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Research paper

A comparative study of different release apparatus in generating *in vitro–in vivo* correlations for extended release formulations

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ABSTRACT

The importance of hydrodynamics in the development of *in vitro–in vivo* correlations (IVIVCs) for a BCS Class II compound housed in a hydrophilic matrix formulation and for a BCS Class I compound housed in an osmotic pump formulation was assessed. *In vitro* release data were collected in media simulating the fasted state conditions in the stomach, small intestine and the ascending colon using the USP II, the USP III and the USP IV release apparatuses. Using the data collected with the USP II apparatus, the plasma profiles were simulated and compared with human plasma profiles obtained after administration of the same dosage forms to healthy fasted volunteers. Data obtained with the USP III and USP IV apparatuses were directly correlated with the deconvoluted human plasma profiles. *In vitro* hydrodynamics affected the release profile from the hydrophilic matrix. For both formulations, based on the values of the difference factor, all three apparatuses were equally useful in predicting the actual *in vivo* profile on an average basis. Although some hydrodynamic variability is likely with low solubility drugs in hydrophilic matrices, the hydrodynamics of USP II, III and IV may all be adequate as a starting point for generating IVIVCs for monolithic dosage forms in the fasted state.

1. Introduction

Oral bioavailability of an extended release (ER) drug product is by definition limited by intraluminal drug release. Correlations between *in vitro* release and *in vivo* plasma profiles (*in vitro–in vivo* correlations, IVIVCs) constitute an integral part of the development of an ER drug product. The main objective of an IVIVC is to reduce the number of bioequivalence studies required during scale-up and postapproval changes [1,2].

Compared with immediate release formulations, drug release kinetics from ER products should be less influenced by environmental factors since the control should reside in the dosage form rather than being subjected to the interplay of drug characteristics with gastrointestinal (GI) physiology. However, robustness of the release profile is always an issue with such dosage forms, particularly with a view to preventing dose dumping. Up till now, the main focus with ER products has been on reflecting changes in gut fluid composition during passage of dosage form along the fasted [3–6] and the fed [5,7] GI tract, with comparatively little attention being paid to the simulation of GI hydrodynamics.

The objective of the present investigation was to assess the importance of *in vitro* hydrodynamics, i.e. of type/intensity of agitation, media volumes and prevalence of sink conditions, in developing IVIVCs for extended release products that house compounds with high intestinal permeability when using release media simulating the intraluminal conditions in the fasted state. Two monolithic ER products were evaluated, one carbomer (hydrophilic) matrix device and one osmotic pump. Although data with carbomer matrix formulations have not been published to date, it has been shown that hydrodynamics can have an impact on the *in vitro* release profile from HPMC (hydrophilic) matrix formulations [8–13] and that they may be important for the prediction of plasma levels [13]. On the other hand, a frequently cited advantage of osmotic pumps is their relative insensitivity to hydrodynamics [14]. Even so, it has been observed that the release rate may vary with the hydrodynamics (at least when simulated gastric fluid is used as the release medium [15]). Also, the delivery rate of potassium chloride from a simple osmotic pump was observed to be affected at high agitation rates and under turbulent fluid flow [16]. However, it is not known whether the effect of hydrodynamics is crucial for the development of an IVIVC model for osmotic pumps.

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2. Materials and methods

2.1. Materials

A swellable and eroding carbomer matrix tablet (155 mg; round tablet with diameter of 7 mm) containing a poorly soluble compound BRL-49653 (8 mg per tablet) and an osmotic pump (90 mg weight; hexagonal shape with the distance between two opposite sides being 5 mm) containing the highly soluble compound salbutamol (Volmax®, 4 mg/tab) were tested. Physicochemical characteristics of BRL-49653 and salbutamol (as salbutamol sulphate) are presented in Table 1. GSK data and literature data [19], respectively, confirm that both compounds are highly permeable in the small intestine. Formulations and pure drug substances for standard curves were supplied by GSK (Harlow, UK). Reagents for preparing the release media were of analytical grade, whereas those used for the analysis of samples were of HPLC grade.

2.2. In vitro release studies

2.2.1. Release media

Experiments were performed in triplicate at 37 °C in simulated gastric fluid (SGF [20]) that had a pH of 1.8, in fasted state simulating intestinal fluid (FaSSIF [21]) and in simulated colonic fluid (SCoF [4]).

2.2.2. USP II release apparatus [22]

A Distek® dissolution system (model 2100B, North Brunswick, NJ, USA) and an Erweka® dissolution system (model DT6, Erweka GmbH, Heusenstamm, Germany) were used. In all cases, the volume of the release medium was 500 ml. After confirming that rotational speed of the paddle did not affect the release rates in SGF (for speeds between 50 and 150 rpm), experiments in FaSSIF and SCoF were performed with the paddle rotating at 100 rpm. Three-milliliter samples were withdrawn (with replacement) and immediately filtered through a 0.45 μm Teflon filter (Titan® filter 0.45 μm (Scientific Resources Inc., NJ, USA). Absence of drug adsorption onto the filters was confirmed in preliminary experiments (data not shown). An appropriate volume of the filtrate was analyzed with HPLC.

For both compounds, the analytical methodology was based on methods provided by GSK. For BRL-49653, a reversed-phase Hypersil® ODS column (250 × 4.6 mm, 5 μm particle size) was used. The mobile phase was composed of aqueous buffer solution of sodium dihydrogen phosphate 0.05 M (pH 6.8) and acetonitrile and triethylamine (70:30:0.08, v/v/v). The flow rate of the mobile phase was 2 ml/min. Injection volume was 50 μl. Analysis was performed at ambient temperature, and the wavelength of detection was set at 247 nm. For salbutamol, a reversed-phase Hypersil® BDS C8 column (150 × 4.6 mm, 5 μm particle size) was used. Gradient conditions were applied, as shown in Table 2. The flow rate of the mobile phase was 1 ml/min. Injection volume was 100 μl. Analysis was performed at ambient temperature, and the wavelength of detection was set at 230 nm.

Table 1
Physicochemical characteristics of the compounds studied in the present investigation.

	MW	pKa	Solubility in water (mg/ml)	Log P
BRL-49653[a]	473.5	5.4 (acidic) 6.8 (basic)	0.45 (pH 4.0) 0.08 (pH 6.0) 0.06 (pH 8.0)	2.1
Salbutamol sulphate	239.3[b]	10.4 (acidic)[c] 9.1 (basic)[c]	250 (25 °C)[a]	0.11[d]

[a] Physicochemical data provided by GSK.
[b] Substance identifier, Sci Finder Scholar 2007 (American Chemical Society, http://www.cas.org/SCIFINDER/SCHOLAR/).
[c] [17].
[d] [18].

Table 2
The gradient conditions of mobile phase applied for the analysis of salbutamol with HPLC[a].

Time (min)	Solvent A[b] (%)	Solvent B[c] (%)
0	95	5
9	95	5
12	70	30
13	70	30
16	20	80
22	20	80
25	95	5
30	95	5

[a] GSK data on file.
[b] Solvent A is 0.05% triethylamine in 0.025 M sodium dihydrogen phosphate (pH 3.0, adjusted with 10% aq. phosphoric acid).
[c] Solvent B is 0.05% triethylamine in acetonitrile/methanol (65:35).

2.2.3. USP III release apparatus [22]

A Caleva BioDis® Release Rate Tester (RRT 8, CALEVA Ltd, Dorset, England) was used. Each product was sequentially tested in three media simulating the fasted state composition of the GI lumen as indicated in Table 3. Selected dip rates were based on established experience from screening different dip rates and mesh screen combination and their impact on drug release from different types of dosage forms [23]. The medium volume was 200 ml in each of the dissolution vessels, and the mesh size used was 420 μm at top and bottom. Three-milliliter samples were withdrawn and immediately filtered through a 0.45 μm Teflon filter (Rezist® FP 030/2, Schleicher & Schuell GmbH, Dassel, Germany). An appropriate volume of the filtrate was analyzed with HPLC as described above for the experiments with the USP II apparatus.

2.2.4. USP IV release apparatus [22]

An Erweka® flow-through dissolution tester (model DFZ60, Erweka GmbH, Heusenstamm, Germany) equipped with Ø 12 mm cells that were connected to an Erweka® piston pump (model HKP60) was used. A 5mm-size glass bead was positioned in the tip of the cell, 1.7gr of 1mm-size glass beads were added, then a glass fiber filter (MNGF1: 0.7 μm pore size, 25 mm diameter, Macherey-Nagel, Germany) was placed on the top of the cell. During the experiment, the tablet was mounted on a holder. Each product was sequentially tested in three media simulating the fasted-state composition of the GI lumen as indicated in Table 4. Duration of exposure to the various media and corresponding flow

Table 3
Conditions applied to the Biodis experiments.

Medium	Period from beginning of experiment (min)	Dip rate (dpm)
SGF	0–60	15
FaSSIF	60–300	10
SCoF	300–480	10

Table 4
Conditions applied to the flow-through experiments.

Medium	Period from beginning of experiment (min)	Flow rate (ml/min)
SGF	0–60	8
FaSSIF	60–300	4
SCoF	300–480	4

rates were designed to achieve a balance between the fluid volumes into which the tablet releases its contents intraluminally and the physiological residence times of monolithic extended release products in the GI lumen. The lack of radial water flux in the *in vitro* test system was also taken into account in the experimental design [4]. From the cell, the release medium was collected in volumetric cylinders (ca. 250 ml), and samples were subsequently analyzed with HPLC as described above for the experiments with the USP II apparatus.

2.3. Human data

Individual *in vivo* plasma concentration vs. time data after single dose administration of the BRL-49653 carbomer matrix formulation to 20 fasted healthy volunteers were provided by GSK. The values of the elimination rate constant and of the volume of distribution of BRL-49653 are 0.174 h^{-1} and 15.4 l, respectively (GSK data on file, based on a multiple study derived pharmacokinetic model).

Individual *in vivo* plasma concentration vs. time data after single dose administration of one Volmax® tablet to 18 fasted healthy volunteers were provided by GSK. Mean data after intravenous administration of 1.5 mg salbutamol to 10 subjects were obtained from the literature [24].

2.4. Treatment of data

2.4.1. Treatment of plasma data to obtain the cumulative amount absorbed

The weighting function for deconvoluting the individual oral data of BRL-49653 matrix formulation was described based on the volume of distribution and the elimination rate constant values given in Section 2.3. Due to the negligible first-pass metabolism of BRL-49653 (GSK data on file), deconvolution of oral data provided the amount absorbed vs. time profiles.

For Volmax®, after fitting a bi-exponential function to intravenous data [24], the salbutamol plasma concentration vs. time profile was best described by the following equation:

$$C = 41.18 * \exp(-2.88 * t) + 7.20 * \exp(-0.18 * t) \quad (1)$$

Cumulative amount absorbed vs. time plots were constructed by deconvolution of the individual oral data and assuming that 63% of the absorbed salbutamol is metabolized during its first-pass from the liver [24,25].

In all cases, deconvolution was performed with PCDCON (PCDCON, W.R. Gillespie, 1992) (on a random sample basis, it was confirmed that WinNonlin® gives identical results).

2.4.2. Modelling of USP II data to project in vivo plasma profiles

Since only one medium was studied per test, data collected with the USP II apparatus were modelled to project *in vivo* plasma profiles. Modelling was applied to individual release data sets using Sigmaplot 2000 (version 6.00, SPSS Inc.). For the BRL-49653 matrix, the first-order model was fitted to the data collected in SGF and in SCoF best. The Weibull function was the best model for the data in FaSSIF. For Volmax®, the power model gave the best fit to the data collected in SGF, whereas the Weibull model gave the best fit to the data in FaSSIF and SCoF. Best fits were decided on the basis of coefficient of determination, the normality test, and the constant variance test [26]. Simulated plasma profiles were then constructed by applying a previously published procedure [27]. Gastric emptying of the matrix formulation or of the osmotic pump was assumed to occur 1 h after administration [28,29] and, since both compounds are highly permeable (Table 1), the transport through the intestinal mucosa was assumed to occur without limitations. First-pass effect for BRL-49653 and salbutamol were assumed to be negligible (GSK data on file) and 63% [24,25], respectively. To obtain an estimate of the variability of the simulated profile, upper and lower simulated profiles were constructed by taking into account the standard deviations of the constants of the models that were fitted to the individual data sets.

2.4.3. Treatment of USP III and USP IV data

Unlike with the data collected with USP II apparatus, data from Type III and Type IV were compared directly with the deconvoluted plasma profiles. To obtain an estimate of the variability of the release profile, upper and lower release profiles were constructed by taking into account the standard deviation of the amount released.

2.4.4. Profiles comparisons

The difference between a mean simulated and a mean actual plasma profile or between a mean% cumulative amount released and a mean% cumulative amount absorbed data set was assessed with the difference factor, $f_{1,area}$ [30]. The difference factor reflects the sum of absolute point differences; its value can be any positive number, and it increases with the difference between the two profiles [30]. For the comparison of a mean simulated profile with a mean actual plasma profile, $f_{1,area}$ was estimated by using all actual data. For the comparisons of percentage cumulative amounts, $f_{1,area}$ was estimated by using data up to 6 h. In all cases, the *in vivo* data were used as the reference data set. By multiplying the difference factor by 100, the percentage difference of the test profile from the reference profile is obtained [30].

3. Results and discussion

3.1. In vitro release data

Figs. 1 and 2 show the *in vitro* release data of the BRL-49653 matrix and the Volmax® formulations, respectively.

For BRL-49653 carbomer matrix formulation, medium composition significantly affects the release rates. In SGF, specifically, the release of BRL-49653 is comparatively faster, regardless of the experimental setup (Fig. 1). This is in accordance with the fact that BRL-49653, being a weak base (Table 1), has higher solubility at acidic pH. In addition, literature data show that for carbomer matrices, release profiles are slowed at high pH according to the pKa of the carbomer used [31]. The release profile of the BRL-49653 formulation also varies with the hydrodynamics as the value of the difference factor for the comparison of the profile obtained with USP III apparatus with the profile obtained with the USP IV apparatus is 0.42 (if the USP III profile is used as reference) or 0.73 (if the USP IV profile is used as reference), indicating 42 or 73% difference between the two profiles, respectively. In addition, during the first hour, the percent release was higher when using the USP II apparatus than when using the USP IV apparatus (Fig. 1). The latter is in accordance with previous data showing that drug release from ER products into SGF is slower with USP IV apparatus than with USP II apparatus [15].

For Volmax®, neither medium composition nor hydrodynamics are important for the release profile (Fig. 2). The value of the difference factor for the comparison of the profile obtained with USP III with the profile obtained with the USP IV apparatus is 0.05 (regardless of which profile is used as reference).

3.2. In vitro–in vivo correlations

The simulated plasma profiles constructed by using *in vitro* release data from USP II apparatus (after modelling, see Section 2.4.2) and the *in vitro* release data collected with USP III or USP IV

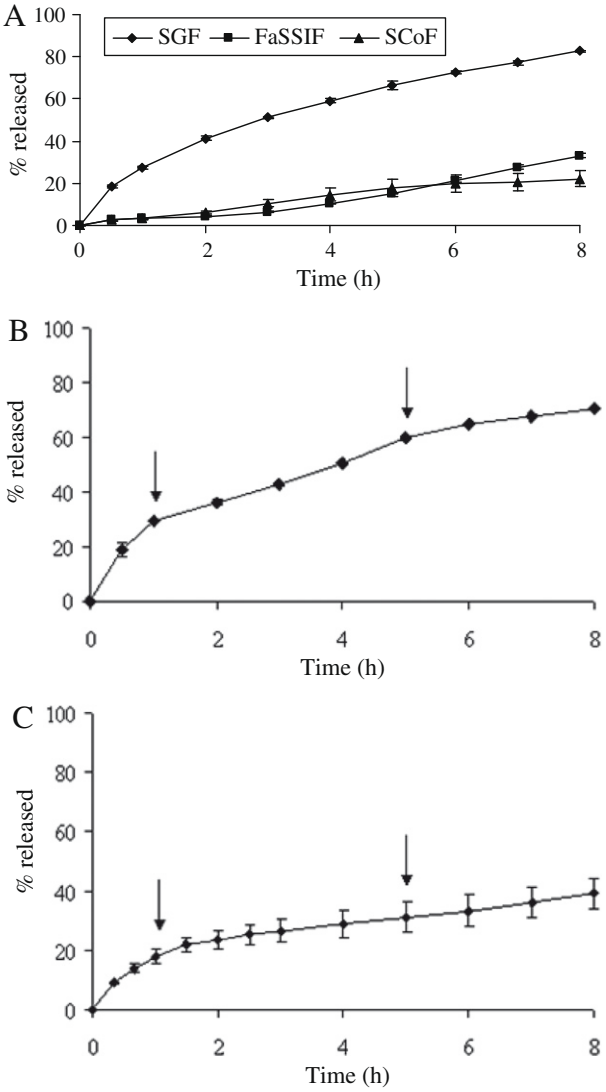

Fig. 1. Mean ± SD data for the percentage cumulative amount of BRL-49653 released *in vitro* using the USP II apparatus (A), the USP III apparatus (B) and the USP IV apparatus (C). An arrow indicates a medium change.

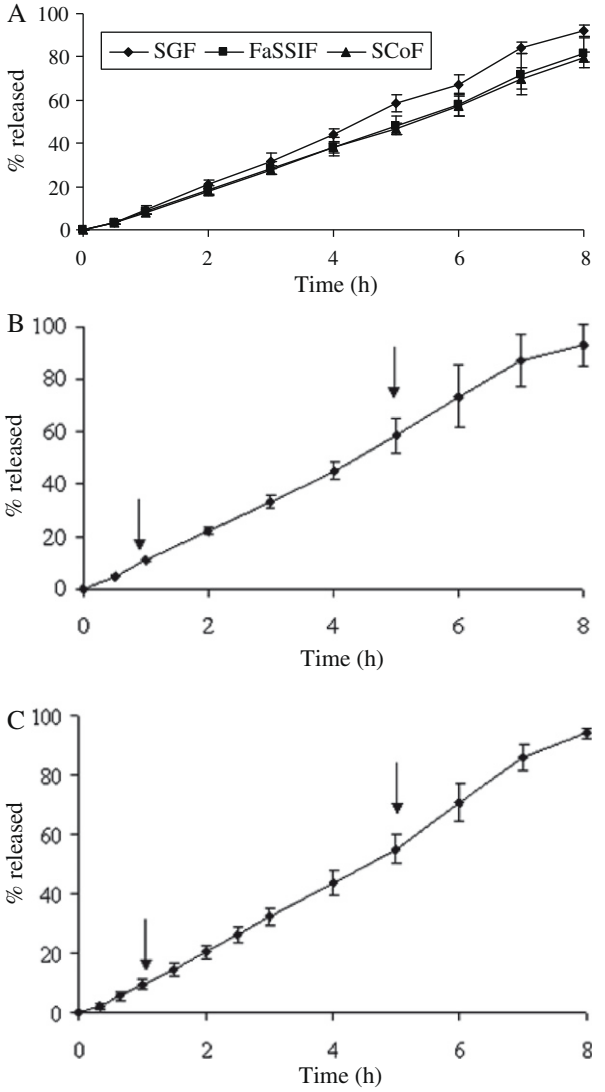

Fig. 2. Mean ± SD data for the percentage cumulative amount of salbutamol released *in vitro* using the USP II apparatus (A), the USP III apparatus (B) and the USP IV apparatus (C). An arrow indicates a medium change.

apparatus appear equally useful in predicting the corresponding *in vivo* profiles on an average basis, for both formulations (Figs. 3 and 4). The difference between predicted and actual profile is 24–44%, regardless of the *in vitro* setup used (Table 5). Therefore, even for the BRL-49653 formulation, for which the profile when using the USP III apparatus was up to 70% different than the profile obtained with the USP IV apparatus, no advantage of any one particular method could be concluded with respect to developing IVIVCs in the fasted state.

A global assessment of *in vitro* hydrodynamics applied in the present study can be based on the Reynolds numbers. The (dimensionless) Reynolds number is used to characterize the laminar–turbulent transition and is commonly described as the ratio of momentum forces to viscous forces in a moving fluid [32]. With the *in vitro* setups used in the present study, Reynolds numbers for the bulk flow vary from less than 30 (when using the USP IV apparatus) [33] to more than 2000 (when using the USP II apparatus) [32], whereas there are no published data for the USP III apparatus. Since the Reynolds number characterizing laminar–turbulent transition for bulk flow in a pipe that behaves in a hydraulically smooth manner is about 2300 [32], hydrodynamics in the *in vitro* setups used in the present study created bulk flow conditions in both the laminar and turbulent regions.

It would be interesting to know how intraluminal hydrodynamics compare to those in the *in vitro* setups used in the present study, However, hydrodynamics themselves cannot be pinned down precisely, since on one hand, both flow rates and viscosity of luminal contents vary dramatically [32] and, on the other hand, the intestine does not behave like a conventional pipe, because the gut wall contracts.

Based on the preceding discussion, it is logical to conclude that *in vitro* hydrodynamics applied in the present study and, by implication, typical fasted state intraluminal hydrodynamics are not as important for the oral absorption of most monolithic ER products (at least of those with low drug load and sizes up to about 7 mm) as other factors such as fluid composition and residence time. Such a possibility is of interest especially for eroding matrices exemplified by the carbomer matrix formulation, as it would imply that despite their theoretical mechanistic vulnerability, the crushing forces during transport through the pylorus and, more importantly, during passage through the ileocecal valve [13] are unable

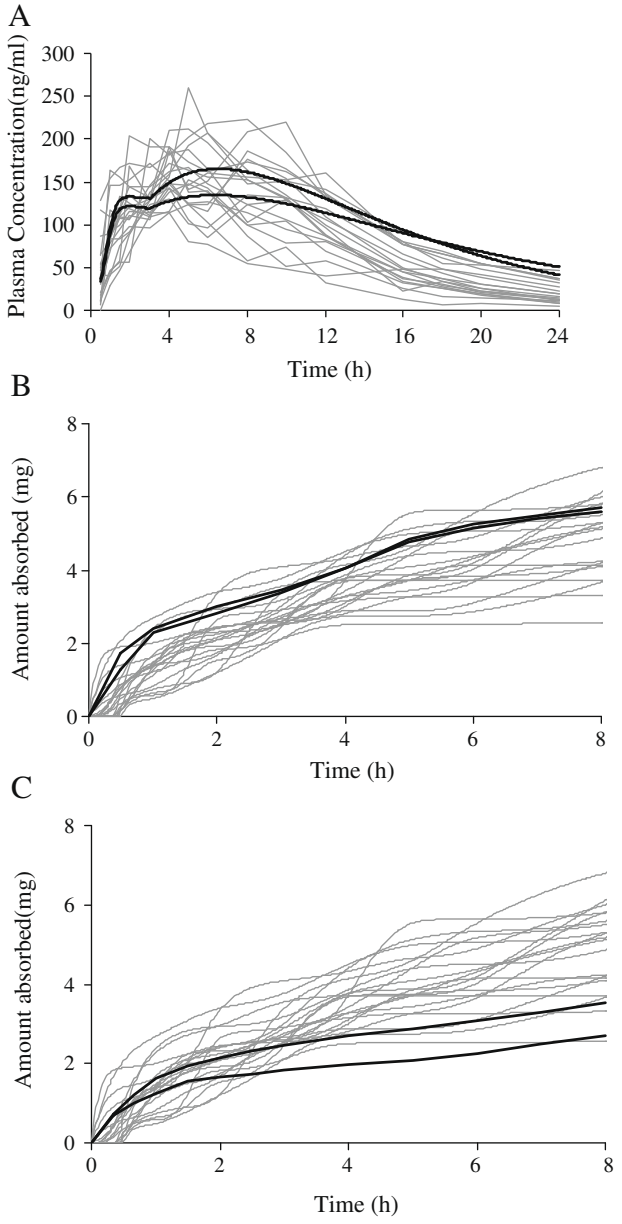

Fig. 3. (A) The actual individual plasma profiles of BRL-49653 (n = 20, grey lines) vs. the upper and lower simulated plasma profiles constructed by taking into account the standard deviation of the constants of the models that were best fitted to the USP II release data (black lines); (B) the individual cumulative amounts of BRL-49653 absorbed (grey lines) vs. the upper and lower cumulative BRL-49653 release profiles that were constructed by taking into account the standard deviation of the amount released when using the USP III apparatus (black lines); (C) the individual cumulative amounts of BRL-49653 absorbed (grey lines) vs. the upper and lower cumulative BRL-49653 release profiles that were constructed by taking into account the standard deviation of the amount released when using the USP IV apparatus (black lines).

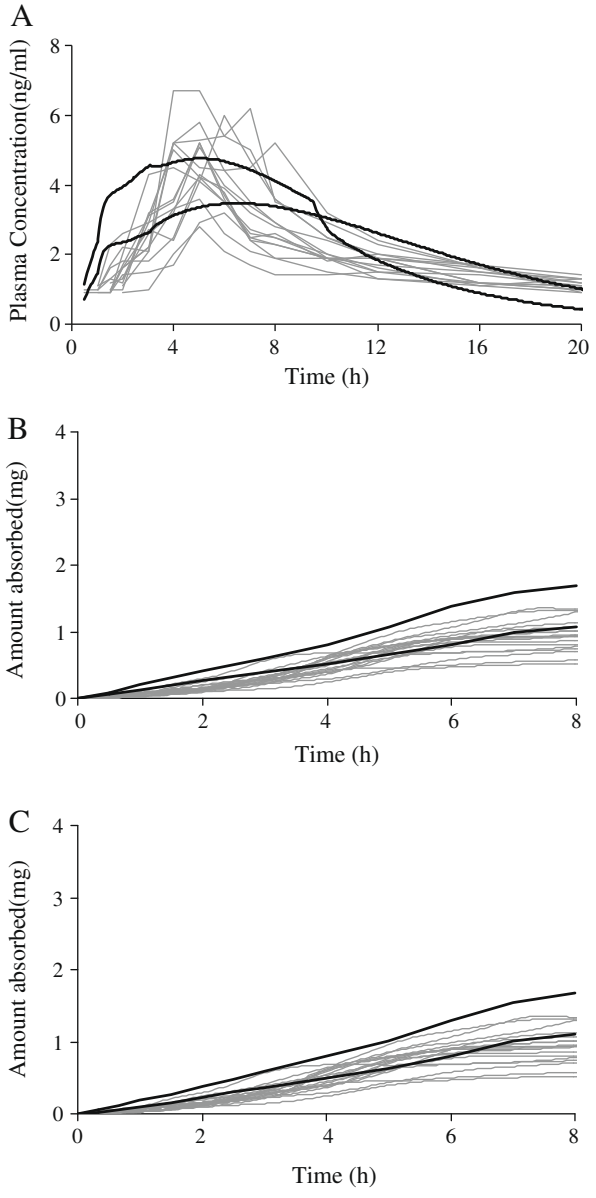

Fig. 4. (A) The actual individual plasma profiles of salbutamol (n = 18, grey lines) vs. the upper and lower simulated plasma profiles constructed by taking into account the standard deviation of the constants of the models that were best fitted to the USP II release data (black lines); (B) the individual cumulative amounts of salbutamol absorbed (grey lines) vs. the upper and lower cumulative salbutamol release profiles that were constructed by taking into account the standard deviation of the amount released when using the USP III apparatus (black lines); (C) the individual cumulative amounts of salbutamol absorbed (grey lines) vs. the upper and lower cumulative salbutamol release profiles that were constructed by taking into account the standard deviation of the amount released when using the USP IV apparatus (black lines).

Table 5
Estimated values of the difference factor $f_{1,area}$ [30], for the difference of the mean actual *in vivo* profiles of BRL-49653 matrix tablet and Volmax® from the corresponding mean predicted *in vivo* profiles that were generated by using *in vitro* release data collected with the USP II, USP III and USP IV release apparatuses.

	USP II apparatus	USP III apparatus	USP IV apparatus
BRL-49653 carbomer matrix tablet	0.26	0.24	0.31
Volmax®	0.32	0.44	0.39

to significantly change the release mechanism from eroding matrix formulations, at least in the fasted state.

In contrast, it is interesting to note that in a recent study, after dosing an HPMC matrix formulation, but not after dosing a pellet formulation, multiple peaks in individual diclofenac plasma concentration profiles were observed [13]. These peaks were attributed to the strongly accelerated drug release during biorelevant physical stress events that are known to be possible at least during the gastric emptying and ileocecal movement [13]. It is worth mentioning that the carbomer matrix tablet in the present study is smaller and lighter (7 mm/155 mg vs. 9 mm/300 mg) with a

lower drug load (8 mg vs.100 mg) than the hydrophilic matrix formulation tested in the previous report (Voltaren Retard®, [13]). In addition, the matrix in the previous report is HPMC rather than carbomer, and the drug is a weak acid rather than a weak base. It is likely that these differences affect robustness to hydrodynamics.

In conclusion, this study shows that the hydrodynamics of USP II, III and IV may all be adequate as a starting point for generating IVIVCs of up to ~7 mm monolithic dosage forms with low drug load, at least in the fasted state.

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