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Justification of Biowaiver for Carbamazepine, a Low Soluble High Permeable Compound, in Solid Dosage Forms Based on IVIVC and Gastrointestinal Simulation

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Abstract: The aim of the present study was to use gastrointestinal simulation technology and in vitro−in vivo correlation (IVIVC) as tools to investigate a possible extension of biowaiver criteria to BCS class II drugs using carbamazepine (CBZ) as a candidate compound. Gastrointestinal simulation based on the advanced compartmental absorption and transit model implemented in GastroPlus was used. Actual in vitro and in vivo data generated in CBZ bioequivalence studies were used for correlation purposes. The simulated plasma profile, based on the CBZ physicochemical and pharmacokinetic properties, was almost identical with that observed in vivo. Parameter sensitivity analysis (PSA) indicated that the percent of drug absorbed is relatively insensitive to the variation of the input parameters. Additionally, plasma concentration−time profiles were simulated based on dissolution profiles observed under the different experimental conditions. Regardless of the differences observed in vitro, the predicted pharmacokinetic profiles were similar in the extent of drug exposure (AUC) while there were certain differences in parameters defining the drug absorption rate (C_{max}, t_{max}). High level A IVIVC was established for the pooled data set ($r = 0.9624$), indicating that 1% SLS may be considered as the universal biorelevant dissolution medium for both the IR and CR CBZ tablets. The proposed methodology involving gastrointestinal simulation technology and IVIVC suggests that there is a rationale for considering CBZ biowaiver extension and introduction of the wider dissolution specifications for CBZ immediate release tablets.

Keywords: BCS; bioequivalence; carbamazepine; gastrointestinal simulation; IVIVC

Introduction

Generic drug products developed to provide more cost-effective drug treatment have to exhibit the same effectiveness, safety and quality profile as the corresponding reference drug. In order to meet such criteria and approve medicinal products' interchangeability, the similarity of rate and extent of drug absorption (i.e., bioequivalence) between the investigated and the innovator product has to be demonstrated. Therefore, the bioequivalence evaluation is a critical component of the Abbreviated New Drug Application review process for oral solid dosage forms. Generally, it is required to carry out a bioequivalence (BE) investigation as a relevant clinical study in healthy volunteers during the premarketing phase of a drug development.[1,2] However, the generic drug approval process has evolved over the past 30 years. Today,

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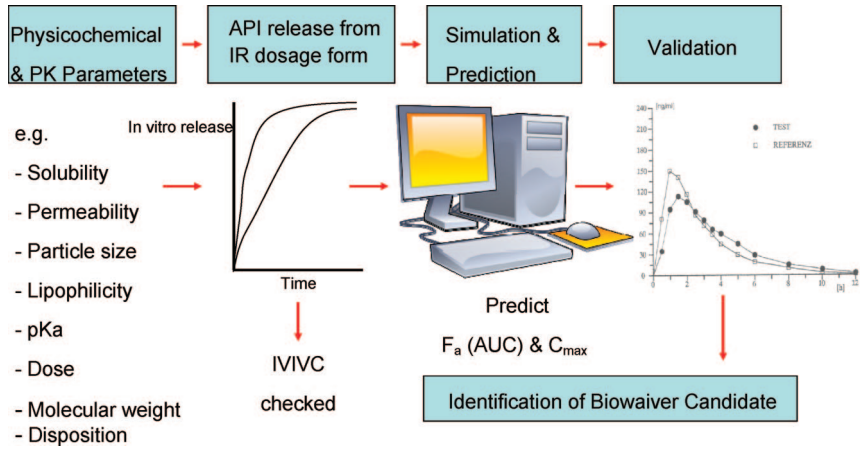
Scheme 1



under certain circumstances, drug agencies may waive the requirement for in vivo bioequivalence and/or bioavailability studies. A biowaiver request has to be scientifically justified with regard to a drug substance and drug product related characteristics, taking into account an appropriate risk analysis when necessary. The Biopharmaceutics Classification System (BCS) has been introduced as a scientific framework for classifying drug substances according to their aqueous solubility and intestinal permeability.[3] It is based on the mechanistic assumptions that a rate and an extent of oral drug absorption are governed by drug solubility, intestinal permeability and dissolution rate from the dosage form administered.[4] One of the goals of BCS is to identify classes of drugs for which bioequivalence may be established based solely on the in vitro dissolution data, i.e., which would be eligible for biowaiver. At present, the biowaiver concept is adopted and recommended for immediate release drug products containing high solubility and high permeability compounds (BCS class I drugs).[1,2] Biowaiver extension have also been discussed for BCS class III drugs, as well as for the class II drugs under the presumption that they dissolve completely during the gastrointestinal passage.[5,6] For the BCS class II compounds dissolution is the rate-limiting step

Table 1. Summary of the Input Parameters Employed for Gastrointestinal Simulation

parameter	
molecular weight	238.29
solubility	0.12 mg/mL[a]
log *P*	2.45[b]
pK_a	11.83[c]
human jejunal permeability (P_{eff})	4.3×10^{-4} cm/s[d]
dose	400 mg
dose volume	250 mL
mean precipitation time	900 s[e]
drug particle density	1.2 g/mL[e]
effective particle radius	25 μm[e]
diffusion coefficient	0.8689×10^{-5} cm^2/s
unbound percent in plasma (f_u)	30%[f]
clearance (CL)	0.024 L/h/kg
volume of distribution (V_c)	1.26 L/kg[f]
elimination half-life ($t_{1/2}$)	36.39 h
body weight	72 kg (IR tablets)
	68.9 kg (CR tablets)
simulation time	120 h (IR tablets)
	144 h (CR tablets)

[a] Literature value taken from ref 11. [b] Literature value taken from ref 12. [c] Literature value taken from ref 13. [d] Literature value taken from ref 14. [e] Default GastroPlus values. [f] Literature value taken from ref 15.

to absorption depending on the various factors such as the pH value and ionic strength, volume of the gastrointestinal fluids available for dissolution and presence of surfactants. Dissolution testing is generally accepted as the quality control test method that measures the effect of drug substance properties and formulation factors on drug release from the dosage form, which makes it interesting as an indicator of the drug product bioperformance. However, it might, also, to a variable degree, be sensitive to the experimental conditions employed. It has been previously demonstrated that gastrointestinal simulation technology (GST) in combination with in vitro−in vivo correlation (IVIVC) can be successfully applied to justify a biowaiver according to Scheme 1. Since in vivo drug disposition prediction may be affected by the input dissolution rate, the influence of the in

(1) FDA/CDER Guidance for industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations, 2003.
(2) EMEA/CPMP Note for guidance on the investigation of bioavailability and bioequivalence, 2001.
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Table 2. Mean Pharmacokinetic Parameters Calculated from the Individual $C-t$ Plasma Profiles

	C_{max} (mg/L)	t_{max} (h)	$AUC_{0\rightarrow t}$ (μg h/mL)	$AUC_{0\rightarrow\infty}$ (μg h/mL)
CBZ IR product (test)	4.74 ± 1.27	8.6 ± 2.8	220.42 ± 55.94	259.03 ± 69.02
CBZ IR product (reference)	4.34 ± 1.24	9.7 ± 4.5	211.37 ± 52.97	259.15 ± 63.97
CBZ CR product (test)	3.88 ± 0.90	14.7 ± 7.2	211.54 ± 47.67	241.94 ± 58.31
CBZ CR product (reference)	3.65 ± 1.42	14.3 ± 9.3	202.77 ± 79.95	236.80 ± 87.23

vitro conditions is to be carefully evaluated and defined in order to achieve accurate simulation of the pharmacokinetic profile.

In this paper, the biowaiver concept for the class II drugs has been further elaborated on using carbamazepine (CBZ) as a model drug. CBZ is a widely used antiepileptic drug with a low aqueous solubility and high permeability. Besides its poor aqueous solubility, other attributes such as narrow therapeutic index and relatively high variability have been recognized as obstacles for CBZ generic substitution and/or products interchangeability and further limit its exemption from in vivo bioequivalence studies.[7,8]

The aim of the present study was to use GST as a tool to investigate a possibility for biowaiver extension to CBZ IR tablets and propose dissolution media that would be predictive of the drug product in vivo behavior. GST was used to predict (i) the fraction of dose absorbed and the drug disposition based on its physicochemical and pharmacokinetic parameters and (ii) plasma concentration−time profiles based on the different in vitro dissolution rates used as the input function. Biowaiver justification was discussed in terms of the extent in which the simulated in vivo profiles were affected by the differences in drug dissolution rates observed in vitro. Such an approach would allow more biorelevant specification limits for CBZ tablet dissolution to be established. Additionally, the risk of therapeutic failure associated with granting a marketing authorization for a generic drug product based on the in vitro data may be assessed more accurately.

Materials and Methods

In Vivo Study. The results of two separate in vivo single-dose, fasted, open label, randomized, two sequence, two periods, crossover bioequivalence studies of CBZ immediate release (IR) and CBZ controlled release (CR) tablets (in-house data on file) were used.

A relative bioavailability study of the CBZ IR tablets was performed in a group of 18 healthy volunteers of both sexes (age range 29−37 years, mean 33; body weight 70−81 kg, mean 72) using Tegretol, Novartis as a reference product. Each volunteer received a 400 mg CBZ dose (two IR tablets) with a 20 day washout period. Blood samples were taken at the following intervals: predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96 and 120 h after dosing.

A bioequivalence study of the CBZ CR tablets was performed in a group of 24 healthy volunteers of both sexes (age range 20−52 years, mean 31.8; body weight 50−96 kg, mean 69.8) using Tegretol CR, Novartis as a reference. Each volunteer received a 400 mg CBZ dose (one CR tablet) with a 20 day washout period. Blood samples were taken at the following intervals: predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 120 and 144 h after dosing.

CBZ concentration in the collected blood samples was determined by a validated HPLC method. The following parameters were derived from the mean plasma concentration time profiles: peak plasma concentration (C_{max}), area under the curve (AUC_{0-t}, $AUC_{0-\infty}$) and time to reach peak concentration (t_{max}).

In Vitro Study. Dissolution studies of the investigated IR and CR CBZ tablets were performed in the USP rotating paddle apparatus (Erweka DT 70, Germany) at 75 rpm using 900 mL of dissolution media. In the case of IR tablets, different dissolution media were evaluated: water, 0.1, 0.25, 0.5 and 1% sodium lauryl sulfate (SLS) aqueous solution, 0.1 M HCl, USP acetate buffer pH 4.5 and USP phosphate buffer pH 6.8. Media samples were withdrawn after 10, 20, 30, 45, 60, 75, 90, 105 and 120 min. In the case of CR tablets, drug release studies were performed in water, 1% SLS and according to the half-change methodology (HCM).[9] (In a HCM, one-half of the medium was removed at one hour time intervals and replaced with buffer having higher pH value thus providing a continuous pH gradient. The initial medium was simulated gastric fluid without pepsin and the second medium was the simulated intestinal fluid (SIF) pH 7.5 without pancreatin). Samples were withdrawn at one hour time intervals for eight hours. The amount of dissolved CBZ was determined UV spectrophotometrically at 285 ± 2 nm (spectrophotometer HP 8453). All tests were performed with six tablets and the mean values reported. The similarity factor value, f_2, was used to compare the dissolution profiles observed.[8]

Gastrointestinal Simulation. Gastrointestinal simulation based on the advanced compartmental absorption and transit (ACAT) model (GastroPlus version 5.3.0, SimulationsPlus, Lancaster, CA) was used. The form of the ACAT model implemented in GastroPlus is modeled by a system of coupled linear and nonlinear rate equations. The equations include the consideration of six states of drug substance (unreleased, undissolved, dissolved, degraded, metabolized, and absorbed), 18 compartments (stomach, six compartments

(7) Martindale: The Complete Drug Reference, 2007.

(8) FDA/CDER Guidance for industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, 2000.

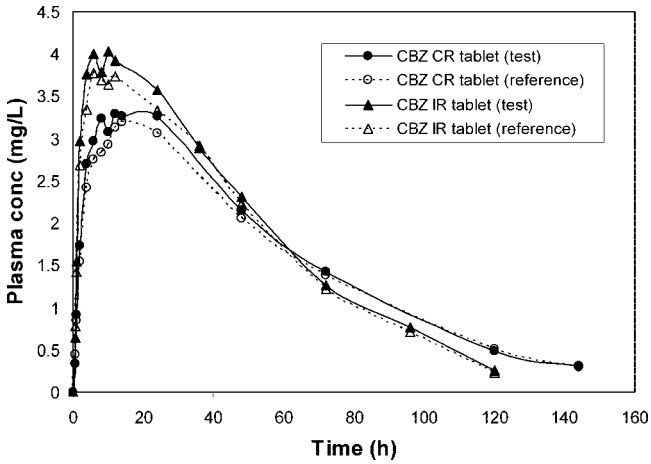

Figure 1. Mean carbamazepine plasma concentration profiles observed in the in vivo bioequivalence studies of carbamazepine IR ($n = 18$) and CR tablets ($n = 24$).

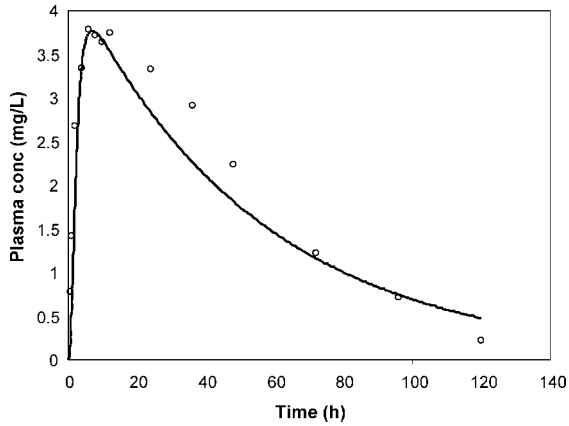

Figure 2. Predicted (line) and observed (○) mean carbamazepine plasma $C-t$ profiles following administration of a single 400 mg dose from the IR drug product.

for the small intestine, two colon and nine enterocyte compartments), three states of excreted material (unreleased, undissolved, and dissolved), and the concentration of drug in physiologically based organ compartments, when tissue partition and flow rate parameters are available. The total amount of absorbed material is summed over the integrated amounts being absorbed/exsorbed from each absorption/transit compartment.[10]

The in vivo drug absorption and disposition was simulated based on CBZ physicochemical and pharmacokinetic properties and drug dissolution kinetics observed in vitro. A range of input parameters related to the drug substance and dosage form characteristics were experimentally determined and/or taken from the literature and employed for simulation purposes (Table 1). It should be noted that, although the literature data on CBZ aqueous solubility ranged from 0.12

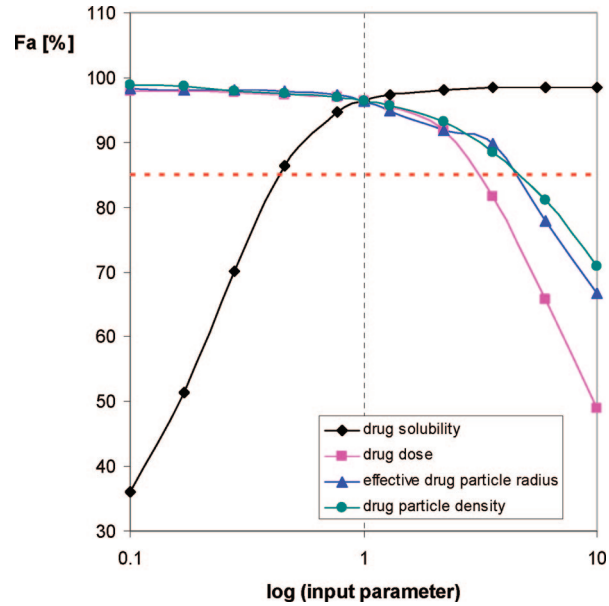

Figure 3. Parameter sensitivity analysis (PSA): the dependence of fraction CBZ absorbed on different input parameters. The center of the *X*-axis for each of the parameters tested represents the value that was used in the simulations.

to 0.26 mg/mL,[11,16,17] the lower value was chosen for these simulations in order to apply the more stringent approach. For CBZ immediate release dosage forms the "IR tablet mode" was specified; in the case of CBZ controlled release formulations, the "CR integral tablets mode" was specified. Parameter sensitivity analysis (PSA) was used to assess the importance of the selected input parameters in predicting percent of drug absorbed.

Results and Discussion

In Vivo Study. Results of the in vivo bioequivalence studies of CBZ IR tablets and CBZ CR tablets are

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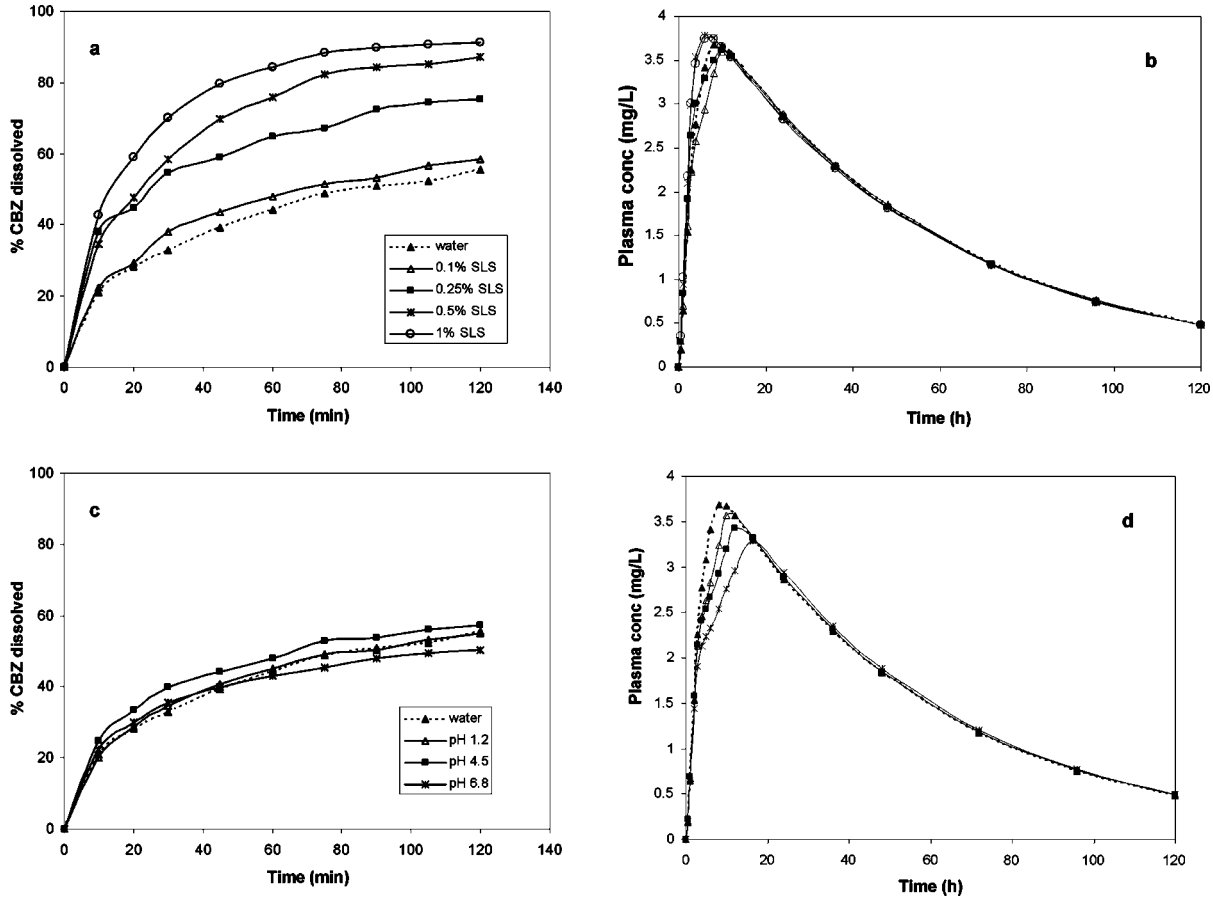

Figure 4. CBZ IR tablets dissolution profiles in various dissolution media and the corresponding simulated in vivo profiles.

Table 3. The Pharmacokinetic Parameters Predicted Based on CBZ IR Tablets Dissolution in Various Media

dissolution media	C_{max} (mg/L)	% PE	$AUC_{0\rightarrow t}$ (μg h/mL)	$AUC_{0\rightarrow\infty}$ (μg h/mL)	% PE	t_{max} (h)	F_a (%)
pH 6.8	3.29	−12.96	194.4	220.9	−3.58	16.5	95.5
0.1% SLS	3.60	−4.76	199.7	225.8	−1.44	10.5	97.6
0.25% SLS	3.61	−4.5	200.6	226.5	−1.13	9.9	98.9
0.5% SLS	3.79	+0.26	202.1	227.7	−0.61	6.6	98.4
1% SLS	3.77	−0.26	201.9	227.5	−0.70	6.9	98.3
in vivo obs[a]	3.78		224.6	229.1		6.0	N/A

[a] Refers to the data obtained/calculated based on the mean $C-t$ profile observed for the reference product in the relevant in vivo BE study.

summarized in Table 2 and Figure 1. Mean pharmacokinetic parameters calculated from the individual carbamazepine plasma profiles observed in vivo are given in Table 2, while the mean $C-t$profiles are graphically presented in Figure 1.

Gastrointestinal Absorption Simulation. Gastrointestinal simulation for CBZ IR tablets, based on the input physicochemical and pharmacokinetic data presented in Table 1, was performed by using the GastroPlus Single Simulation Mode. The predicted fraction of drug absorbed (F_a) was 98.02%. This result is in accordance with the published data stating almost 100% bioavailability of CBZ after oral administration.[12] The simulated plasma concentration−time profile is presented in Figure 2 together with the mean plasma profile observed for the reference IR product in the single dose BE study. The predicted pharmacokinetic parameters and those observed in vivo were almost identical; predicted C_{max} was 3.76 μg/mL, while the observed one was 3.78 μg/mL; the predicted and the observed t_{max} were 6 and 7 h, respectively; while the predicted/observed AUC_{0-t} and $AUC_{0-\infty}$ values were 201.2/224.6 μg h/mL and 226.9/229.1 μg h/mL, respectively.

Parameter sensitivity analysis (PSA) was performed for drug solubility, dose, effective particle radius and drug particle density. The selected parameters were varied in the range covering one tenth to 10-fold actual input parameter value (i.e., according to the default GastroPlus setting). The results obtained indicate that the extent of drug absorption is rather insensitive to the variation of the input parameters

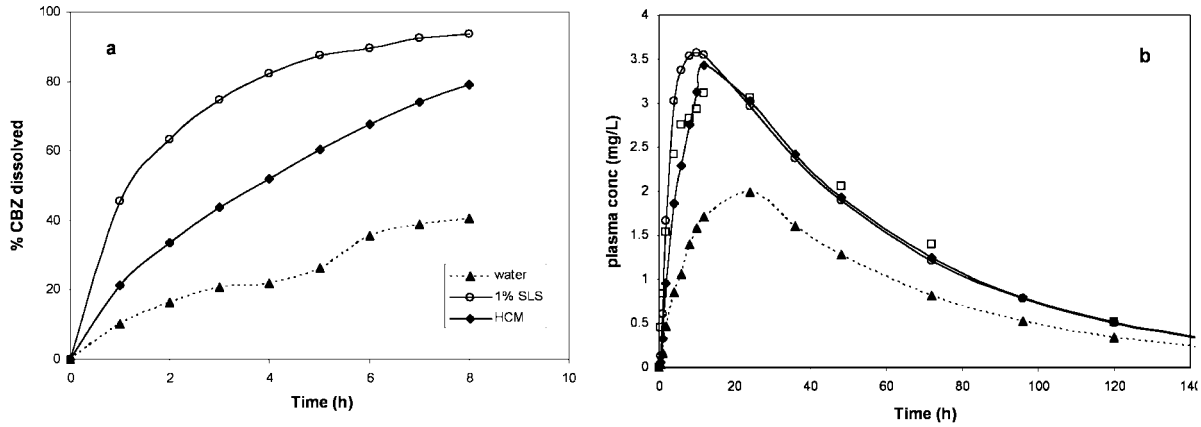

Figure 5. CBZ CR tablets dissolution profiles in various dissolution media and the corresponding simulated in vivo profiles (open square symbols refer to the actual in vivo data).

Table 4. The Pharmacokinetic Parameters Predicted Based on CBZ CR Tablets Dissolution in Various Media

dissolution media	C_{max} (mg/L)	% PE	$AUC_{0\rightarrow t}$ (μg h/mL)	$AUC_{0\rightarrow\infty}$ (μg h/mL)	% PE	t_{max} (h)	F_a (%)
water	2.06	−35.42	131.6	143.2	−39.37	21.2	59.6
half-change method	3.45	+8.15	210.6	228.1	−3.43	13.8	95.6
1% SLS	3.56	+11.60	215.6	232.8	−1.44	9.9	97.5
in vivo obsd[a]	3.19		223.9	236.2		14.0	N/A

[a] Refers to the data obtained/calculated based on the mean $C-t$ profile observed for the reference product in the relevant in vivo BE study.

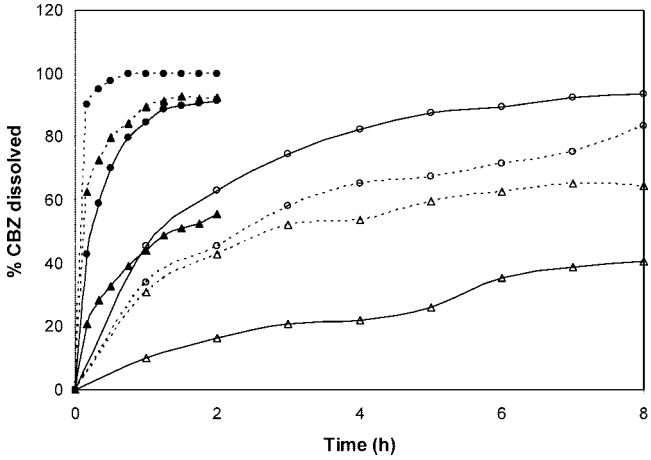

Figure 6. Comparative dissolution data for generic (dotted line) and reference (solid line) CBZ tablets in water (triangle) and 1% SLS (circle) (open symbols refer to CR tablets, closed symbols refer to IR tablets).

tested (Figure 3). From the PSA performed for CBZ solubility in the range from 0.012 mg/mL to 1.2 mg/mL, it is expected that complete absorption (i.e., $F_a > 85\%$) can be achieved with CBZ solubility even as low as 0.05 mg/mL. Such results assume that an eventual CBZ transformation to less soluble polymorph would not cause bioavailability problems. Simulation of particle radius variation in the range from 2.5 to 250 μm indicate that high bioavailability would be achieved with CBZ particle sizes up to 90 μm. The PSA for the administered dose range from 40 mg to 4000 mg revealed that single doses up to 1200 mg would not impair the extent of drug absorption.

Influence of the Drug Dissolution on Gastrointestinal Simulation for IR Tablets. Dissolution data obtained under the various experimental conditions for the reference CBZ IR tablets (Figure 4a, c) were used as the input function in the GastroPlus Single Simulation Mode with the aim to evaluate the influence of in vitro drug dissolution rate on CBZ plasma concentration profiles. The simulation results are presented in Figure 4b, d. Regardless of the differences observed in vitro, the predicted pharmacokinetic profiles were similar in the extent of drug exposure (AUC) while there were certain differences in parameters defining the drug absorption rate (C_{max}, t_{max}). The quality of simulation was measured by the percentage of prediction error (%PE) between the simulated and data observed in vivo. The pharmacokinetic parameters predicted on the basis of the different input CBZ dissolution rates, as well as the relevant prediction error statistics, are given in Table 3. The best matching between the predicted and the observed C_{max} and AUC values was accomplished for the drug dissolution in 0.5% and 1% SLS. Interestingly, the simulated in vivo profiles did not appear to be strongly affected by the differences in drug dissolution rate. This is well in accordance with theory in which it can be shown that the bioavailability parameter C_{max} of a compound with a long elimination half-life is less affected by changes in the input rate when compared to a compound exhibiting a short elimination half-life.

The deviations between the predicted C_{max} and t_{max} values obtained for the different pH dissolution media were not consistent with the in vitro results. CBZ dissolution profiles in water, media pH 1.2, 4.5 and 6.8 were almost superimposable with the calculated f_2 in the range from 62.8 to 91.0.

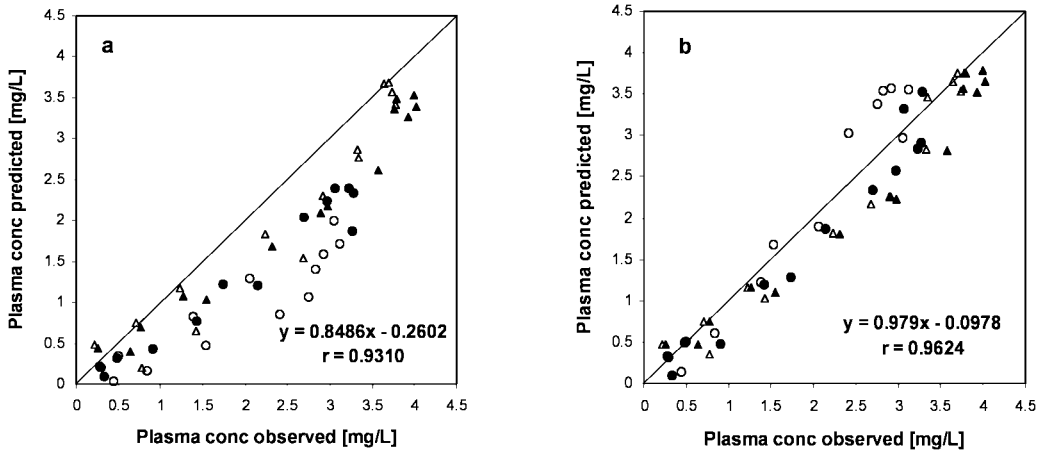

Figure 7. IVIVC plot for CBZ tablets in (a) water and (b) 1% SLS (test IR tablets (▲); reference IR tablets (△); test CR tablets (●); reference CR tablets (○)).

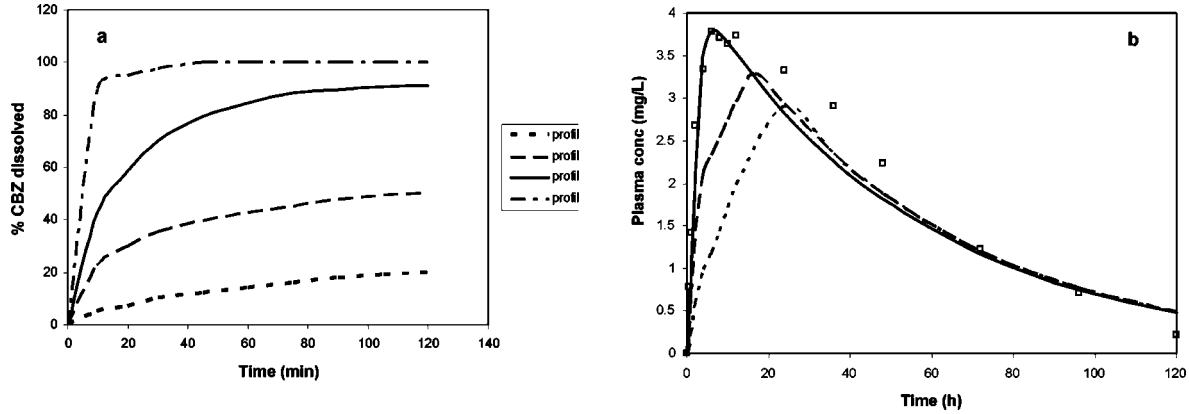

Figure 8. Virtual CBZ dissolution profiles and the corresponding simulated in vivo profiles used to justify lower dissolution acceptance criteria. The simulated profiles III and IV overlap. Open square symbols refer to the actual in vivo data.

Such data are in accordance with pH independent CBZ solubility. The plateau at approximately 50% CBZ dissolved was reached after two hours of investigation for all media without surfactant. The plateau observed coincides well with the CBZ saturated solubility. It may be postulated that the differences obtained are due to a simulation artifact resulting from the software approximation of the time needed to accomplish 100% drug dissolution which was estimated as 5.5 and 15.4 h for water and pH 6.8 media, respectively.

Influence of Drug Dissolution on Gastrointestinal Simulation for CR Tablets. With the aim to evaluate the influence of in vitro drug dissolution rate on CBZ plasma concentration profiles, dissolution data obtained under the various experimental conditions for the reference CBZ CR tablets (Figure 5a) were used as an input function in the GastroPlus Single Simulation Mode. The results obtained are shown in Figure 5b. Although the significant differences between the dissolution profiles were observed in vitro, simulated profiles based on CBZ dissolution in 1% SLS and HCM were similar and in a good agreement with the data observed in vivo. Pharmacokinetic profile predicted on the base of the CR tablets dissolution in water indicates slow and incomplete drug absorption. Such result is in accordance with the slow and incomplete drug release observed in vitro as well as with the software calculated 39.29 h to be the time needed for 100% drug dissolution to be accomplished. That time overages the physiologically relevant gastrointestinal transit time. Both the pharmacokinetic parameters predicted on the basis of the different input CBZ dissolution rates and the relevant prediction error statistics are given in Table 4.

In Vitro−in Vivo Correlation. Drug dissolution data obtained for both the IR and the CR tablets in water and media containing 1% SLS (Figure 6) were used to predict CBZ plasma concentration profiles in order to develop a level A in vitro−in vivo correlation (IVIVC) model. IVIVC plots of the predicted data vs the observed ones in vivo are presented in Figure 7. Linear regression analysis of the pooled data for both the generic and reference IR and CR tablets indicate high level A IVIVC. The calculated correlation coefficients were 0.9310 and 0.9624 for predictions based on the in vitro data observed in water and 1% SLS, respectively. Corresponding slopes of the regression lines were 0.8486 and 0.9790. The results obtained suggest that 1% SLS may be considered as the universal biorelevant dissolution medium for both the IR and CR CBZ tablets.

Biowaiver Justification and Risk Analysis. In order to identify biorelevant dissolution specifications, a set of virtual in vitro inputs was used for gastrointestinal simulations of CBZ pharmacokinetic profiles. Virtual in vitro inputs and the corresponding simulated plasma profiles are shown in Figure 8. Since C_{max} was more sensitive than AUC to the difference in drug input kinetics, C_{max} was used as the primary bioequivalence criterion. Borderline in vivo profile showing 20% deviation in C_{max} value compared to the actual C_{max} observed in vivo was generated with the input as low as 20% drug dissolved after 2 h (Figure 8, profile I). However, a large deviation in t_{max} values between the observed and predicted profiles (i.e., 6.0 and 24 h) was evident, suggesting that additional constraints should be introduced for dissolution acceptance criteria to be defined.

The obtained results of gastrointestinal simulation and IVIVC modeling indicate that, in spite of a correlation between the in vitro and in vivo data, the predicted plasma concentration profiles are rather insensitive to the differences in drug input kinetics. Such data are in accordance with the literature data reporting that CBZ products showing different dissolution kinetics were found to be bioequivalent.[18,19] This findings would allow much wider dissolution specifications to be set compared to current USP recommendations (USP specification is not less than 75% dissolved in 60 min).[20] Since CBZ in vivo behavior is determined by its pharmacokinetic characteristics (i.e., long elimination half-life) rather than the dosage form properties, it was possible to obtain an universal IVIVC model for both the IR and CR products. Therefore, further generalization of such concept to other compounds should be carefully evaluated on a case by case basis.

Although the literature data from CBZ BE studies are somewhat contradictory and therefore inconclusive, the results from the independent sources[19] indicate that though CBZ absorption from generic products is usually slightly faster, there is no sound evidence that it is the cause of the adverse drug reactions. Such data are supported by our simulations indicating that high dissolution rates were not related to the significant increase in C_{max} values (Figure 8, profile IV).

The proposed methodology involving gastrointestinal simulation technology and IVIVC suggests that there is a rationale for considering CBZ biowaiver extension. At present, other factors such as its narrow therapeutic index and vital indication are the limitations for granting marketing authorization based on the in vitro data alone. In such a situation, a risk associated with a therapy failure and occurrence of dose-dependent adverse drug reactions when a drug is administered in a target patient population should be evaluated additionally.

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