Influence of Various Media on the Dissolution Profiles of Immediate-Release Quetiapine Tablets in India

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ABSTRACT

Dissolution testing was performed to evaluate the drug release from tablets. To mimic actual in vivo conditions, various foods and beverages were added to the dissolution media, and the release profiles were investigated. Indian people tend to have milk, curds, or eggs during their meals and then take their medications immediately after meals, whereas Americans tend to take medications with beverages. To evaluate drug release profiles in the presence and absence of these foods and beverages, in vitro dissolution testing was conducted using three different Indian quetiapine fumarate tablet brands. The effect on drug release was evaluated by adding 100 mL milk (3.1% protein), 100 g curd (4.1% protein), and 50 g raw and boiled egg white individually to 0.1 N HCl, and the release was compared with that in only 0.1 N HCl as per the Indian Pharmacopeia (IP) (1). The study was conducted for 3 h in triplicate, and the results show a significant difference among the brands in each medium with food. The maximum release obtained for each brand in 0.1 N HCl was 90%; in the presence of milk, curd, raw egg, and boiled egg it was approximately 7.06%, 2.42%, 29.56%, 24.08%, respectively, indicating that the drug was unavailable. Studies were also conducted with beverages and antacids; 200 mL of Thums Up, Sprite, and ENO were added individually to 0.1 N HCl and the release results compared. Results indicate a decrease of around 15% in availability in the presence of beverages and a 37% decrease in the presence of antacids. The results were statistically compared using one-way ANOVA at its Q value (45 min).

KEYWORDS: Quetiapine tablets; in vitro dissolution; milk; curd; egg; beverages; antacids.

INTRODUCTION

Quetiapine is classified as BCS Class 2 and is used to treat atypical antipsychotic conditions, schizophrenia, and bipolar disorders (*2*). Studies (*3*) for the effect of beverages on the in vitro disintegration of immediate-release (IR) pain medications show a hindrance in drug absorption; therefore, similar dissolution studies were carried out on quetiapine fumarate IR tablets to check the effect of food and beverages on drug release as the drug is reported to be highly protein bound in vivo.

Most drugs are taken orally, but it is difficult to understand how these drugs are absorbed from the gastrointestinal tract into the body. The effectiveness of dosage forms such as tablets and capsules depends on drug dissolution in the fluids of the gastrointestinal tract prior to absorption into the systemic circulation. The rate of dissolution of the tablet or capsule is therefore crucial.

One of the problems facing the pharmaceutical industry is the optimization of the amount of drug available to the body (i.e., bioavailability). Drug release in the human body can be measured in vivo by measuring the plasma or urine concentration in the subject. However, there are certain obvious impracticalities involved in employing such techniques on a routine basis. These difficulties have led to the introduction of official in vitro tests that are now rigorously and comprehensively defined in the respective pharmacopoeia.

Tablet dissolution is a standardized way of measuring the rate of drug release from a dosage form. The basic functions of the dissolution test are:

1. Optimize therapeutic effectiveness during product development and stability assessment stages.

2. Routinely monitor production quality to ensure uniformity among production lots.

3. Assess bioequivalence to show that products from distinct batches or from different plants have the same biological activity.

4. Aid in the prediction of bioavailability (*4*).

The main aim of the study was to check the effect of food proteins and beverages on the drug release profile of quetiapine fumarate tablet, so in vitro dissolution studies

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were performed. The problem with the compendial test media is that they do not accurately mimic the highly variable and dynamic environment of the human gut. Gastric conditions (i.e., condition in which the tablet is taken by the patient) were mimicked by the addition of 100 g of milk (3.1% protein), 100 g curd (4.1% protein), 50 g raw egg white, and 50 g boiled egg white to 0.1 N hydrochloric acid solution. In addition, the effect of drug release was checked in the presence of Thums Up (strongly carbonated drink), Sprite (mildly carbonated drink), and ENO (antacid effervescent granules). The selection of food was based upon the dietary habits of Indian and American people.

EXPERIMENTAL

Materials
Quetiapine fumarate 100-mg tablets of three different brands (A, Batch No. DR 3251; B, Batch No. CV30A004; and C, Batch No. BSN2933) were purchased in Mumbai, India. Quetiapine fumarate IP was obtained as a gift sample from Microlabs, Mumbai, India. Milk (3.1% protein) and curd (4.1% protein) containing 3% fat were obtained from Amul, Mumbai, India. Eggs were obtained from a poultry house in Mumbai, India. Thums Up and Sprite were purchased from Coca Cola, India. ENO (Regular) was obtained from GlaxoSmithKline Pharmaceuticals Limited, India.

Hydrochloric acid, sodium acetate, sodium chloride, and glacial acetic acid were all analytical reagent grade and were obtained from Research Lab, India.

Instruments
Apparatus 1 and 2 (Electrolab, model TDT-08L) were used for performing in vitro drug release studies. A pH meter (Lab India, Pico+ model) was used to measure pH. An Eppendorf Remi model RM-12 CBL centrifuge was used for centrifugation of samples. A UV–vis spectrophotometer (Lamda 25, Perkin Elmer) was used for the determination of drug released.

Dissolution Studies
Dissolution studies were conducted as per *IP* (*1*) using Apparatus 2 and 900 mL of 0.1 N HCl as the medium at 37 °C and 50 rpm. Readings were taken at predetermined intervals at 248 nm using a UV spectrophotometer in which the specific dissolution medium was used as a blank. The release profiles of the brands were compared statistically using one-way ANOVA. The dissolution profiles were calculated using linearity plots in individual media.

Sample Treatment
In the case of milk, curd, and egg media, sample treatment was required before taking the readings. The samples were placed in tubes and centrifuged at 12000 rpm at 4 °C for 15 min. After treatment, coagulation of milk and curd protein was observed at the top of the tube, and egg protein settled at the bottom. Thereafter, clear medium containing free drug was taken from each tube with the help of a syringe and transferred to the microcuvettes, and readings were taken at 248 nm. No interference was observed at 248 nm in the presence of food.

Dissolution Procedure Modification
The studies were modified for clear visibility of tablets in the presence of food. To determine whether or not tablet residue remained at the end of dissolution, the studies were conducted in Apparatus 1 at 100 rpm.

Medium Preparation
Various foods were added to 0.1 N HCl (pH 1.2) as specified above. Fed-state gastric simulated fluid (FeSSGF) was prepared as per FDA (*5*), and the pH was adjusted to 5.

Dissolution testing was performed in 0.1 N HCl with milk (pH 1.3), 0.1 N HCl with curd (pH 1.3), FeSSGF (pH 6.5), 0.1 N HCl with raw egg white (pH 1.3), and 0.1 N HCl with boiled egg white (pH 1.3). The drug release profiles of three different brands of quetiapine fumarate marketed tablets (100 mg) were investigated in triplicate using Apparatus 1 and 900 mL of medium at 37 °C and 100 rpm. Ten-milliliter samples were withdrawn at regular intervals for 3 h, and the volume was kept constant by replacement with an equal volume of fresh buffer/medium at 37 °C. Absorbances were measured at predetermined intervals by UV at 248 nm. The method was modified slightly for milk, curd, and FeSSGF by adding glacial acetic acid to precipitate casein.

Dissolution profiles for various media were calculated, and the available free drug was found by calculating *AUC* using the trapezoidal rule. One-way ANOVA at 45 min (*Q* value for 0.1 N HCl) (*1*) was applied to determine if there was a significant difference in the release among brands.

Dissolution in the Presence of Beverages and Antacids
For dissolution in the presence of beverages and antacids, 200 mL of each beverage (Thums Up, Sprite, and ENO) was added to 700 mL of 0.1 N HCl, and dissolution studies were performed as per *IP*.

RESULTS AND DISCUSSION

The release profile of drug quetiapine fumarate was analyzed using a UV spectrophotometer, and the absorbance was measured at 248 nm. The linearity plot gave an equation of $y = 0.044 x - 0.0201$, $R^2 = 1$. The dissolution profiles of the three brands in 0.1 N HCl using Apparatus 1 and 2 were the same. The release was >85% for all three brands, and all passed the *IP* criterion (NLT 70% in 45 min). The RSD values indicate that there was not much variation among the tablets of each specific brand. One-way ANOVA was applied, and at the *Q* point, there was no significant difference (p = 0.352) in the release among the brands. The *AUC* for all three brands was 100% in 0.1 N HCl. Furthermore, the drug release profiles drastically decreased when the dissolution studies were carried out with the addition of 100 mL of milk. The dissolution release was <8% for all three brands. There was much variation among the individual tablets of each brand; it can be correlated that the foaming caused by milk interferes in the disintegration of the tablets. The *AUC* values of Brands A, B, and C are 9.3%, 7.9%, and 14% available free drug, respectively. The release of drug at its *Q* value was compared using one-way ANOVA, and a significant difference (p = 0.000) was found. The dissolution studies were then carried out with the addition of 100 g curd. The drug release profile decreased more with curd than with milk. The dissolution release was <2.5% for all three brands. There was much variation among the individual tablets for each brand; it can be correlated that the foaming caused by milk interferes in the disintegration of the tablets. A comparison of the *AUC* values shows that the amount of available free drug for Brands A, B, and C was 6.5%, 4.5%, and 4.1%, respectively. The release of drug at its *Q* point was compared using one-way ANOVA, and there was a significant difference (p = 0.007). The dissolution studies were then performed in FeSSGF, and all the three brands did not disintegrate even after 1 h (Figure 1).

Brand A   Brand B   Brand C

Figure 1. Partially disintegrated tablets after 1 h.

There is a significant difference between the release profiles in the presence of milk and curd. First, Amul Taaza was the milk used for the study, and according to its label claim, each serving of 100 mL contains 3.1 g of protein and 150 mg of calcium (*6*). The curd used for the study was Amul Masti Dahi, and according to its label claim (*7*), each serving of 100 g contains 4.1 g of protein and 183 mg of calcium. The total fat content in both milk and curd was constant (i.e., 3 g).

The interaction between quetiapine fumarate and calcium has been reported (*8*), so in the presence of calcium, drug bioavailability will decrease because of complexation with calcium. Quetiapine fumarate is a dibenzothiazepine, and an in vitro milk–drug interaction study (*9*) using radiolabeled benzodiazepines proved that the major fraction of binding occurs with the casein protein. Therefore, in the presence of food (milk/curd), drug bioavailability is drastically decreased not only because of quetiapine–calcium complexation but also because the adsorption of quetiapine on the surface of protein (casein) decreases the amount of absorbable quetiapine present (*10*). Studies (*3*) have indicated that the presence of milk delays tablet disintegration time. Thus, the release results for tablets in the presence of curd are much less than those in milk because of the comparatively higher calcium and protein (casein) content in curd. When FeSSGF is considered, the buffer itself contains 50% milk, which completely prevents tablet disintegration even after 1 h, and the 0% release can be directly correlated.

The dissolution studies were then carried out with the addition of 50 g of egg white (equivalent to two eggs). Drug release profiles decreased less than those with milk. The dissolution release was <30% for all three brands; there was not much variation among the individual tablets for each brand. The *AUC* values for Brands A, B, and C showed 58.7%, 78.5%, and 68.7% available free drug, respectively. The release at the *Q* point was compared using one-way ANOVA, and there was a significant difference (p = 0.000). Furthermore, dissolution studies carried out with the addition of 50 g boiled egg white (equivalent to two eggs) showed drug release profiles almost similar to those with raw egg white. The dissolution release was <25% for all three brands. In addition, there was not much variation among individual tablets for each brand. The comparative *AUC* values for Brands A, B, and C showed 66%, 64.5%, and 68.9% available free drug, respectively. The release at the *Q* point using one-way ANOVA showed
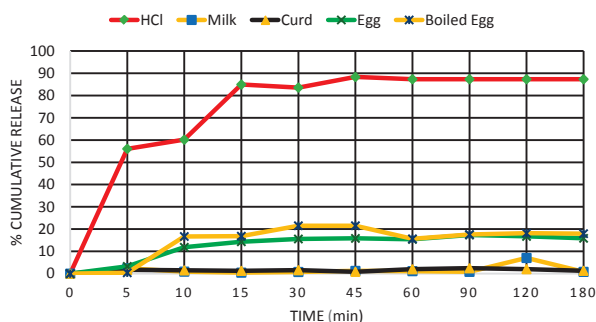
Figure 2. Comparative dissolution profiles of Brand A in various media.
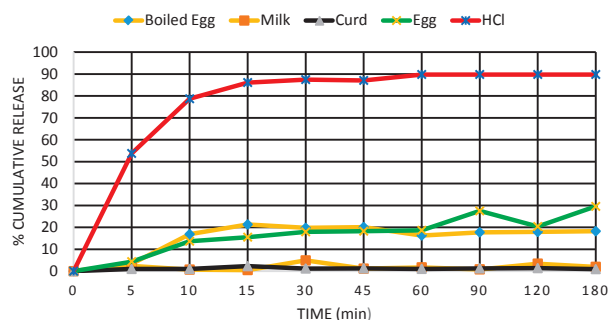

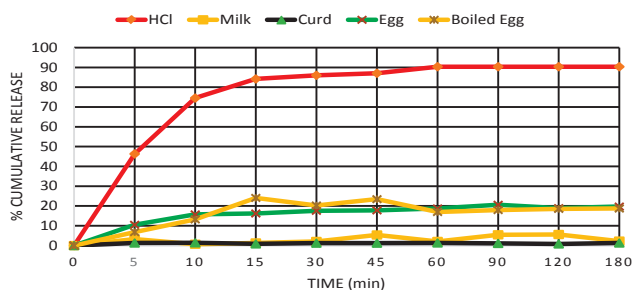Figure 3. Comparative dissolution profiles of Brand B in various media.

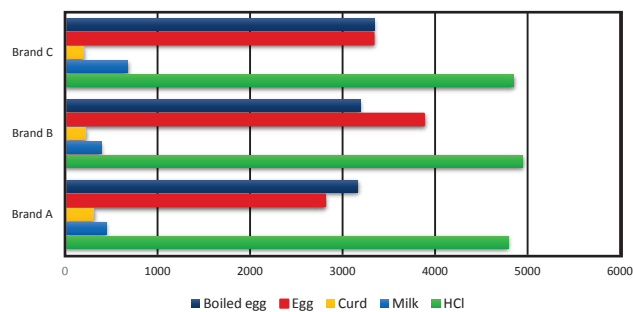Figure 4. Comparative dissolution profiles of Brand C in various media.

Figure 5. Comparison of AUC values for different brands in various media.

a significant difference (p = 0.005). The comparative graphs for the release profiles in various media for Brands A, B, and C are shown in Figures 2, 3, and 4, respectively. The comparative *AUC* values for various media are shown in Figure 5.

Quetiapine fumarate is reported to be 83% bound to plasma proteins (albumin) (*11*). Similar results were obtained using egg albumin in the dissolution medium. When an egg is boiled, proteins in the egg white undergo denaturation, which results in breaking of weak bonds between the proteins such that the proteins become uncoiled. The uncoiled proteins aggregate and form new chemical bonds. The results for boiled and raw egg white were similar; hence, the boiling of an egg does not affect the drug-interaction site. The protein (albumin) may cause quetiapine fumarate to adsorb on its surface. These results show that the interaction of quetiapine with food is very structure specific.

The dissolution studies were then carried out with the addition of 200 mL Thums Up and Sprite (equivalent to one bottle). The drug release profiles show a slower release when compared with only 0.1 N HCl. The dissolution release for all three brands was <85% in Thums Up and Sprite and <80% in ENO; there was not much variation

among individual tablets for each brand. The *AUC* values of Brands A, B, and C showed 87.8%, 92.4%, and 83.6% available free drug for Thums Up; 84.6%, 91.8%, and 89.4% for Sprite, and 87.3%, 78.9%, and 64.4% for ENO, respectively. The release values at the *Q* point were compared using one-way ANOVA, and there were no significant differences *(p* = 0.000) for Thums Up, Sprite, or ENO.

The presence of carbonated drinks causes variation in the disintegration behavior of tablets. In the presence of beverages and antacids, all three brands showed a delay in disintegration. Only Brand A passed the *Q* point in the presence of both beverages and antacids. Brands B and C failed to pass the *Q* point in the presence of antacids (ENO).

CONCLUSION
The drug release profiles were evaluated in the absence and presence of protein-rich food. Drug-binding is very specific and depends upon the type and amount of protein present. The in vitro studies show that quetiapine fumarate tablets should be avoided with milk, curd, and egg (raw or boiled). The presence of protein-rich food greatly decreases the release of drug, and beverages and antacids also affect the dose that needs to be delivered to the patient. In vivo studies should be conducted to

determine the IVIVC for similar conditions. If the IVIVC results are similar, then instructions should be included in the package insert to avoid protein-rich food and beverages (milk, curds, egg) as well as antacids so that the patient receives maximum drug availability.

ACKNOWLEDGMENT

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