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Impact of Calcium-Vitamin D Combination Tablets on the Dissolution Pattern of Four Different Brands of Rosuvastatin Calcium Tablets: An UV Analysis

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Abstract

This study was designed to find out the impact of calcium-vitamin-D combination tablets on the dissolution profile of rosuvastatin calcium tablets. For this purpose one of the highly prescribed brands of calcium-vitamin D supplement was chosen along with four different brands of rosuvastatin calcium tablets. The experiments were carried out using USP apparatus II and UV spectroscopy. Initially the dissolution pattern for each of the four rosuvastatin calcium brands was observed individually. After that these were co-administered with the calcium-vitamin D supplement tablets to see if there is any change in their dissolution pattern. A significant decline in the dissolution rate was observed in all the co-administered experiments. In case of brand A, B and C the dissolution rate decreased to around 20%. At the same time, this drop in dissolution was the lowest for Brand D which was approximately 10%. The probable reason behind this decreased dissolution may be due to the common ion effect. This study therefore suggests not to take calcium-vitamin D supplement along with the rosuvastatin calcium tablets at the same time. There should be sufficient gap between their intakes.

Keywords: Rosuvastatin, Calcium, Vitamin D, UV spectroscopy, USP apparatus II, dissolution.

Introduction

Hyperlipidemia and dyslipidemia can cause atherosclerosis and increases the risk for stroke, coronary heart disease and peripheral vascular disease [1, 2].Statins are a class of drugs that are used to lower the level of cholesterol in the blood. These drugs reduce the production of cholesterol in the liver by blocking an enzyme, hydroxy methyl glutaryl-coenzyme A reductase (HMG-CoA reductase), which is responsible for the production of cholesterol. So, statins are called HMG-CoA reductase inhibitors [3, 4, and 5]. In the statin class the seventh drug is rosuvastatin calcium that was approved by US FDA in August, 2003[6] Rosuvastatin is a white amorphous powder that has a melting point of 122° C. This drug is moderately soluble in water and methanol and to some extent it is also soluble in ethanol [7]. The molecular formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$ and the chemical name is bis{(E)-7-[4-(4-fluorophenyl)-6-isopropyl2[methyl(methylsulfonyl) amino]pyrimidine-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid}calcium salt. The molecular weight of rosuvastatin is 1001.14.

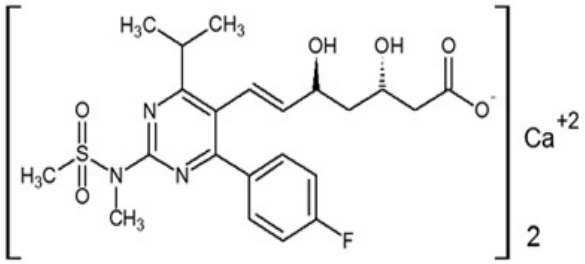

Figure: Chemical structure of rosuvastatin calcium [8]

Rosuvastatin is indicated for various conditions such as hyperlipidemia, hypertriglyceridemia, homozygous familial hypercholesterolemia, primary dysbetalipoproteinemia, and primary prevention of cardiovascular disease and also to slow down the progression of atherosclerosis [7, 9]. Bone is a living tissue that has the ability to constantly break down and builds back up. The bone mass in adult is acquired by the age of 20[10]. For the formation of this bone mass calcium is essential. If the bone mass drops due to deterioration of bone tissue then a clinical condition arises this is termed as 'Osteoporosis' [11]. This disease is an indicator of aging also [12]. Osteoporosis can cause bones to be susceptible to fractures and the risk for breakdown of bone also increases. Research has shown that women who have reduced net calcium absorption, lower rate of bone formation and higher rate of urinary calcium excretion may face some complications during menstruation. Reduced calcium retention and lower bone mass can also induce amenorrhea [10]. Asian and White women are at higher risk of affected by osteoporosis [13]. Common effect of vitamin D deficiency includes thin or brittle bones, bone softening in children (Rickets'), insulin resistance and impaired immune system functioning. Research suggests that deficiency of vitamin D can play a role in depressive disorder. Another study suggest that breast cancer growth in animal model has become faster when there was a deficiency of vitamin D [14, 15]

The inhibitory effect of rosuvastatin for HMG-CoA reductase was found to be more potent than other statins. This drug also has a high degree of selectivity for hepatic cell than the non hepatic cell, so the adverse effects are minimized. Again, the hepatic CYP enzymes metabolizes rosuvastatin in a relatively low amount and so the bioavailability is moderate and the elimination half-life is moderately prolonged [16]. Among the side effects of rosuvastatin rhabdomyolysis (muscle damage) is notable [17]. In some studies it was found that vitamin D supplement can reduce this side effect of statins as the level of vitamin D rises when they are administered with statins [18]. This research project was done to observe the impact of calcium and vitamin D supplement when they are co-administered with rosuvastatin drug. In Bangladesh different brands of rosuvastatin are available. Among them four different brands were chosen and their dissolution profile were tested along with calcium and vitamin D supplement.

Materials and Methods

Four different brands of rosuvastatin calcium (table 1) and one brand of calcium and vitamin D supplement (table 2) from Bangladesh were taken for the dissolution test. USP apparatus II, UV visible spectrophotometer, distilled water, test tube, volumetric flask, filter paper, funnel etc. were used during the test.

Table 1: Different brands of Rosuvastatin with their code:

Name of Drug	Manufacturing Date	Expiry Date	Price per tablet (BDT)
A	April-2016	April-2018	20.00
B	June-2016	June-2018	18.00
C	June-2016	June-2018	15.00
D	May-2016	May-2018	16.00

Table 2: Calcium supplement with its code:

Code	Ingredients	Manufacturing Date	Expiry Date	Price per tablet (BDT)
CS1	Calcium (500 mg) + Vitamin D (200 IU)	April-2016	April-2018	4.00

Table 3: Dissolution test conditions for rosuvastatin calcium and calcium-vitamin D supplement:

Dissolution Test Apparatus	USP Apparatus II Type
Dissolution Media	Distilled Water (p^H 7.0)
Temperature	37±0.5°C
Agitation	50 rpm
UV Detection	Wavelength 241 nm

Preparation of Standard Curve:

A stock solution X of 0.01 mg/ml of rosuvastatin calcium was prepared by dissolving 10 tablets of a brand in 100 ml distilled water. Then from the stock solution different concentrations of the drug was prepared by distilled water and the concentrations are- .001, .002, .003, .004, .005, .006, .007, .008, .009 mg/ml. The same procedure was done for brand B, C and D. These concentration were selected by trial and error method to satisfy the Beer-Lambert law that is to keep the absorbance between 0.1 and 1[19].

Dissolution Test:

USP apparatus II (paddle) was used for the *In vitro* dissolution test. 900 ml of distilled water was added in each of the vessel and at a time six vessels were used. The dissolution tester was preheated to reach a temperature of 37±0.5°C. 50 RPM was set for dissolution. Once the machine was ready, one rosuvastatin calcium tablet was placed in each vessel and the time counts then started. 5 ml of sample was collected from each vessel after the following time interval that are 10, 20, 30, 40, 50 and 60 minutes. To minimize the loss of the sample, 5 ml of freshly prepared distilled water was added after the withdrawal of each sample. The withdrawn samples were filtered and the absorbance was measured at 241 nm. For the dissolution of rosuvastatin calcium and calcium and vitamin D supplement the same procedure was followed.

Results and Discussion:

For the calculation of drug release from the Rosuvastatin tablets, four standard curves were prepared within the concentration range 0-0.009 microgram/ml. From the standard curve of Rosuvastatin, we derived an equation and the curves provided sufficient linearity with a correlation coefficient (R^2) which are given below in the table:

Table 4: Standard Curve Equation and the value of R^2 of different brands

Brand Name	Standard Curve Equation	R^2
A	y = 39.65x + 0.001	0.997
B	y = 38.27x + 0.001	0.995
C	y = 39.91x + 0.003	0.993
D	y = 37.59x + 0.002	0.992

Here, x= Concentration of drug and y= Absorbance at 241 nm

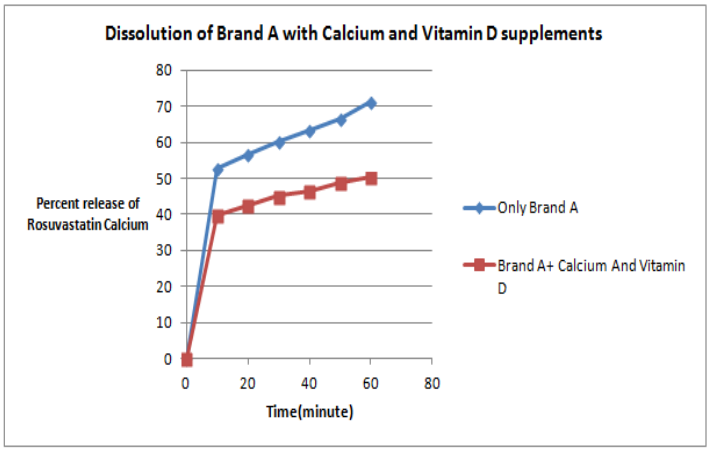

Figure 1: Percent of drug release of Rosuvastatin Calcium with time from Brand A with Calcium and Vitamin D supplements

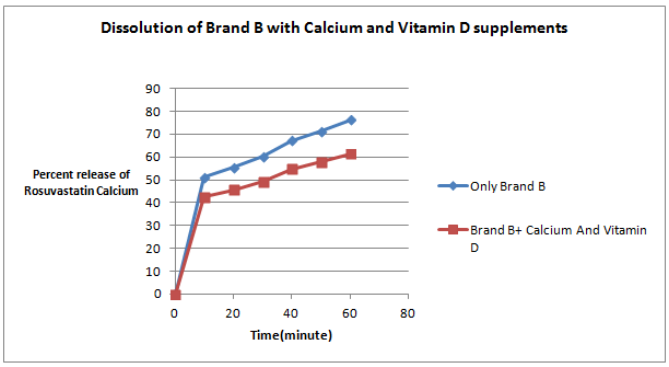

Figure 2: Percent of drug release of Rosuvastatin Calcium with time from Brand B with Calcium and Vitamin D supplements

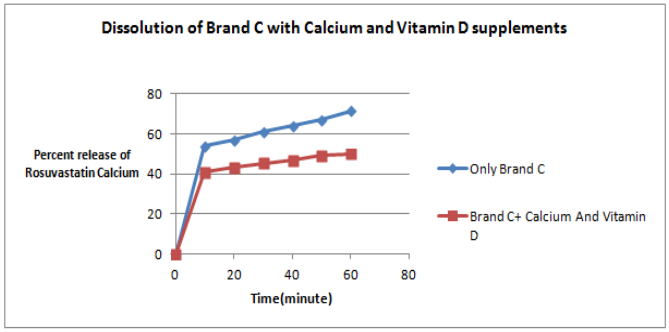

Figure 3: Percent of drug release of Rosuvastatin Calcium with time from Brand C with Calcium and Vitamin D supplements

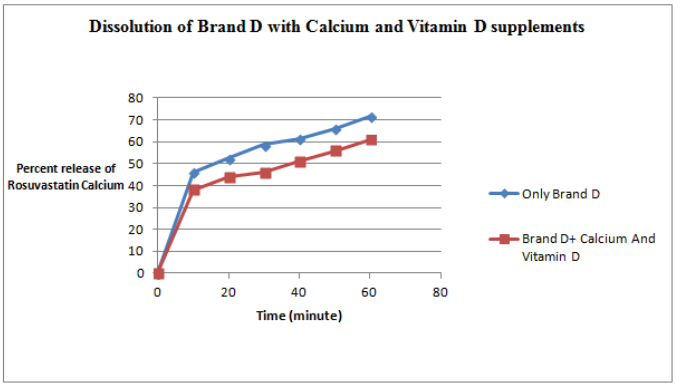

Figure 4: Percent of drug release of Rosuvastatin Calcium with time from Brand D with Calcium and Vitamin D supplements

Drug dissolution is the process by which active pharmaceutical ingredient get dissolved in the dissolution media. In other words, it can be said that dissolution is phase conversion process of API. There are a number of physiological and physicochemical factors, which can directly or indirectly alter dissolution pattern [20]. One of the approaches to improve drug dissolution is salt formation. Most of the drugs are weakly acidic or weakly basic. Therefore, many of them have poor aqueous solubility. To enhance their solubility salt formation is very helpful [21].

When Rosuvastatin Calcium tablet was examined with Calcium carbonate and vitamin D, the dissolution profile of Rosuvastatin Calcium was altered. In figure 1, 2, 3 and 4, impact of Calcium and Vitamin D supplements on drug dissolution rate of Rosuvastatin from Brand A, B, C and D are shown respectively. Brand A, after 60 minutes of dissolution test, the average percent of drug release was 71.13%. On the other hand, Brand A in the presence of Calcium and Vitamin D supplements showed 50.25% of drug release after 60 minutes of test. In case of Brand B, after 60 minutes of dissolution, it displayed 76.24% of drug release alone but upon testing with Calcium and Vitamin D supplements it showed 61.42% of drug release. In figure 3 and 4, we can see that after 60 minutes of dissolution test, alone Brand C and D provided 71.37% and 71.46% of drug release respectively but in the presence of Calcium and Vitamin D supplements they both gave 50.03% and 61.01% of drug release at 60 minutes of dissolution test. So it is clear that the dissolution rate or the drug release of Rosuvastatin Calcium decreases with time when it is experimented with calcium and vitamin D supplement and the impact of calcium and vitamin D supplement on dissolution of Rosuvastatin is increased with time. The incident of decrease of drug release may happen due to the common ion effect [22]. It is quite possible because the active drug rosuvastatin is formulated with calcium ion. Therefore, when it is administered with calcium supplement, the

common ion calcium may interfere with the drug release from the rosuvastatin calcium tablets. According to Le Hotelier's principle, if the concentration of any ion is increased in the solution then the equilibrium of the solution is shifted to the left to make a balance between free ion and bound ion. As a result the solubility of the salt is reduced. [23, 24]

In conclusion, it can be suggested that Rosuvastatin and Calcium and Vitamin D supplements should not be used concomitantly. There should be at least 2 hours time interval for administering these two drugs. [25]

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