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Research Article

Theme: Towards Integrated ADME Prediction: Past, Present, and Future Directions
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An Investigation into the Importance of "Very Rapid Dissolution" Criteria for Drug Bioequivalence Demonstration using Gastrointestinal Simulation Technology

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Abstract. The Biopharmaceutics Classification System (BCS) is based on the mechanistic assumptions that the rate and extent of oral drug absorption are governed by drug solubility, intestinal permeability, and dissolution rate from the dosage form administered. 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. On the basis of BCS, currently, the biowaiver concept is adopted and recommended for immediate release of drug products containing highly soluble and highly permeable compounds (BCS class 1 drugs). Dissolution testing properties are proposed to be more stringent: very rapid dissolution is demanded when generic drug application is submitted with the exemption of *in vivo* bioequivalence study. In the present paper, Gastrointestinal Simulation Technology has been applied in order to evaluate the potential for different *in vitro* drug dissolution kinetics to influence dosage forms *in vivo* behavior and the relevance of "very rapid dissolution" criteria to be met (i.e., more than 85% of dose dissolved in 15 min).

KEY WORDS: BCS; bioequivalence; dissolution; gastrointestinal simulation.

INTRODUCTION

With the introduction of Biopharmaceutics Classification System (BCS) and the biowaiver concept, the essential requirement in generic drug approval process, the demonstration of similarity of rate and extent of drug absorption between the investigated and the reference, innovator product, has been shifted from the *in vivo* human bioequivalence study to the possibility to waive it based on the surrogate *in vitro* data (1). The BCS has been introduced as a scientific framework for classifying drug substances according to their aqueous solubility and intestinal permeability (2). It is based on the mechanistic assumptions that the rate and extent of oral drug absorption are governed by drug solubility, intestinal permeability, and dissolution rate from the dosage form administered (3). 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 the immediate release of drug products containing highly soluble and highly permeable compounds (BCS class 1 drugs) (4,5). Biowaiver extensions have also been discussed for BCS class 3 drugs (6) as well as for class 2 drugs under the presumption that they dissolve completely during the gastrointestinal passage (7). Not only generic drug manufacturers may benefit from biowaiver applications. BCS principles are increasingly used in the development of New Chemical Entities where BCS-based waiver of *in vivo* studies can result in significant savings, particularly during the late stages of clinical testing when formulation adjustments are performed (8).

The general recognition of the low risk associated with the biowaiver decision for class 1 drugs initiated further discussions regarding the appropriate regulatory requirements and recommendations. While the ICH Q6 Guideline (9) recognizes that for highly soluble or highly permeable drug substances, the requirement for dissolution testing, under certain circumstances, might be replaced by disintegration testing; the regulatory authorities in Europe tend to ask for more stringent dissolution specifications in order to justify the biowaiver application (10). In the present paper, Gastrointestinal Simulation Technology (GST) has been applied in order to evaluate the potential for different *in vitro* drug-dissolution kinetics to influence dosage forms *in vivo* behavior and the relevance of

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Table I. Summary of the Losartan-Potassium Input Parameters Employed for Gastrointestinal Simulation

Parameter	
Molecular weight	422.92
pKa	5[a]
logP	4.01[a]
Solubility	100 mg/mL[b]
Human jejunal permeability (P_{eff})	1.15×10^{-4} cm/s[b]
Dose	50 mg
Dose volume	250 ml
Mean precipitation time	900 s[c]
Drug particle density	1.2 g/ml[c]
Effective particle radius	25 μm[c]
Diffusion coefficient	0.75×10^{5} cm^2/s
First Pass Extraction	67%[a]
Unbound percent in plasma (f_u)	3%[d]
Clearance (CL)	36 L/h[d]
Volume of distribution (V_c)	1.5 L/kg
Elimination half-life ($t_{1/2}$)	1.99 h[d]
Body weight	69 kg
Simulation time	16 h

[a] Literature value taken from (12)
[b] Literature value taken from (13)
[c] Default GastroPlus values
[d] Literature value taken from (14)

"very rapid dissolution" criteria (i.e., more than 85% of dose dissolved in 15 min). Gastrointestinal simulation studies were performed for a range of BCS class 1 model drugs (including ketoprofen as border line class I/II substance) based on the virtual set of *in vitro* profiles representing the lower boundary of "rapid" and "very rapid" dissolution specifications.

MATERIALS AND METHODS

Gastrointestinal Simulation

Gastrointestinal simulation based on the Advanced Compartmental Absorption and Transit model (GastroPlus ® version 5.3.0., SimulationsPlus, Lancaster, CA, USA) was used. The equations, implemented in GastroPlus®, include the consideration of six states of drug substance (unreleased, undissolved, dissolved, degraded, metabolized, and absorbed), 18 compartments (stomach, six compartments for the small intestine, two colon compartments, 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 or exsorbed from each absorption or transit compartment (11).

Drug absorption and disposition was simulated based on the physicochemical, pharmacokinetic, and virtual drug dissolution properties of the selected model drugs. 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. A representative GastroPlus® input dataset is shown for losartan potassium (Table I). Simulation models used for the other model drugs investigated, i.e., prednisolon, propranolol, and ketoprofen, were described and validated previously (7). Part of the validation process included virtual trial simulations assuming distributions of physiological variables such as transit times in the various compartments, pH values in all compartments, and pharmacokinetic parameters as, e.g., systemic clearance and first-pass effect. Random samples of all stochastic variables were generated for each simulation. The final results were based on virtual trials with 100 volunteers which were compared to known ranges of concentration *versus* time profiles.

In Vitro Data

The *in vitro* dissolution profiles used as the input data were generated on the basis of the case scenario covering the situation in which comparative dissolution profiles (1) could be described as "rapid" (i.e., more than 85% drug dissolved in 30 min); but (2) not similar (i.e., similarity factor value, f_2, is 35.37); (3) one of the profiles is "very rapid" (i.e., more than 85% drug dissolved in 15 min); (4) when the 15-min data points are exempted, the profiles are regarded as similar (f_2= 50.04). The described dissolution profiles are presented in Fig. 1.

RESULTS AND DISCUSSION

Gastrointestinal Simulation—Model Validation

Gastrointestinal simulation results for losartan IR tablets are presented in Fig. 2, together with the actual *in vivo C–t* plasma profile observed in the single dose human bioequivalence study (*in-house data on file*). The predicted pharmacokinetic parameters and those observed *in vivo* were almost identical as measured by the percent prediction error values (PE) which were less than 10% for C_{max} and AUC values ($PE_{C_{max}}$ was 5.8%, $PE_{AUC_{0-t}}$ was 1.9%, $PE_{AUC_{0-\infty}}$ was 1.5% and $PE_{t_{max}}$ was 10.4%). Good prediction patterns were achieved for the other model substances as well (data supporting the validation for these substances were published previously) (7).

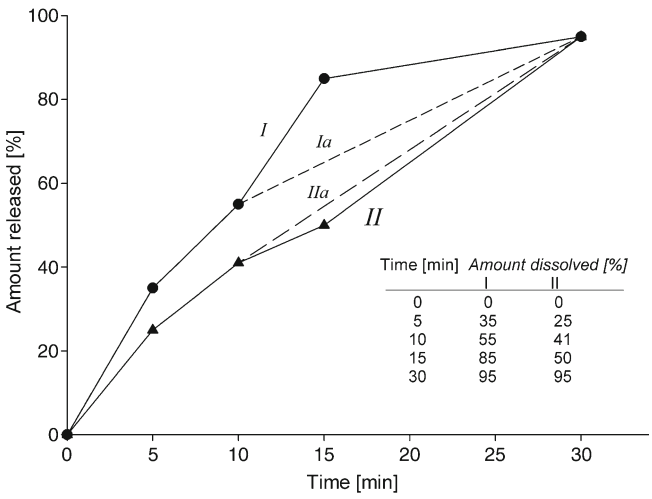

Fig. 1. Virtual drug dissolution profiles

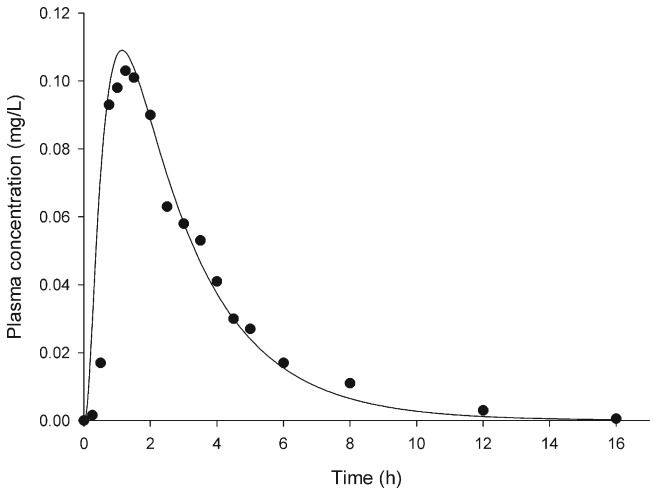

Fig. 2. Predicted (*line*) and observed (*filled circles*) mean losartan plasma *C–t* profiles following administration of a single 50-mg dose from the IR drug product

Gastrointestinal Simulation—Influence of Dissolution Rate on Drug Disposition Prediction

Pharmacokinetic parameters predicted by GST based on different input dissolution profiles (I and II, with or without 15-min data point) are presented in Table II, together with the actual data observed in the relevant *in vivo* studies. According to the results obtained, it is evident that regardless of the different physicochemical and/or pharmacokinetic properties of the selected model drugs, predicted drug behavior *in vivo* remains almost unaffected by the differences in the *in vitro* input kinetics employed.

It is generally accepted that in the case of highly soluble drugs, drug absorption rate is limited by gastric emptying time. Although relatively variable, gastric emptying time under fasting conditions accounts to approximately 60 min (15). In our simulations, the transit time in the stomach compartment was set at 0.25 h, representing the lowest physiologically relevant value. This was considered as the most discriminative simulation approach since it was expected that the differences in the early time points of the input data would have the major impact on drug absorption rate parameters (C_{max}, t_{max}). However, there were no differences observed in the predicted profiles whether the complete drug dissolution occurred in 15 min or the percent drug dissolved in 15 min was 50%. Virtual dissolution profiles representing "rapid dissolution" scenario (II, Ia, and IIa) resulted in the superimposable predicted drug plasma *C–t* curves when compared to the "very rapid dissolution" (dissolution profile I). Such data indicate that the specification of "not less than 85% dissolution in 30 min" should be considered as a rational requirement for biowaiver justification in the case of highly soluble drugs. Results of the present simulations are in accordance with *in vivo* data reported suggesting that differences in the dissolution profiles during the first 30 min may not be relevant for rapidly dissolving formulations of BCS class 1 drugs (8). Such findings support the proposal for single-point dissolution requirement for highly soluble drugs to be reconsidered. The results obtained also indicate that the 15-min data point is of no critical importance and that similarity factor (f_2) value higher than 50 may be too conservative for dissolution profiles comparison and merits further evaluation.

BCS-based biowaiver justification, although becoming increasingly routine, still face many barriers that limit its broader application. Lack of international harmonization on the topic, as well as the uncertainty of acceptance by the regulatory agency, are quoted as the reasons for the reluctance to apply for biowaivers (16). Modeling and simulation is generally, underutilized in assessing bioequivalence in the pharmaceutical industry due to lack of confidence in the fundamentals of this approach and lack of experience with

Table II. Pharmacokinetic Parameters Predicted Based on the Virtual Dissolution Profiles (I, Ia, II, and IIa)

Pharmacokinetic parameter	Predicted I	Predicted Ia	Predicted II	Predicted IIa	*In vivo* observed
Losartan (50 mg)					
C_{max} (μg/mL)	0.111	0.110	0.111	0.111	0.103
AUC_{0-t} (μg h/L)	370.73	370.27	370.73	370.29	363.38
$AUC_{0-\infty}$ (μg h/L)	371.35	370.89	371.35	370.91	365.13
t_{max} (h)	1.23	1.23	1.23	1.23	1.25
Propranolol (40 mg)					
C_{max} (μg/mL)	0.027	0.027	0.026	0.027	0.028
AUC_{0-t} (μg h/L)	192.92	192.95	193.11	193.03	227.80
$AUC_{0-\infty}$ (μg h/L)	201.25	201.27	201.37	201.32	–
t_{max} (h)	2.32	2.32	2.32	2.32	–
Ketoprofen (50 mg)					
C_{max} (μg/mL)	2.267	2.263	2.242	2.257	3.100–4.500
AUC_{0-t} (μg h/L)	9,755.1	9,755.1	9,755.1	9,755.3	–
$AUC_{0-\infty}$ (μg h/L)	9,771.7	9,771.7	9,771.7	9,771.7	11,524.5
t_{max} (h)	1.36	1.36	1.44	1.36	1.30
Prednisolon (5 mg)					
C_{max} (μg/mL)	0.161	0.161	0.160	0.160	0.144
AUC_{0-t} (μg h/L)	644.7	644.7	644.7	644.7	713.6
$AUC_{0-\infty}$ (μg h/L)	651.9	651.9	651.9	651.9	–
t_{max} (h)	1.72	1.72	1.72	1.72	–

Ia and IIa refer to dissolution profiles without 15-min data point

regulatory acceptance. However, it is the fundamental of a Quality by Design approach in drug development and approval. The results of the present study indicate that Gastrointestinal Simulation Technology may offer the necessary support in internal decision making within a pharmaceutical company when verification of certain formulation and/or manufacturing changes should be performed. A broader use of this method, however, will need further experience including additional compounds and their formulations, preferably studied prospectively both *in vitro* and *in vivo*.

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