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Development and validation of discriminating method of dissolution for fosamprenavir tablets based on in vivo data

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ABSTRACT

The aim of this work is to develop and validate a dissolution test for fosamprenavir tablets (Telzir®) based on in vivo data. The appropriate conditions were determined after testing sink conditions in dissolution medium, rotation speed and stability of the drug. In vivo release profiles were obtained from the literature. The fraction (and percentage) of dose absorbed (FA) was calculated by deconvolution, using the Wagner–Nelson method. For this formulation, the best dissolution conditions were achieved using a USP apparatus 1 900 ml of medium containing HCl 0.01 M at a rotation speed of 75 rpm. Under these conditions a significant linear relationship between fraction of drug absorbed versus dissolved was obtained (R^2 = 0.984) and a level-A IVIVC was established. The in vitro dissolution samples were analyzed using a HPLC method and the validation was performed according to USP protocol. The method showed accuracy, precision, linearity and specificity within the acceptable range. The discriminatory power of the dissolution method was challenged. The kinetics of dissolution was determined using model-dependent methods. The dissolution profiles were best described by the Hixson–Crowell model. The dissolution test was validated and could be applied to evaluate the dissolution profile of fosamprenavir tablets.

1. Introduction

One challenge that remains in Biopharmaceutics research is that of correlating in vitro drug-release profiles with the in vivo pharmacokinetic data [1]. The value of dissolution, as a quality control tool for predicting in vivo performance of a drug product, is significantly enhanced if an in vitro–in vivo relationship is established [2,3]. IVIVC has been defined as a predictive mathematical model describing the relationship between an in vitro property of a dosage form and an in vivo response [4]. The biological properties most commonly used are one or more pharmacokinetic parameters, such as c_{max}, t_{max} or AUC, obtained following the administration of the dosage form. The in vitro dissolution behavior of an active pharmaceutical ingredient from a dosage form under a given set of conditions expressed as percent of drug released is the most commonly used physicochemical property. The relationship between the two properties, biological and physicochemical, is expressed quantitatively [5–7].

Lack of a relationship between the dissolution test results and in vivo behavior would lead to inappropriate control of the critical production parameters by the test and also confound biopharmaceutical interpretation of the dissolution test results. Therefore, in vitro specification limits should be set according to an established relationship between in vivo and in vitro results, best reached through a well-designed IVIVC [1].

Fosamprenavir calcium (Fig. 1) is the phosphate ester prodrug of the human immunodeficiency virus (HIV) protease inhibitor amprenavir [8–10]. Fosamprenavir was first approved by the Food and Drug Administration (FDA) in 2003 [11] and then by the European Medicines Agency in 2004 [12]. It is presented either as coated tablets or as oral suspension [11] and it was developed to overcome adherence barriers with amprenavir formulation, such as pill size and burden, food and water restrictions. Fosamprenavir has poor membrane permeability and it is rapidly converted to amprenavir after oral administration. Dephosphorylation to amprenavir is mediated by intestinal alkaline phosphatase during gastrointestinal absorption [8–10]. According to the Biopharmaceutics Classification System (BCS), fosamprenavir is a class II [13]. Class II drugs are those with low solubilities and high permeabilities. Correlation between in vivo results and dissolution tests is likely to be best for class II drugs because, in their case, the dissolution rate is the primary limiting aspect to absorption [5].

FDA has published the dissolution conditions for fosamprenavir calcium. The proposed method consists of apparatus 2, at 75 rpm, and 250 mM sodium acetate/acetic acid buffer pH 3.5 as dissolution medium [14].

In this context, the objective of this study was to develop and validate a dissolution test for fosamprenavir (Telzir®) tablets based on IVIVC. The in vivo data was obtained from the literature [9,15]. The discriminatory power of the dissolution method was challenged.

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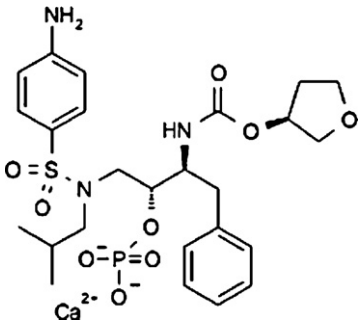

Fig. 1. Fosamprenavir calcium.

The kinetics of dissolution was determined using model-dependent approaches.

2. Materials and methods

2.1. Materials

A fosamprenavir calcium working standard was prepared in our laboratory from raw material, which was purified and characterized using NMR and IR. The Telzir® 700 mg tablets (batch no. R371748) were purchased from the market. The excipients contained in the dosage form (colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone K30, hypromellose, iron oxide red, titanium dioxide, and triacetin) were all of pharmaceutical grade and acquired from different distributors. HPLC grade acetonitrile was obtained from Tedia (Fairfield, USA). Sodium acetate was of analytical grade. Ultra-pure water (Millipore®, Milfor, MA, USA) was used for the dissolution medium and throughout the analysis.

2.2. In vivo study

The average plasma concentration versus time curve was fitted with a non-linear software (Micromath Scientist®, v.2.01) using a one-compartment open model, according to Eq. (1), and the resulting curve and parameters were used to estimate intermediate plasma concentration data points:

$$C = \frac{F \cdot D \cdot K_a}{V_d \cdot (k_a - k_e)} \cdot (e^{-k_e \cdot t} - e^{-k_a \cdot t}) \quad (1)$$

where C is the plasma concentration at time t; k_e is the elimination rate constant; k_a is the absorption rate constant; V_d is the volume of distribution; D is the dose and F is the fraction of the dose absorbed. The percentage of drug absorbed (FA) versus time was calculated using the Wagner–Nelson method [16].

2.3. In vitro study

2.3.1. Dissolution test conditions

The development and validation of the dissolution test was performed using a VANKEL® VK 8000 dissolution auto-sampling station consisting of a VK type bidirectional peristaltic pump, VK 750D digitally controlled heater/circulator, VK 7010 multi-bath dissolution testing station ($n = 8$) with automated sampling manifold.

Dissolution was performed using 900 ml of dissolution medium pre-heated at 37 ± 0.5 °C. Influence of rotation speed, filters, dissolution medium and different apparatus (USP basket and paddle) were evaluated. Sample aliquots were withdrawn at 5, 15, 20, 30, 40, 50 and 60 min and replaced with an equal volume of fresh medium to maintain a constant total volume. An auto sampler was used to withdraw aliquots through a 0.45 μm filter. All the dissolution samples were analyzed by HPLC.

2.3.2. HPLC analysis

The HPLC system consisted of a Shimadzu LC model (Kyoto, Japan) composed of a LC-10AD pump, a SPD-M10ADVP photodiode array (PDA) detector, a SLA-10ADVP system controller, a DGU-14A degasser, a column thermostat oven CTO-10AS and an autoinjector SIL-10AD. Data were acquired and processed using CLASS-VP software (version 6.1). Chromatographic analysis was carried out using a Vertical RP-18 column (150 mm × 4.6 mm i.d., particle size 5 μm), with a Phenomenex® Universal C_{18} guard column. The mobile phase consisted of a mixture of sodium acetate buffer:acetonitrile (75:25, v/v). The flow rate was 1.2 ml min^{-1} and the injection volume was 20 μl. The detection of fosamprenavir was carried out by ultraviolet absorption at 264 nm and all assays were performed at room temperature conditions. A Thornton T50 ultrasonic bath (Metler-Toledo, Bedford, MA) was used for deaeration.

2.3.3. Solubility

Fosamprenavir *sink* conditions were determined in different media. The solubility of the drug was tested using an amount of fosamprenavir equivalent to three times the dose in the pharmaceutical formulation in 900 ml of medium. HCl 0.1 M, HCl 0.01 M, phosphate buffer pH 6.0 and acetate buffer pH 4.5 were tested. Vessels ($n = 3$) containing 250 ml of medium were pre-heated to 37 °C ± 0.5 before adding one tablet of Telzir® (700 mg). The samples were gently rotated. An aliquot (10 ml) was removed from each vessel after 1 and 2 h and filtered. 1 ml of the filtered aliquots were pipetted into 50 ml volumetric flask, neutralized, diluted with mobile phase and injected into the HPLC. The solubility in each medium was determined in triplicate.

2.3.4. In vitro–in vivo correlation

An IVIVC for fosamprenavir was evaluated by plotting the mean percentage of drug absorbed (FA) versus the mean percentage of drug dissolved (FD). Linear regression analysis was used to evaluate the data.

2.4. Validation of the dissolution procedure

The in vitro dissolution method developed was validated according to current guidelines [2,17,18]. Specificity, linearity, accuracy and precision were evaluated. The chromatographic parameters monitored were peak retention time, capacity factor, tailing factor and theoretical plate number.

2.4.1. Specificity

Specificity was evaluated by preparing samples of placebo. The placebo consisted of all the excipients (colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and povidone K30, hypromellose, iron oxide red, titanium dioxide, and triacetin). The estimated concentrations in pharmaceutical formulation (Telzir®) were based on the literature data [19] and calculated for a medium weight of content (~1.165 mg) for the tablets. The samples of the placebo were transferred to separate vessels ($n = 3$), filled with 900 ml of dissolution medium at 37 ± 0.5 °C and stirred for 1 h at 150 rpm using basket (USP apparatus 1). Aliquots were withdrawn and analyzed by HPLC.

2.4.2. Linearity

A stock solution containing 200 μg/ml of fosamprenavir was prepared in methanol. The linearity of the method was evaluated in the 5.0–90.0 μg/ml range using stock solution and dissolution medium. The solutions were injected in triplicate every day, for

Table 1
Mathematical models used.

Zero order kinetics	$Q_t = Q_0 + K_0 t$
First order kinetics	$\log Q_t = \log Q_0 + (K_1 t)/2.303$
Higuchi model	$f_t = K_H t^{1/2}$
Hixson–Crowell model	$W_0^{1/3} - W_t^{1/3} = K_s t$

Q_t, amount of drug dissolved in time t; Q_0, initial amount of drug in the solution; K_0 and K_1, zero order and first order release constants, respectively; f_t, amount of drug released in time t by surface unity; K_H, Higuchi dissolution constant; W_0, initial amount of drug in the pharmaceutical dosage form; W_t, remaining amount of drug in the pharmaceutical dosage form at time t; K_s, a constant incorporating the surface–volume relation.

three consecutive days. The mean peak area versus concentration data was treated by least-squares linear regression analysis.

2.4.3. Accuracy/precision

Accuracy was accomplished by adding known amounts of fosamprenavir reference substance to placebo. Aliquots of 2.7, 4.5 and 6.3 ml of a 10 mg/ml fosamprenavir standard solution dissolved in methanol were added to vessels containing dissolution medium for a final volume of 900 ml (final concentrations were 10.0 μg/ml, 30.0 μg/ml and 50.0 μg/ml, respectively), pre-heated at 37 °C and rotated for 1 h at 150 rpm. Aliquots were withdrawn and analyzed by HPLC. These studies were performed on three different days and the recovery of the added drug substance ($n = 9$) was determined. Placebo samples were prepared in the same way described in the specificity test.

The same solutions used in the accuracy test were analyzed in order to assess the precision of the method. Intra- and inter-day precision was established based on R.S.D. of the results.

2.4.4. Stability studies

Stability of fosamprenavir in the dissolution medium was evaluated using standard and sample. The solutions were kept at 37 ± 0.5 °C for 1 h under light shaking, and were then left at room temperature for 24 h. The sample solution was stored in a glass test tube wrapped securely in paraffin. Aliquots of the samples were tested at time 0, and after 1 and 24 h. The responses for the aged solutions were evaluated using a freshly prepared standard. The assay was performed in triplicate.

2.5. Evaluation of release kinetic

Four mathematical models were applied to evaluate the kinetics of drug release: zero order, first order, Higuchi and Hixon–Crowell, whose equations are shown in Table 1. The curves were constructed applying the kinetic models cited, considering only one point above 80% of the drug released. The mathematical model that best expressed the dissolution profile of fosamprenavir tablets was selected based on the coefficient of determination (R^2) [17,20]. The suitability of models to experimental data was evaluated using the software Scientist™ (Micromath, EUA), based on the model selection criteria (MSC).

2.6. Discriminating power of the test

The discriminatory power of the proposed dissolution test was challenged. Changes in the biopharmaceutical performance of fosamprenavir tablets caused by aging (validity time expired) and temperature storage and humidity (40 °C and 76% RH for 2 and 4 weeks) were evaluated.

2.6.1. Evaluation of dissolution profiles

The dissolution profiles obtained were compared using model-independent method, in which the two profiles were compared only at the observed time points [21]. The model-independent approach includes the difference factor (f_1) and the similarity factor (f_2).

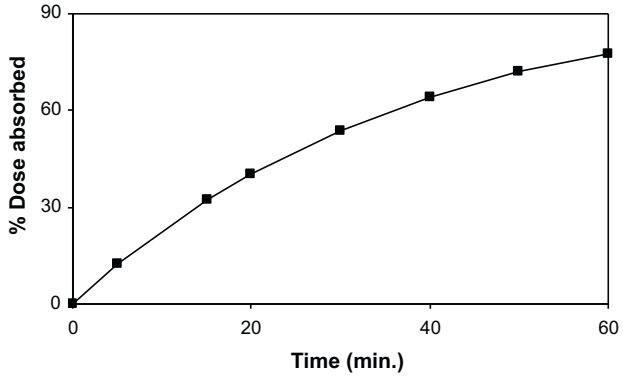

Fig. 2. Percentage of dose absorbed vs. time curve for fosamprenavir tablets using Wagner–Nelson method.

The f_1 factor measures the percent error between two curves over all time points (Eq. (2)):

$$f_1 = \left\{ \frac{\left[\sum_{t=1}^{n} |R_t - T_t|\right]}{\left[\sum_{t=1}^{n} R_t\right]} \right\} \times 100 \quad (2)$$

where n is the number of time points, R_t and T_t are the percent dissolved of the reference and test product, respectively, at each time point. The percent of error is zero when the test and drug reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles [22].

The f_2 factor is a logarithmic transformation of the sum-squared error of differences between the test and the reference products over all time points (Eq. (3)):

$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n}\right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (3)$$

This factor is 100 when the test and reference profiles are identical and moves toward 0 as the similarity decreases [22]. According to the FDA, two dissolution profiles are declared similar if f_1 is between 0 and 15 and if f_2 is between 50 and 100 [3].

3. Results and discussion

3.1. In vivo study

The pharmacokinetic data used to develop the IVIVC was obtained from the literature [9,14]. Based on these results, the plasma concentration versus time profile curve was transformed into percentage of drug absorbed versus time, using the Wagner–Nelson method (Fig. 2). According to the FDA [3], model-dependent techniques such as the Wagner–Nelson and Loo–Riegelman method or model-independent numerical deconvolution are utilized to calculate absorption profiles. Wagner–Nelson and Loo–Riegelman methods are both dependent, the former being used for as a one-compartment model and the latter for two-compartment systems [23]. Considering that the best fit for the in vivo data was obtained using an open one-compartment body model equation, the Wagner–Nelson method was used to obtain the fraction of dose absorbed.

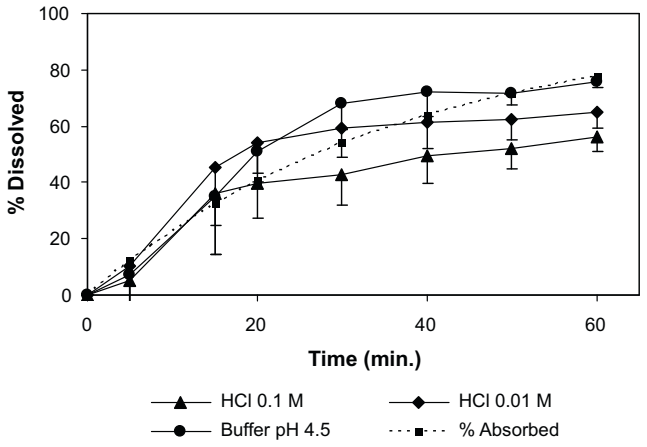

Fig. 3. Mean dissolution profiles of Telzir® tablets ($n = 12$) using 0.1 and 0.01 M HCl, acetate buffer pH 4.5 and percentage dissolved, and apparatus 2 rotating at 50 rpm.

3.2. Solubility determination

The solubility test showed that fosamprenavir was soluble in 0.01 and 0.1 M HCl and acetate buffer, pH 4.5. The solubility in water was not tested, since it is not an ideal dissolution medium [2,17]. According to Furfine and collaborators, solubility of fosamprenavir calcium is strongly pH dependent, being very low at pH 7 (0.3 mg/ml) as compared with peak solubility between pH 3 and 4 (54 mg/ml at pH 3.3) [10]. Thus, the solubility data obtained were used as the basis for the selection of dissolution medium for fosamprenavir tablets and also ensured *sink* conditions. The term *sink* conditions is defined as the volume of medium at least greater than three times that required to form a saturated solution of a drug substance [2,17].

3.3. Development of the dissolution test

Test conditions were selected based on a screening study with USP apparatus 1 (75 rpm, baskets) and USP apparatus 2 (50/75 rpm, paddles). The tablets were tested in 900 ml of 0.01 and 0.1 M HCl and acetate buffer pH 4.5. Dissolution aliquots were analyzed at several time points (5, 15, 30, 40, 50 and 60 min) to generate dissolution profiles in each medium. Each experiment was performed with 12 tablets.

3.3.1. Dissolution profile of fosamprenavir-paddle (USP apparatus 2)

Dissolution using a paddle at 50 and 75 rpm was evaluated. At 50 rpm (Fig. 3), the dissolution rate was similar in all media tested only at initial times (20 min). After 20 min the dissolution rate using HCl 0.1 M was smaller than the absorption rate. The profiles obtained using HCl 0.01 M and buffer acetate were more similar when compared to the absorption rate and a correlation was established using buffer acetate ($R^2 = 0.95$). Using 75 rpm (Fig. 4), the in vitro dissolution profiles were similar to the in vivo dissolution profile using buffer acetate and HCl 0.01 M ($R^2 = 0.96$ and 0.98, respectively). In HCl 0.1 M, fosamprenavir tablets showed a faster dissolution rate.

Under these conditions, the results were highly variable. The R.S.D. was above 20% at the first time points (10 min) and above 10% R.S.D. at later time points. This was attributed to uneven distribution of particles throughout the vessel since the film-coated tablets stuck to the vessel. The use of sinkers was evaluated but was not shown to be useful to solve this problem. Due to these results, other types of equipment were evaluated. Similar situation was observed using FDAís recommended conditions [14].

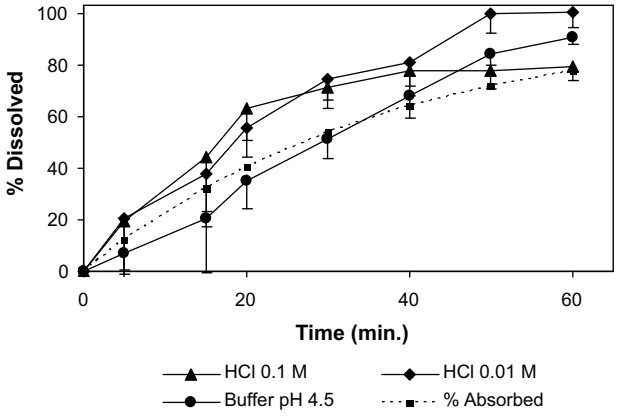

Fig. 4. Mean dissolution profiles of Telzir® tablets ($n = 12$) using 0.1 and 0.01 M HCl, acetate buffer pH 4.5 and percentage dissolved, and apparatus 2 rotating at 75 rpm.

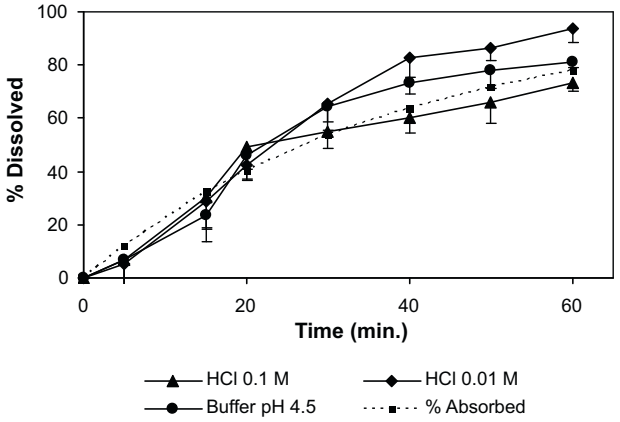

Fig. 5. Mean dissolution profiles of Telzir® tablets ($n = 12$) using 0.1 and 0.01 M HCl, acetate buffer pH 4.5 and percentage dissolved, and apparatus 1 rotating at 75 rpm.

3.3.2. Dissolution profile of fosamprenavir-basket (USP apparatus 1)

In these studies, a basket was evaluated (Fig. 5). The results demonstrated that the in vitro dissolution profile was similar to the in vivo dissolution profile in the three media tested and a good correlation was obtained (Table 2). 0.01 M HCl demonstrated the best correlation (level-A) with the in vivo data (Fig. 6). The level-A correlation was linear and represents a point-to-point relationship between in vitro dissolution and the in vivo dissolution rate [6].

The choice of medium will depend on the purpose of the dissolution test. For batch-to-batch quality testing, selection of the dissolution medium is based, in part, on the solubility data and the dose range of the drug product to ensure sink conditions. On the other hand, when the dissolution test is used to indicate the biopharmaceutical properties of the dosage form, it is more important that the proposed biorelevant test closely simulate the environment in the gastrointestinal (GI) tract than necessarily produce sink conditions [2,16,23]. Thus, 0.01 M HCl was chosen as the dissolu-

Table 2
Regression analysis[a] for the IVIVC.

Medium dissolution	Slope (m)	Intercept (b)	Coefficient of determination (R^2)
HCl 0.1 M	1.01	1.1062	0.970
HCl 0.01 M	0.75	5.8912	0.984
Buffer acetate pH 4.5	0.84	4.6475	0.973

[a] $y = m \cdot x + b$.

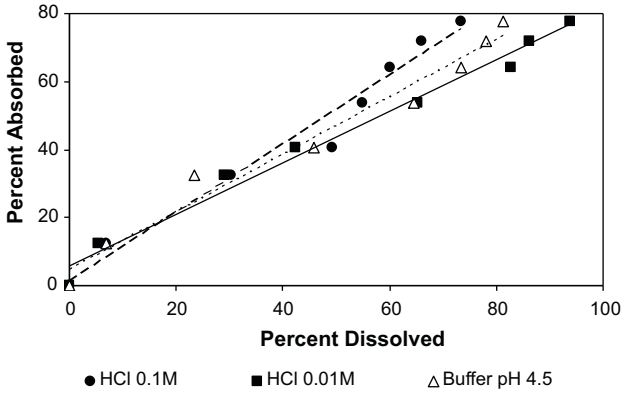

Fig. 6. Plot of mean percentage of dose absorbed versus mean percentage of dose dissolved for Telzir®. The line of best fit is shown for each dissolution medium.

tion medium since it is considered to be biorelevant and the best correlation was obtained using basket at 75 rpm ($R^2 = 0.984$).

The drug dissolution results were reproducible. The R.S.D. was lower than 20% at the first time point (10 min) and lower than 10% R.S.D. at later time points.

3.4. Validation of dissolution method

3.4.1. Specificity

No chromatographic peak from the placebo formulation was observed with the same retention time as fosamprenavir (Fig. 7). The purities of peak were higher than 0.999 and were obtained using a PDA detector. According to the Pharmacopeial Forum and USP 32 [2,17], the lack of chromatographic peaks from the placebo formulation demonstrates the specificity of the method.

3.4.2. Linearity

The recommended range for the calibration curve is from ±20% below the lowest expected concentration to ±20% above the highest expected concentration of the dissolution test [2,17]. The method showed good linearity at concentrations ranging from 5.0 to 90.0 μg/ml. The correlation coefficient was 0.9998. The slope and intercept obtained was 28623 and −12749. The analysis by ANOVA showed significant linear regression and no significant deviation from linearity ($p < 0.05$). These data indicate that the method is linear for fosamprenavir.

Table 3
Precision of the dissolution method.

Concentration (μg/ml)		Precision	
		R.S.D. intra-day	R.S.D. inter-day
Day 1	10.0	1.00	1.18
Day 2	10.0	0.67	
Day 3	10.0	0.65	
Day 1	30.0	1.48	1.39
Day 2	30.0	0.35	
Day 3	30.0	1.74	
Day 1	50.0	0.35	1.73
Day 3	50.0	1.68	
Day 3	50.0	1.40	

3.4.3. Accuracy/precision

The accuracy was demonstrated by the recovery of known amounts of fosamprenavir in the dissolution vessels. Percentage recoveries from 95.0% to 105.0% are recommended for the accuracy test [2,17]. In the accuracy test three concentrations were evaluated (10, 30 and 50 μg/ml) and mean recoveries were 100.8 ± 1.18, 100.4 ± 1.38 and 100.5 ± 1.73%, respectively, corroborating the accuracy of the method.

Repeatability was determined by triplicate injection of standard solutions (10.0 μg/ml, 30.0 μg/ml and 50.0 μg/ml) and the intermediate precision was evaluated for 3 days. The low R.S.D. values obtained for repeatability and intermediate precision show the good precision of the method (Table 3).

3.4.4. Standard and sample solution stability

Fosamprenavir was found to be stable under dissolution test conditions. There was no evidence of degradation of fosamprenavir under these conditions. The results demonstrate that sample and standard solutions remained at 100.0 ± 2.0% over a period of 24 h.

3.5. Evaluation of release kinetic

The dissolution profile (Fig. 4) was used to evaluate the kinetics of drug release. The determination coefficient (R^2) and model selection criteria (MSC) are presented in Table 4. According to the R^2 and MSC, dissolution profiles were better described by the Hixson–Crowell model (Table 4). When this model is used, it is assumed that the release rate is limited by the drug particle dis-

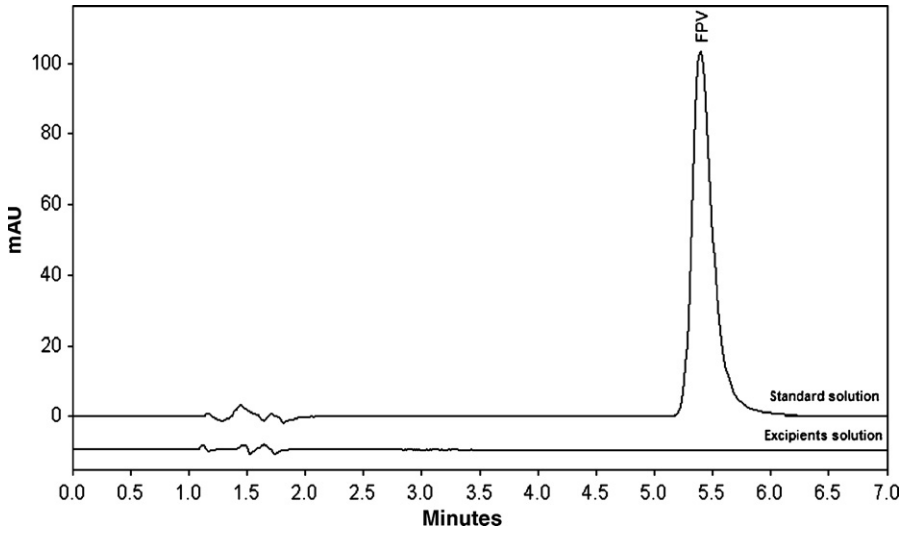

Fig. 7. The specificity of the method show peak of fosamprenavir (FPV) and excipients solution in dissolution medium.

Table 4
Coefficient of determination (R^2) and model selection criteria (MSC) the mathematical models.

Mathematical models	R^2	MSC
Zero order kinetics	0.9619	3.22
First order kinetics	0.9762	2.75
Higuchi model	0.8897	1.87
Hixson–Crowell model	0.9833	3.35

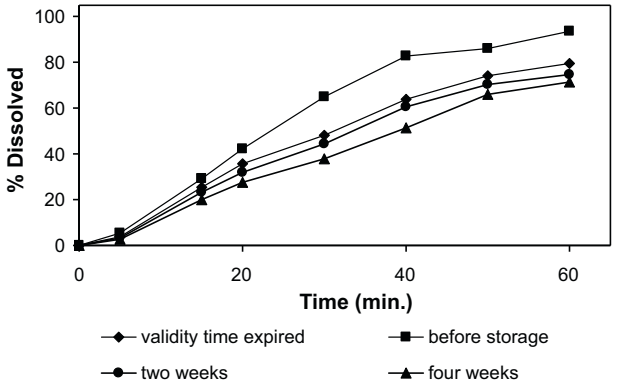

Fig. 8. Changes in the dissolution rate of fosamprenavir tablets after storage and date expired.

Table 5
Comparison of tablets dissolution profiles through difference factor (f_1) and the similarity factor (f_2).

Parameter	Validity time expired	After 2 weeks	After 4 weeks
f_1	19.21	24.84	33.65
f_2	46.31	41.34	34.79

solution rate and not by diffusion that might occur through the polymeric matrix [20].

3.6. Discriminating power of the test

The discriminating power of the dissolution method is the method's ability to detect changes in the drug product [2,17,24]. If significant changes in the drug dissolution characteristics are observed over long-term storage of the dosage form, this would indicate that functional changes are occurring in the drug product, and may compromise its performance in vivo [25]. Thus, the dissolution method developed was challenged. The pharmaceutical dosage forms exhibited a decrease in dissolution rate after storage at 40 °C and 75% RH for 2 and 4 weeks, as well as for the tablets past their expiration date, as shown in Fig. 8.

The dissolution profiles obtained were compared using the difference factor (f_1) and similarity factor (f_2). The results confirmed that the profiles obtained are not similar (Table 5).

4. Conclusions

A level-A in vitro–in vivo correlation was established for fosamprenavir tablets (Telzir®). The in vitro dissolution profile for fosamprenavir was obtained using 900 ml of dissolution medium containing 0.01 M HCl, USP apparatus 1 at 75 rpm and 37 ± 0.5 °C. Kinetics of drug release was best described by the Hixson–Crowell model. The validation results demonstrate that the in vitro dissolution method was accurate, precise, linear and specific. Both the HPLC analytical method and in vitro dissolution test were validated and can be used to evaluate the release profile of fosamprenavir tables.

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