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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