and Brand B are shown respectively. Brand A, after 60 minutes of dissolution test, gave 98% of drug release satisfying the USP specification. However, Brand A, upon testing in the presence of CS1, CS2 and CS3 displayed 50%, 46% and 75% of drug release after 60 minutes respectively. On the other hand, alone Brand B, after 60 minutes of dissolution test, provided 96% drug release fulfilling USP requirement. However, Brand B, upon testing in the presence of CS1, CS2 and CS3 displayed 48%, 49% and 73% of drug release after 60 minutes respectively. These results clearly indicate significant reduction in drug dissolution rate.

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