COMMUNICATION

Very Rapid Dissolution Is Not Needed to Guarantee Bioequivalence for Biopharmaceutics Classification System (BCS) I Drugs

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ABSTRACT: Currently, the EMEA, FDA, and WHO as regulatory authorities accept rapidly dissolving (>85% dissolved in 30 min) biopharmaceutics classification system (BCS) I drug products for biowaiver candidates. In the draft EMEA guideline the requirement has been set tighter, that is, the drug product should be very rapidly dissolving (>85% dissolved in 15 min) to be eligible for a biowaiver. Pharmacokinetic modeling of 32 BCS I drugs was performed to demonstrate that very rapid dissolution is not necessary to guarantee bioequivalence for them. Rapid dissolution and similar dissolution profiles are sufficient criteria for all BCS I drugs. © 2009 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:621–625, 2010

Keywords: bioequivalence; biopharmaceutics classification system (BCS); dissolution rate; absorption; solubility

INTRODUCTION

Biopharmaceutics classification system (BCS) I drugs are currently accepted as eligible for biowaivers. For these drugs, *in vitro* dissolution studies can be used as surrogate for *in vivo* bioequivalence studies. In the draft EMEA guideline on the investigation of bioequivalence, BCS I drugs are accepted as biowaiver candidates if the drug product is very rapidly dissolving, that is, more than 85% is dissolved in 15 min.[1] Currently the FDA, EMEA, and WHO accept BCS I drugs for biowaivers if the drug product is rapidly dissolving, that is, more than 85% is dissolved in 30 min.[2–4] The aim of this article is to present simulations that were performed to study dissolution criteria for 32 BCS I drugs and to evaluate whether dissolution requirements, more than 85% dissolved in 15 or 30 min and similar dissolution profiles or not, are sufficient criteria for BCS I drugs.

MATERIALS AND METHODS

Biopharmaceutical Classification

Simulations were performed with 32 BCS I drugs from the WHO model list of essential medicines. The selection of BCS I drugs was based on the

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work of Lindenberg et al.[5] In this article, the solubility classification is based on experimental *in vitro* solubility data. Permeability classification is done based on *in vivo* absorption data in man or different animal species or *in vitro* Caco-2 permeability data.

Pharmacokinetic Model and Parameters

The compartment absorption and transit model (CAT) of Yu et al.[6] was used in simulations (Fig. 1). Parameters describing the physiology of the gastrointestinal tract, and solubility, permeability, and dissolution of drug substances, as well as pharmacokinetic properties of drug were combined in the CAT model. Parameters describing the physiology of the gastrointestinal tract were the same as used in the study by Kortejärvi et al.[7] It was assumed that solid oral dosage form disintegrates to multiple units in the stomach and both solid multiple units and the dissolved drug empty from stomach into the small intestine.

One-compartment model was combined with the CAT model to predict concentration profiles of each of the 32 BCS I drugs. Drug-related parameters absorption rate (K_a) and elimination rate (K_{el}) constants were drug specific (Tab. 1). Solubility was not taken into account, because all drugs are highly soluble, thus, solubility is not a rate-limiting step for absorption. The absorption rate constant was calculated on the basis of

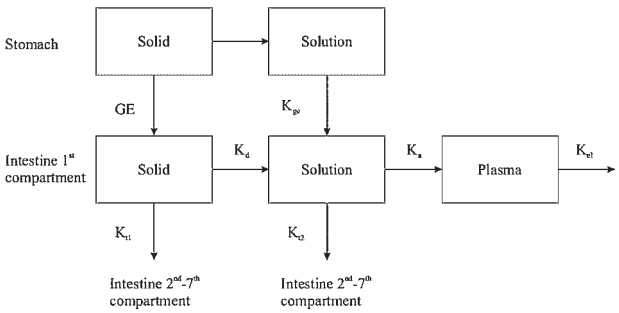

Figure 1. The structure of the CAT model and parameters used in the model: GE is the gastric emptying for solid drugs, K_{ge} the gastric emptying rate constant for dissolved drug, K_d the dissolution rate constant, K_{t1} and K_{t2} are distribution and transit rate constants for solid and dissolved drug, respectively, K_a is the absorption rate constant and K_{el} is the elimination rate constant. The drug distributes, transits, dissolves and absorbs identically from all seven compartments of the intestine.

Table 1. Absorption ($K_a\,h^{-1}$) and Elimination Rate ($K_{el}\,h^{-1}$) Constants for BCS I Drugs

	Drug	K_a	K_{el}
1	Amiloride	0.4901	0.0924
2	Amitriptyline	8.3299	0.0408
3	Chloroquine	4.0802	0.0012
4	Chlorpheniramine	3.8508	0.0315
5	Clomipramine	9.4397	0.0267
6	Cyclophosphamide	1.9896	0.0866
7	Dexamethasone	1.7667	0.1873
8	Diazepam	7.0819	0.0165
9	Diethylcarbamazine	2.4856	0.0866
10	Ethinylestradiol	10.8608	0.0715
11	Ethosuximide	2.2821	0.0131
12	Fluconazole	1.5757	0.0231
13	Isoniazid	1.0230	0.6931
14	Levamisole	2.0587	0.1386
15	Levodopa	0.7161	0.5332
16	Levonorgestrel	9.2380	0.0737
17	Levothyroxine	3.1193	0.0044
18	Nicotinamide	1.6376	0.0883
19	Norethindrone	7.6282	0.0990
20	Phenobarbital	2.2478	0.0070
21	Prednisolone	1.5440	0.2039
22	Proguanil	1.2894	0.0347
23	Propranolol	2.3751	0.2039
24	Pyrazinamide	1.2132	0.0730
25	Pyridoxine	0.7972	0.0017
26	Quinine	2.4380	0.0630
27	Salbutamol	0.4749	0.2888
28	Stavudine	0.8679	0.4951
29	Theophylline	1.2888	0.0963
30	Verapamil	2.2674	0.2476
31	Warfarin	2.9644	0.0239
32	Zidovudine	0.7994	0.5332

physicochemical molecular descriptors, $\log D$ in pH 6.0 and polar surface area (PSA), of the drugs.[8] The following equation was used:

$$\log K_a = 0.623 + 0.154 \log D_{6.0} - 0.007(\mathrm{PSA})$$

This equation predicts passive oral absorption of drugs and therefore drug substances with an active transport mechanism were excluded. Predictability of this equation is reasonable, since it correctly classified 25 out of 32 (78%) BCS I drugs from Lindenberg et al.'s article.[5] Elimination rate constants were obtained from literature, mostly from Obach et al.[9] Theoretical simulations were performed to create contour plots. The CAT model was the same that was used with drug-related simulations, and the range for absorption rate

Table 2. *In Vitro* and *In Vivo* Dissolution Rate Constants Corresponding to Different Dissolution Criteria Required in WHO, FDA, and EMEA Guidelines

	Fig 2A Very Rapid Dissolution 85% in 15 min (EMEA Draft)	**Fig 2B** Rapid Dissolution 85% in 30 min (WHO)	**Fig 2B** Rapid Dissolution and Similar Dissolution Profiles (FDA, Current EMEA)
In vitro K_d	8	4	4 vs. 5.5
In vivo K_d	4	2	2 vs. 2.75
Comparisonof C_{max}	Tablet vs. oral solution	Tablet vs. oral solution	"Slow dissolved" tablet vs. "Fast dissolved" tablet

constant was from 0.4 to 12 h^{-1} and for elimination rate constants 0.001 to 0.9 h^{-1}.

Different dissolution requirements of regulatory authorities were compared (Tab. 2). Dissolution rate constants were calculated to corresponding rapid and very rapid dissolutions, respectively. Time scale factor 2 was used between *in vivo* and *in vitro* dissolution. For rapidly dissolving drug products the requirement for dissolution profile similarity, similarity factor (f_2), was also studied.[10] Similarity factors more than 50 indicate similar dissolution profiles. "Slow dissolved" tablet versus "Fast dissolved" tablet has f_2 51.

Comparison of C_{max} Values

C_{max} is a more sensitive parameter for differences in dissolution rate than area under the curve (AUC).[7,11] Simulations were performed for both tablet and oral solution formulations. C_{max} ratios were calculated (C_{max} tablet/C_{max} oral solution or C_{max} "Slow dissolved" tablet/C_{max} "Fast dissolved" tablet). Drugs that have C_{max} ratio more than 0.9 can be considered to have low risk to fail in a bioequivalence study. In bioequivalence studies the test product is considered bioequivalent with the reference product, if 90% confidence intervals for the ratio of the mean for C_{max} and AUC is 0.8–1.25.

RESULTS AND DISCUSSION

Simulations covered a wide range of BCS I drugs with different absorption and elimination properties (Tab. 1). Elimination rates varied from 0.0012 to 0.69 h^{-1}, corresponding to elimination half-lives of 1–570 h and absorption rate constants varied from 0.48 to 10.9 h^{-1}. In all simulations the time scale factor 2 was selected between *in vivo* and *in vitro* dissolution. *In vivo* dissolution is probably slower, because in the gastrointestinal tract lower volumes of liquids are available and stirring conditions are less effective than in dissolution vessel. C_{max} ratios were calculated tablet versus oral solution, when dissolution requirement very rapid or rapid was studied (Tab. 2). In theory, immediate-release oral formulation can be extremely fast dissolving and behaves like oral solution. C_{max} of "Slow dissolved" versus "Fast dissolved" tablet was compared, when dissolution requirement was rapid and dissolution profiles were similar.

All 32 BCS I drugs have low risk to fail in bioequivalency study (Fig. 2A–C). C_{max} ratios were more than 0.9, that is, less than 10% differences were observed in C_{max} values. Maximum differences in C_{max} were observed with rapidly eliminating isoniazid (elimination half-life of 1 h), the drug number 13 in contour plots. Difference in C_{max} was <1%, 6%, and 4% when dissolution requirement was very rapid, rapid or rapid and similar dissolution profiles, respectively. Based on simulations of 32 BCS I drugs, there is no need to tighten the dissolution criteria from rapid to very rapid for BCS I drugs.

Theoretically BCS I drugs, which dissolve, absorb, and eliminate rapidly, have more than 10% difference in C_{max} (see shaded upper right corner in Fig 2B). However, current dissolution criteria in FDA and EMEA guidelines, rapid dissolution and similar dissolution profiles, are reliable and sufficient for all BCS I drugs, because <8% difference in C_{max} were observed (Fig. 2C). Very rapid dissolution suggested in draft EMEA guideline is unnecessary strict and conservative criterion for BCS I drugs (Fig. 2A).

CONCLUSION

Based on theoretical and 32 drug-related simulations of BCS I drugs, rapid dissolution and similar

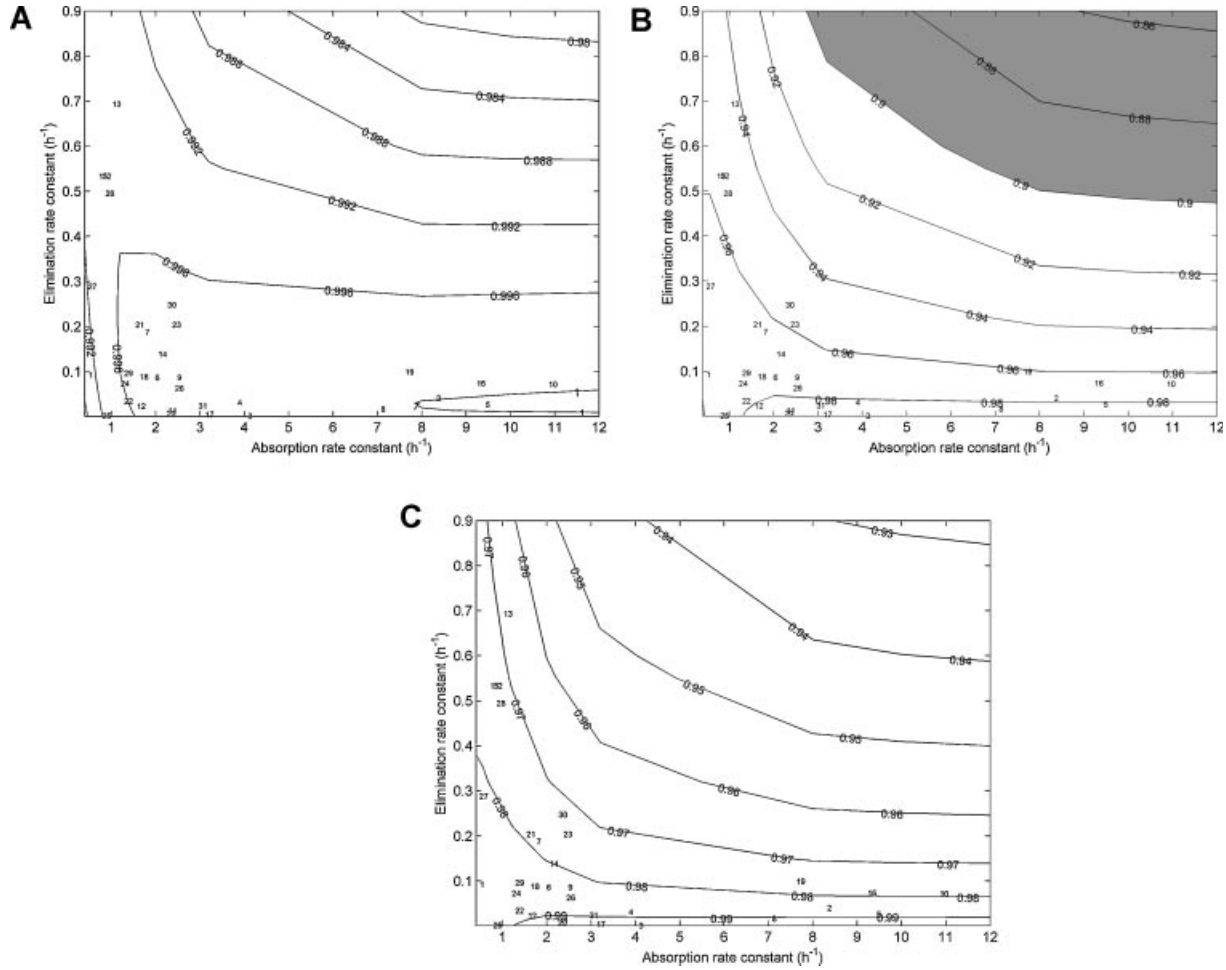

Figure 2. A–C: C_{max} ratios of BCS I drugs with different dissolution requirements: (A) very rapid dissolution, (B) rapid dissolution, and (C) rapid dissolution and similar dissolution profiles. Each drug is presented as a number 1–32. In the shaded area in the contour plot C_{max} difference is more than 10%.

dissolution profiles are reasonable requirements for all BCS I drugs. Tighter dissolution criterion, very rapidly dissolving, suggested in draft EMEA guideline, is unnecessarily strict for BCS I drugs and will reduce possibilities to submit BCS biowaiver applications.

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