

# Establishment of a Bioequivalence-Indicating Dissolution Specification for Candesartan Cilexetil Tablets Using a Convolution Model

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## ABSTRACT

The aim of the present work was to establish a bioequivalence-indicating dissolution specification for candesartan cilexetil tablets. The discriminating power of the selected medium (0.25% Polysorbate 20 in pH 6.5 phosphate buffer) was assessed relative to that of 0.35% Polysorbate 20 in pH 6.5 phosphate buffer, a medium recommended by the U.S. FDA. Plasma concentration–time profiles of candesartan cilexetil tablets were derived from in vitro dissolution data by a convolution model. In solubility studies, 0.25% Polysorbate 20 in pH 6.5 phosphate buffer provided sink conditions for candesartan cilexetil 16-mg tablets. The method was more sensitive to the concentration of Polysorbate 20 than to paddle rotation speed and was able to distinguish depressed dissolution of mismanufactured tablets in samples taken at 20- and 30-min intervals. Verification of the model performed on innovator samples revealed the closeness of the predicted  $C_{max}$  and  $AUC_{0-\alpha}$  values to the reported values. A two-point dissolution specification is proposed for post-approval changes, and a one-point dissolution specification for quality control release of production batches.

**KEYWORDS:** IVIVC; convolution model; pharmacokinetics; dissolution.

## INTRODUCTION

The dissolution rate of a drug provides a suitable indication of product quality during formulation development and shelf life. Water-insoluble drugs like candesartan cilexetil offer challenges in the development of a discriminatory dissolution medium. The addition of surfactants is a common practice to obtain sink conditions by facilitating the drug release process at the solid–liquid interface and micelle solubilization in the bulk (1, 2). However, when used in a concentration higher than the critical micelle concentration, they may negatively affect the dissolution rate by reducing the diffusion rate of the drug and may interfere with disintegration time (3–6).

The agitation speed of the basket or paddle also assumes importance in the uniform distribution of drug throughout the dissolution medium. The recommended agitation speeds for basket assemblies are 50 and 100 rpm, whereas paddle apparatus are run at 50 and 75 rpm (7). Quite often, mild dissolution conditions provide more discriminatory power than higher agitation speeds. However mild agitation speeds may result in coning due to poor hydrodynamics in the dissolution vessel, and in such cases, higher agitation speeds may provide superior

discrimination by reducing variability (7).

In vitro–in vivo correlation (IVIVC) is an invaluable tool in pharmaceutical development in improving product quality and decreasing development costs by reducing product development time and the number of clinical pharmacokinetics studies required (8). Certain scale-up and post-approval changes can be implemented without performing bioequivalence studies because IVIVC serves as a surrogate for in vivo bioavailability studies (8).

Candesartan cilexetil is a selective AT1 subtype angiotensin receptor antagonist used for the management of hypertension (9). It has poor water solubility and high permeability and belongs to Class 2 of the Biopharmaceutics Classification System (BCS) (10). Candesartan cilexetil undergoes hydrolysis at the ester link after oral administration to form the active drug, candesartan. It has an elimination half life of 5–9 h and absolute bioavailability of approximately 15%. The peak serum concentration is reached 3–4 h after ingestion (10, 11). After single and repeated administration, the pharmacokinetics of candesartan is linear for oral doses up to 32 mg of candesartan cilexetil (10, 12).

The purpose of the present work was to establish bioequivalence-indicating dissolution specifications for

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candesartan cilexetil 16-mg tablets. Dissolution media were chosen to increase the probability of passing bioequivalence in latter product development stages (13). Such a specification will provide a useful insight of product performance during product development, and after validation, will facilitate implementation of post-approval changes without the necessity of performing bioequivalence studies. Currently, lower strengths of a product qualify for biowaiver based on (1) linear elimination kinetics over the therapeutic dose range, (2) the strengths being proportionally similar, and (3) the same dissolution behavior when tested by the same dissolution procedure (14, 15). The proposed model can be used to predict the pharmacokinetic profile of candesartan cilexetil 16-mg tablets. Together with the above three biowaiver qualification parameters, the predicted plasma concentration profile can strengthen the case for a biowaiver for Class 2 drugs. However, this approach is suitable during initial product development stages when there is no or little pharmacokinetic data available. Subsequent bioequivalence studies performed at latter stages of product development can further validate the model.

The deconvolution technique is the most commonly used method for IVIVC. However, the mathematical models used for this purpose are not unbiased in evaluating in vivo dissolution results, and often this approach requires multiple products with different in vivo release characteristics to define dissolution conditions having sufficient discriminatory power (15). Further, although blood concentration data of the drug will be available at some point, it may not be available during the product development stage.

The convolution technique is simple and provides a very good platform to develop bioequivalent formulations during the product development stage. Based on the superposition principle, convolution is a model-independent method for computing in vivo absorption and modeling in vitro–in vivo data. The in vivo pharmacokinetic parameters are predicted by using drug release profiles as input functions and pharmacokinetic parameters of reference formulation as a weighted function.

During the product development stage, dissolution serves as a vital indicator of in vivo performance. Shargel et al. (16) used a linear regression convolution technique to compare actual observed blood levels in humans against the predicted blood levels. However, their model assumed similarity of in vitro and in vivo variability. In vivo systems are generally more variable, and hence to overcome this, it was suggested (17) to use normalized parameters  $C_{max}$  (maximum plasma drug concentration) and  $AUC$  (area under the plasma concentration-versus-time curve).

## MATERIALS AND METHODS

Candesartan drug substance, tablets, and working standard were gifted by Blue Nile Pharmaceutical Factory,

Sudan. Polysorbate 20 of analytical grade was purchased from SD Fine Chemicals Limited, India. All other reagents and chemicals were of analytical grade and were used as received. The different brands of candesartan cilexetil 16-mg tablets used in this study were products A, B, and C (candesartan 16-mg, Blue Nile Pharmaceutical Factory, batch No. 2CAA; 2CAA2, 2CAAJ01, respectively), product D (candesartan 16-mg, Blopress batch No. 856236, Hikma Pharma, Jordan), and product E (Atacand 16-mg, AstraZeneca, UK, batch No. NB8547, innovator tablets). The tablets were evaluated for quality control tests (weight and content uniformity), stored as indicated on the product labels, and used prior to their expiry dates.

### Preparation of Stock Solutions and Calibration Curve

The solvent mixture used was 0.35% Polysorbate 20 in pH 6.5 phosphate buffer. Candesartan cilexetil (100 mg) was accurately weighed into a 100-mL volumetric flask, and 10 mL of methanol was added. This was sonicated for 10 min and brought to volume with the corresponding buffer medium. The standard solution was sonicated for 5 min, and 10 mL of this solution was further diluted to 100 mL with the same medium.

Six aliquots of candesartan cilexetil solutions prepared from the above stock solution were taken in triplicate into 100-mL volumetric flasks in such amounts as to obtain final concentrations of 5.0, 10.0, 20.0, 30.0, and 40.0  $\mu\text{g}/\text{mL}$  and brought to volume with the solvent mixture. First-derivative absorbance values at 270.1 nm (ID270.1) were measured (Shimadzu 1800 series, Japan). The peak-to-zero method for calibration curve in the first-derivative UV spectrophotometric method was used (18).

### Solubility Studies

The saturation solubility of candesartan cilexetil was determined in 0.1 N HCl (hydrochloric acid), pH 4.5 acetate buffer, pH 6.5 phosphate buffer, 0.25% Polysorbate 20 in pH 6.5 phosphate buffer, 0.35% Polysorbate 20 in pH 6.5 phosphate buffer, 0.45% Polysorbate 20 in pH 6.5 phosphate buffer, 0.55% Polysorbate 20 in pH 6.5 phosphate buffer, and 0.7% Polysorbate 20 in pH 6.5 phosphate buffer.

An excess quantity of the drug (100 mg candesartan cilexetil) was weighed and added separately to 100 mL of the above-mentioned media in conical flasks. The mixtures were shaken for 48 h in a mechanical shaker at  $37 \pm 1$  °C. The solutions were then filtered through 0.2- $\mu\text{m}$  Whatmann filters, and ID270.1 values were measured by UV spectrophotometry (18). The studies were repeated three times, and mean data were recorded.

### Dissolution Studies

The dissolution study was performed using USP Apparatus 2 at  $37 \pm 0.5$  °C with paddle speeds of  $50 \pm 2$  rpm and  $75 \pm 2$  rpm in 900 mL dissolution medium. The dissolution medium recommended by FDA for candesartan 16-mg tablets is 0.35% polysorbate in pH 6.5 phosphate

buffer (19). Aliquots of 10 mL dissolution medium were taken at different time intervals and filtered through 0.45- $\mu\text{m}$  membrane filter.  $\text{ID}_{270.1}$  values were recorded, and the percentage drug release was calculated from the standard curve prepared as mentioned above. Withdrawn samples were replaced with 10 mL of fresh dissolution medium to maintain sink conditions and constant dissolution medium volume.

### Establishment of Dissolution Specifications Using Convolution Model

The drug plasma concentration–time profile was derived from the in vitro dissolution profile by a convolution model proposed by Qureshi (17). The data were analyzed using Microsoft Excel software. The dissolution profiles of the tablets were recorded. The amount released within a sample interval was calculated by the formula

$$(\% \text{ drug released} \times \text{product strength} / 100)$$

The observed amount of drug in the blood was calculated by multiplying the amount by the bioavailability of the drug. Finally, the concentration of drug in blood was calculated by using the formula (17)

$$\text{Concentration} = \frac{\text{amount} \times \text{bioavailability} \times 1000}{\text{volume of distribution of drug} \times \text{body weight}}$$

The volume of distribution, bioavailability, and elimination half-life of candesartan cilexetil are 0.13 L/kg, 0.14, and 4–9 h, respectively (20–22). The elimination rate constant is  $0.693/t_{1/2}$ . The model was verified by comparing the reported  $C_{\text{max}}$  and  $AUC_{0-\alpha}$  with predicted values, which were derived from the dissolution profile results of Atacand tablets.

### Data Analysis

Dissolution profiles were compared by the Student's *t*-test. To compare the significance of the difference in dissolution rates between the means of two groups, the Student's *t*-test was performed on the entire dissolution profile in all the cases. The in vitro dissolution data were analyzed by the estimation of the similarity factor ( $f_2$ ). Dissolution profile comparisons are performed using model-independent or model-dependent methods. In a model-independent method,  $f_1$  and  $f_2$  values are used to compare dissolution profiles. The  $f_1$  value represents the percentage difference between the two curves at each time point and is a measurement of the relative error between the two curves. The  $f_2$  value is a measurement of the similarity in the percentage dissolution between the two curves and is a logarithmic reciprocal square-root transformation of the sum-of-squared error.

The area under the curve from administration to time *t* ( $AUC_{0-t}$ ) was calculated by the linear trapezoidal rule. The area under the curve extrapolated to infinity ( $AUC_{0-\infty}$ ) was calculated as  $AUC_{0-t} + C_t/K_e$ , where  $C_t$  is the last measurable plasma concentration and  $K_e$  is the elimination rate constant.

## RESULTS

### Solubility Studies

The results of the solubility study and the influence of Polysorbate 20 on sink conditions for candesartan cilexetil 16-mg tablets are summarized in Table 1.

The solubility increased as pH increased, and in pH 6.5 phosphate buffer, the solubility was 3.933  $\mu\text{g}/\text{mL}$  in comparison with solubility values of 2.405 and 2.615  $\mu\text{g}/\text{mL}$  obtained in 0.1 N HCl and pH 4.6 acetate buffer, respectively.

A significant increase in solubility was also noticed when Polysorbate 20 was added to the pH 6.5 phosphate buffer medium. Polysorbate 20 was selected because it

Table 1. Solubility of Candesartan Cilexetil in Various Media

Medium	Solubility ( $\mu\text{g}/\text{mL}$ ) (mean $\pm$ SD)	Sink conditions (CS/CD)	
		16 mg	32 mg
0.1 N HCl	2.405 $\pm$ 0.35	0.15	0.08
pH 4.6 acetate buffer	2.615 $\pm$ 0.23	0.16	0.08
pH 6.5 phosphate buffer	3.933 $\pm$ 0.74	0.25	0.12
0.25% Polysorbate 20 in pH 6.5 phosphate buffer	58.264 $\pm$ 2.65	3.64	1.82
0.35% Polysorbate 20 in pH 6.5 phosphate buffer	78.138 $\pm$ 2.00	4.89	2.44
0.45% Polysorbate 20 in pH 6.5 phosphate buffer	95.084 $\pm$ 1.34	5.94	2.97
0.55% Polysorbate 20 in pH 6.5 phosphate buffer	182.45 $\pm$ 4.87	11.40	5.70
0.7% Polysorbate 20 in pH 6.5 phosphate buffer	239.02 $\pm$ 8.36	14.94	7.47

is recommended by the FDA for performing dissolution of candesartan cilexetil tablets (19). As shown in Table 1, solubility increased with an increase in Polysorbate 20 concentration.

A solubility value of 58.264 µg/mL, obtained with 0.25% Polysorbate 20 in pH 6.5 phosphate buffer, would allow achievement of a  $C_S/C_D$  value of 3.64 for candesartan 16-mg tablets.

### Dissolution Release Studies

Dissolution profiles of various candesartan cilexetil 16-mg tablet formulations are provided in Figure 1. The statistical evaluation (Student's *t*-test at the 5% significance level) of the percentage cumulative drug released at 50 and 75 rpm for tablet formulations A, B, C, and D in pH 6.5 phosphate buffer containing Polysorbate 20 is shown in Table 2. A *p* value less than or equal to the significance level (0.05) indicates that there is a statistically significant difference in the percentage cumulative drug release in the formulations.

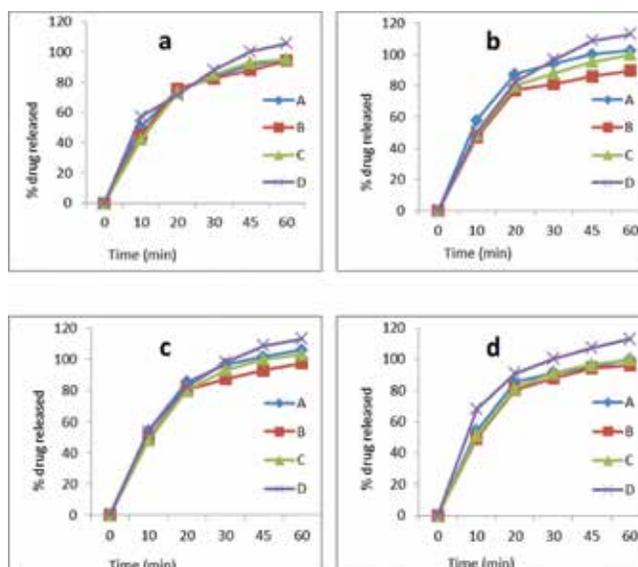


Figure 1. Mean % cumulative dissolution data of candesartan cilexetil tablets (*n* = 6) in 0.25% Polysorbate 20 in pH 6.5 phosphate buffer at (a) 50 rpm and (b) 75 rpm, and in 0.35% Polysorbate 20 in pH 6.5 phosphate buffer at (c) 50 rpm and (d) 75 rpm.

Table 2. Statistical Evaluation of Dissolution Results

Dissolution Time	Comparison of dissolution profiles in pH 6.5 phosphate buffer containing 0.25% Polysorbate 20 at 50 and 75 rpm								Comparison of dissolution profiles at 50 rpm in pH 6.5 phosphate buffer containing 0.25% and 0.35% Polysorbate 20							
	A		B		C		D		A		B		C		D	
	T	P	T	P	T	P	T	P	T	P	T	P	T	P	T	P
D10	4.006	0.0102 (S)	0.7980	0.4611 (NS)	2.9347	0.0325 (S)	4.1537	0.0089 (S)	1.3667	0.2300 (NS)	1.5811	0.1747 (NS)	5.4412	0.0028 (S)	1.3422	0.2373 (NS)
D20	8.3031	0.0004 (S)	1.1416	0.3053 (NS)	4.0467	0.0099 (S)	3.1194	0.0263 (S)	9.0181	0.0002 (S)	3.8730	0.0117 (S)	4.0467	0.0099 (S)	4.8924	0.0045 (S)
D30	4.1628	0.0088 (S)	1.7276	0.1446 (NS)	1.5811	0.1747 (NS)	3.3910	0.0194 (S)	4.0833	0.0095 (S)	3.1623	0.0250 (S)	7.0000	0.0009 (S)	5.7283	0.0022 (S)
D45	7.3596	0.0007 (S)	1.3835	0.2251 (NS)	1.5811	0.1747 (NS)	3.3538	0.0202 (S)	6.6134	0.0012 (S)	3.1623	0.0250 (S)	-	-	6.1842	0.0016 (S)
D60	2.9063	0.0335 (S)	2.4046	0.0613 (NS)	3.1623	0.0250 (S)	3.8730	0.0117 (S)	6.9656	0.0009 (S)	1.1678	0.2956 (NS)	3.7963	0.0127 (S)	3.8730	0.0117 (S)
	Comparison of dissolution profiles in pH 6.5 phosphate buffer containing 0.35% Polysorbate 20 at 50 and 75 rpm								Comparison of dissolution profiles at 75 rpm in pH 6.5 phosphate buffer containing 0.25% and 0.35% Polysorbate 20							
	A		0.0007		C		D		A		B		C		D	
	T	(S)	T	P	T	P	T	P	T	P	T	P	T	P	T	P
D10	0.2669	0.0335	-	-	2.2361	0.0756 (NS)	4.4721	0.0066 (S)	2.2361	0.0756 (NS)	1.2112	0.2799 (NS)	1.0000	0.3632 (NS)	3.7268	0.0136 (NS)
D20	-	(S)	-	-	1.0000	0.3632 (NS)	2.4445	0.0583 (NS)	0.1816	0.3632 (NS)	2.7448	0.0406 (S)	1.0000	0.3632 (NS)	2.9066	0.0335 (S)
D30	1.3484	0.2354 (NS)	0.5423	0.6109 (NS)	1.5811	0.1747 (NS)	1.5811	0.1747 (NS)	0.6742	0.5301 (NS)	4.3314	0.0075 (S)	2.2361	0.0756 (NS)	2.2361	0.0756 (NS)
D45	5.0000	0.0041 (S)	0.4152	0.6952 (NS)	2.2361	0.0756 (NS)	0.4152	0.6952 (NS)	3.1623	0.0250 (S)	4.2105	0.0084 (S)	0.5423	0.6109 (NS)	0.3492	0.7412 (NS)
D60	5.0000	0.0041 (S)	0.2370	0.8220 (NS)	2.2361	0.0756 (NS)	-	-	0.7906	0.4650 (NS)	4.3765	0.0072 (S)	-	-	-	-

\*S= Significant (*p* < 0.05); NS= Non significant (*p* > 0.05)  
# A, B, C and D: Denote the tablet formulations used  
D= dissolution time;

The percentage drug released after 10 min in 0.25% polysorbate in pH 6.5 phosphate buffer stirred at 50 rpm was 50.5%, 44.8%, 42.0%, and 57.3%, respectively, for formulations A, B, C, and D. When the paddle speed was increased to 75 rpm, drug release increased to 57.9%, 46.8%, and 48.6% for formulations A, B, and C, respectively, although formulation D surprisingly exhibited a lower percentage drug release (50.1%) at 10 min. The percentage

drug release at subsequent time points was higher (*p* < 0.05) than the percentage drug release observed at 50 rpm. In formulation A, drug release was significantly higher (*p* < 0.05) at all the time points, whereas, in the case of formulation C, drug release increased significantly (*p* < 0.05) at 10, 20, and 60 min. Formulation B exhibited an insignificant increase in dissolution at the faster paddle speed.

Table 3. Comparison of Dissolution Profiles Using Similarity Factor ( $f_2$  value)

Method	A	B	C
pH 6.5 phosphate buffer with 0.25% Polysorbate 20 at 50 rpm	56.43	50.14	51.96
pH 6.5 phosphate buffer with 0.25% Polysorbate 20 at 75 rpm	55.97	44.86	51.13
pH 6.5 phosphate buffer with 0.35% Polysorbate 20 at 50 rpm	86.92	63.79	71.64
pH 6.5 phosphate buffer with 0.35% Polysorbate 20 at 75 rpm	55.22	47.96	50.83

Similarly, at a fixed paddle speed of 50 rpm, an increase in polysorbate concentration significantly ( $p < 0.05$ ) increased the percentage cumulative drug release in formulations A, B, C, and D at 20, 30, and 45 min. Furthermore, at 50 rpm, an increased polysorbate concentration caused a significant ( $p < 0.05$ ) increase in dissolution (97.5%) of formulation B after 60 min.

At 75 rpm, the effect of a higher polysorbate concentration was evident in formulation B, which showed a higher ( $p < 0.05$ ) percentage release at 20, 30, 45, and 60 min, whereas formulation D exhibited faster ( $p < 0.05$ ) dissolution at 10 and 20 min.

At a higher polysorbate concentration (0.35%), the percentage drug release from formulation D after 10 min at 75 rpm increased significantly ( $p < 0.05$ ) to 68.0% from 53.7% at 50 rpm.

The effect of increased paddle speed at a higher polysorbate concentration in the dissolution medium was insignificant ( $p > 0.05$ ) at 20 and 30 min for formulations A, B, and C, whereas, in the case of formulation D, a significant increase in dissolution was observed at 10 min.

The similarity factor ( $f_2$ ) values of formulations A, B, and C calculated with reference to formulation D are presented in Table 3.

### Dissolution Profile of Mismanufactured Tablets

Two factorial experiments at two levels were performed to evaluate the discriminatory power of the dissolution method in differentiating mismanufactured tablets (high hardness tablets with disintegration time [DT] of more than 10 min). The concentration of polysorbate (0.25% and 0.35%) at two paddle speeds (50 rpm and 75 rpm) were the factors studied.

The percentage drug release for normal tablets at 10- and 20-min intervals were 45.60% and 72.29%, respectively. The release was depressed in mismanufactured tablets to 30.97% and 60.96% at 10 and 20 min, respectively (Figure 2). As shown in Figure 2, approximately 15% and 12% differences in dissolution rate were observed at 10- and 20-min sampling points between normal and mismanufactured tablets at 50 rpm. This difference in dissolution decreased at a higher polysorbate concentration (0.35%) and paddle speed (75 rpm).

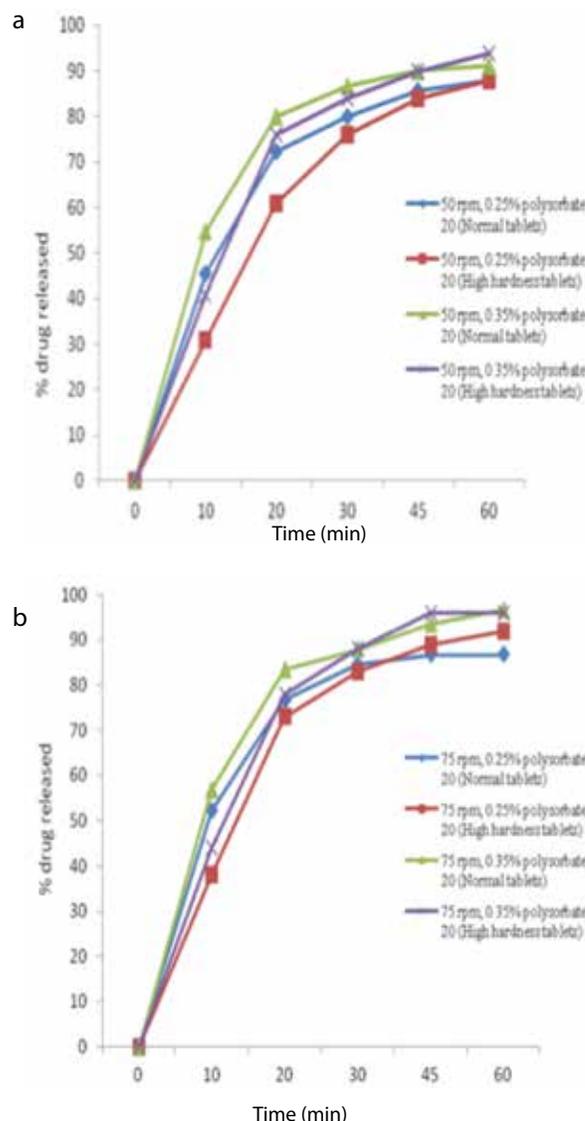


Figure 2. Dissolution profiles of mismanufactured tablets at (a) 50 rpm and (b) 75 rpm.

### Use of Convolution Methodology to Predict Plasma Drug Concentrations

#### Evaluation of Predictability of the Model

The percent prediction errors for  $C_{max}$  or  $AUC_{0-\infty}$  can be determined as follows (16, 19, 20):

$$\% \text{ prediction error} = \frac{\text{observed parameter} - \text{predicted parameter}}{\text{observed parameter}} \times 100$$

A value of 10% prediction error confirms the external predictability of the model. A value between 10% and 20% is inconclusive and needs additional data. A percentage prediction error of greater than 20% is indicative of inadequate predictability (21).

The model was verified by performing the dissolution profile (Figure 3) of candesartan tablet innovator samples (Atacand tablets) at 50 rpm.

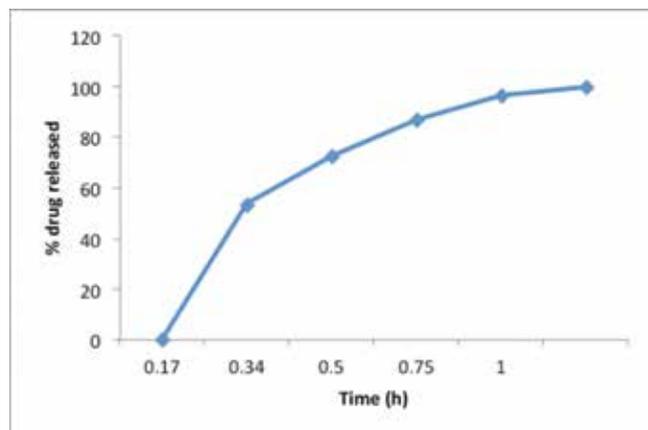


Figure 3. Dissolution profile of 16-mg candesartan cilexetil tablets (Atacand tablets).

The predicted plasma concentration–time profile for the Atacand tablets is shown in Figure 4.

The predicted  $C_{max}$  and  $AUC_{0-\infty}$  were 223 ng/mL and 1689 ng.h/mL, respectively. The values are very close to the reported values of 208 ng/mL and 1430 ng.h/mL for  $C_{max}$ , and  $AUC_{0-\infty}$ , respectively (11–19, 22). The percentage prediction errors were less than 6.7% and 15% for  $C_{max}$  and  $AUC_{0-\infty}$ , respectively.

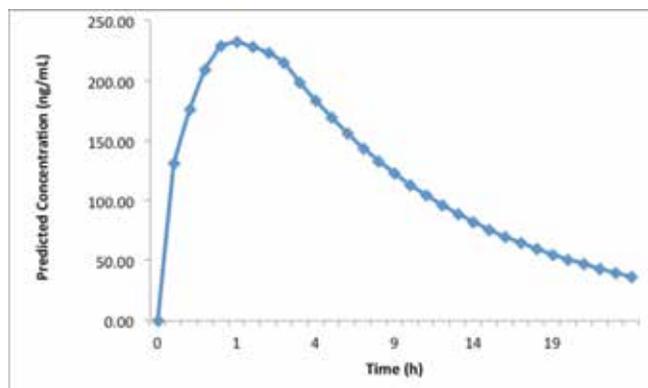


Figure 4. Derived plasma concentration–time profile of 16-mg candesartan cilexetil tablets (Atacand tablets).

#### Establishment of a Dissolution Specification

The predicted pharmacokinetic parameters of formulations A, D, and E are given in Table 4. The pharmacokinetic parameters were predicted by systematically varying the dissolution release at 10- and 60-min intervals. The estimated pharmacokinetic parameters

and the ratio of upper and lower levels corresponding to upper and lower limits of dissolution specifications are shown in Table 5.

Table 4. Predicted Pharmacokinetic Parameters of Formulations A, D, and E

Product	Predicted $C_{max}$ ng/mL	Predicted $AUC_{0-\infty}$ ng.h/mL
A	213	1610
D	238	1796
E	223	1689

## DISCUSSION

The BCS is based on the solubility and permeability characteristics of a drug (23). Due to its role in dissolution, solubility impacts systemic availability of Class 2 drugs. According to the modified Noyes–Whitney equation (24), the dissolution rate of drugs is proportional to:

$$\text{dissolution rate } \left( \frac{dc}{dt} \right) = \frac{DA}{hv} (C_s - C)$$

where  $D$  is the diffusion coefficient,  $h$  is the thickness of the diffusion layer at the solid–liquid interface,  $A$  is the surface area of drug exposed to the dissolution medium,  $v$  is the volume of dissolution medium,  $C_s$  is the concentration of a saturated solution of solute in the dissolution medium at the experimental temperature, and  $C$  is the concentration of drug in solution at time  $t$ .

Grant et al. (25) have attributed heat of solvation and heat of fusion as the two factors that govern aqueous solubility. The poor solubility of lipophilic compounds is due to their small heat of solvation, which is not sufficient to overcome the strong hydrogen bonds between water molecules. Similarly, crystalline substances with high melting points and heats of fusion greater than heats of solvation have poor aqueous solubility. Solubility plays a very important role in selecting a dissolution medium for a drug substance in a particular dosage form (23). Nicklasson et al. (26) established a correlation between solubility and the intrinsic dissolution rate of different drug substances in various media.

Drugs with higher solubility usually do not have dissolution-limited bioavailability problems. The solubility of ionizable drugs (weak acids and bases) depends upon the pH of the medium and the  $pK_a$  of the compound (27). Hence, to predict the effect of solubility on dissolution, the aqueous solubility of the drug substance over the physiologically relevant pH range of 1–7.5 should be determined.

Table 5. Estimation of Pharmacokinetic Parameters at Various Simulated Dissolution Profiles

Variable		$C_{max}$ (ng.h/mL)			$AUC_{0-\alpha}$ (ng.h/mL)		
% drug release at 10 min (specification width)	% drug released at 60 min (specification width)	Upper	Lower	Upper/lower	Upper	Lower	Upper/lower
$\pm 10$	--	223.0	223.91	0.995	1689	1688	1.001
$\pm 20$	--	223.0	224.41	0.994	1689	1688	1.001
--	$-10^a$	225.12	206.81	1.088	1695	1525	1.111
$\pm 10$	$-10^a$	224.62	207.34	1.083	1696	1525--	1.112

<sup>a</sup> Assuming upper % release as 100%.

The dose/solubility ratios of the highest available tablet strength, candesartan 32-mg tablets, in 0.1 N HCl, pH 4.5 and 6.8 buffers are 13305.61, 12237.09, and 8136.28 mg/mL, respectively (Table 1). All the ratios are much greater than the critical limit of 250 mL for highly soluble drugs (23). Candesartan cilexetil is a BCS Class 2 drug. The addition of 0.25% Polysorbate 20 achieved sink conditions for 16-mg candesartan cilexetil tablets. Sink conditions is the ratio of saturation solubility/dose in 900 mL dissolution medium ( $C_s/C_D$ ) and must be  $\geq 3.0$  (28).

A discriminatory dissolution method plays an important role in the development of formulations, evaluation of their stability and consistency, and for post-approval changes. The FDA recommends Apparatus 2, a paddle speed of 50 rpm, and pH 6.5 phosphate buffer with 0.35% Polysorbate 20 as the dissolution medium for candesartan cilexetil 8 and 16-mg tablets (18).

With a variation in the concentration of Polysorbate 20, a significant difference in dissolution profiles at 50 rpm was noticed. The dissolution medium with 0.25% polysorbate showed better discriminatory power as was evident by the low  $f_2$  values. The observations are in agreement with the statistical results. The dissolution profiles of mismanufactured tablets (high-hardness tablets) can be distinguished from those of low-hardness tablets in a dissolution medium with 0.25% phosphate buffer at 50 rpm. The method is able to distinguish depressed dissolution in samples taken at 20- and 30-min intervals.

IVIVC serves as a very useful tool in pharmaceutical development and reduction of product development costs. These correlations can be used to provide specifications for dissolution tests and can obviate the need for in vivo bioequivalence studies (20). In the deconvolution model, the dissolution profile is derived from the blood drug concentration profile, whereas in the convolution model, a blood drug concentration–time profile is obtained using dissolution data and pharmacokinetic parameters. The convolution technique is a simple, realistic, and practical approach to develop IVIVC (17, 20). The method of Qureshi (17) was used to derive a plasma concentration–time profile of candesartan cilexetil tablets from the dissolution profile and to test its discriminatory power.

For quality control batch release, not less than 90% drug release at 60 min (based on simulations performed in Table 5) will ensure that point estimates for  $C_{max}$  and  $AUC_{0-\alpha}$  of tablets fall within the 0.90–1.112 range of the reference

product and is likely to meet bioequivalence requirements (Table 5). Post-approval changes in formulations can be controlled by a two-point dissolution specification at 10 min and 60 min. The batches that release drug within 10% of the release specification after 10 min ( $50 \pm 10\%$ ) have  $C_{max}$  values between 0.90 and 1.10 of the reference product. Two-point specifications are also recommended by guidance documents for slowly dissolving or poorly water-soluble drug products like carbamazepine (29).

## CONCLUSIONS

Two-point dissolution is being increasingly recommended for characterizing the quality of poorly water-soluble and slowly dissolving drugs (BCS Class 2). The first dissolution point is selected to include a dissolution range, and the other is selected at a latter point to ensure 85% drug dissolution. The first point would represent a potential warning due to higher or lower absorption, while the second point ensures complete absorption of the intended dose.

In conclusion, the convolution method for establishing a dissolution specification for candesartan cilexetil is a useful tool in initial product development stages and for post-approval changes. However, further pharmacokinetic data from studies in human volunteers are needed to establish and validate the model.

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