

The Flow Through Cell Methodology in the Evaluation of Intraluminal Drug Release Characteristics

Nikoletta Fotaki¹ and Christos Reppas^{1,2}

email: reppas@pharm.uoa.gr

Abstract

In this paper the usefulness of the flow through cell apparatus in the evaluation of intraluminal drug release characteristics is reviewed. Initially, the basic characteristics of this setup are presented. Then, the relative advantages and disadvantages of the flow through cell apparatus over other *in vitro* release setups are summarized. Finally, potential applications of this setup are discussed according to the solubility characteristics of the tested compound and the release characteristics of the dosage form.

1. INTRODUCTION

The history of the flow through cell methodology in drug release testing of oral dosage forms begins in the 1950's. The first attempt for the development of the flow-cell method was probably made in the laboratories of the U.S. Food and Drug Administration in 1957 (1,2). Since then, various flow-cell devices have been described (2-7). The flow through cell was recommended as an alternative *in vitro* drug release testing apparatus by the Dissolution Tests working group of the Fédération Internationale Pharmaceutique (F.I.P.) in 1981 (2). Afterwards, the method was incorporated in various pharmacopoeias (2).

In the USP the flow through cell apparatus is described as Apparatus 4 (8). The assembly consists of a reservoir containing the release medium, a pump that forces the release medium upwards through the vertically positioned flow-cell, and a water bath. The pump usually has a flow rate delivery capacity between 4 and 16 mL/min, with typical flow rates being 4, 8, and 16 mL/min. Usually the bottom cone of the cell is filled with small glass beads of about 1 mm diameter and with one bead of about 5 mm positioned at the apex to protect the fluid entry tube, whereas a filter (most frequently, a glass-fiber filter) is positioned at the inner top of the cell (8). Most frequently, the flow through cell apparatus is used as an open system with fresh solvent from the reservoir continuously passing through the cell where the dosage form is initially accommodated. However, it is also possible to operate it as a closed system by recycling a fixed volume of liquid. The design of the cell provides well-defined geometry and hydrodynamics. With slight changes in the cell design, the same apparatus can be used for testing of tablets, powders, suppositories, or gelatin capsules, either hard or soft. (8-10). For orally administered solid dosage forms, two different cells are described (8): the large cell (22.6 mm i.d.) and the small cell (12 mm i.d.). Cell diameters can be associated with flow rates according to the parameters presented in Table 1 (2,4). It is important to note that linear flow velocity is the parameter that defines hydrodynamic "agitation" of the fluid on the specimen. By

taking into account the small intestinal transit times and the total length of the small intestine (11-13), the average (estimated) axial velocity is about 1.5 and 1.3 cm/min under fasted and fed state conditions, respectively. Using the USP flow through cell apparatus, similar axial velocities correspond to flow rates less than 8 mL/min (Table 1).

2. OPEN VS CLOSED *IN VITRO* DRUG RELEASE SETUPS

One of the distinct advantages of the flow through cell apparatus over the more traditional closed *in vitro* setups such as the rotating paddle and the rotating basket apparatus (8) is that media and/or flow rate changes can be easily performed within a single run. This facilitates testing of formulation robustness with respect to variations in intraluminal environment. Furthermore, carry-over effects can be identified and *in vitro-in vivo* correlations should be easier because a single profile corresponding to the release in the entire gastrointestinal (GI) lumen is obtainable.

Another advantage of the flow through apparatus when used as an open system is that intraluminal hydrodynamics are more efficiently simulated compared with other *in vitro* setups. Specifically, when compared with closed systems, it is possible to sustain sink conditions in the flow through apparatus for longer periods. Maintenance of sink conditions is especially important for poorly soluble drugs and,

Table 1: Diameters of the cells used for testing orally administered solid products with the flow through apparatus, cross-sectional areas of the cells and linear flow velocities corresponding to specific flow rates (2, 4).

Diameter (mm)	Area (cm ²)	Volumetric flow (mL/min)				
		2	4	8	16	32
Linear flow velocity (cm/min)						
11.3	1	2	4	8	16	32
22.6	4	0.5	1	2	4	8

¹Laboratory of Biopharmaceutics and Pharmacokinetics, University of Athens, Athens, Greece

²Corresponding author, School of Pharmacy, Laboratory of Biopharmaceutics and Pharmacokinetics, University of Athens, Panepistimiopolis, 157 01 Zografou, Greece

therefore, the development of *in vitro-in vivo* correlations should be easier with the flow through apparatus (14). With closed systems, *in vitro-in vivo* correlations could also be obtained but in this case the modeling of the *in vitro* data is necessary (15).

A third advantage might also be that floating or other special dosage forms are more easily studied with the flow through apparatus (16).

A disadvantage of the flow through cell apparatus may be that the use of heterogenous media, such as media simulating the gastric composition in the fed state (17), is problematic, because an efficient filtering process and maintenance of desired flow rates might not be possible.

Finally, a key difference between an open and a closed *in vitro* release system is that, with the former, raw data are collected in non-cumulative form. Data collected with the flow through cell apparatus are amounts dissolved at specific time intervals (and not at specific time points), so that they can be assumed as rough estimates of release rates. Unless data are used in quality control testing and, therefore, total label claim is of interest, transformation to the cumulative form does not offer any specific advantage whereas any mistake(s) associated with the estimation of the total drug released during a specific time interval will be transferred to the next time interval (18). Further, if a model is to be fitted to the data, by converting them to the cumulative form, the fundamental assumption of independence of errors is violated (18).

3. THE FLOW THROUGH CELL APPARATUS FOR THE PREDICTION OF THE *IN VIVO* PERFORMANCE OF ORALLY ADMINISTERED DOSAGE FORMS

3.1 Immediate Release Dosage forms

3.1.1 Drugs with high solubility (19)

For highly soluble compounds the flow through cell apparatus can be used for the assessment of intraluminal disintegration characteristics.

For example, it has been successfully used for assessing the disintegration of cross-linked gelatin capsules containing amoxicillin (20). Lag times prior to the initiation of dissolution process in media simulating the gastrointestinal contents in the fasted state [Fasted State Simulating Gastric Fluid (21) for 45 min at 8 mL/min followed by FaSSiF (22) for 210 min at 8 mL/min] were close to *in vivo* disintegration times of the capsules in the fasted gastrointestinal lumen (23) whereas both *in vitro* and *in vivo* data were dependent on the degree of cross-linking of gelatin (20, 23).

More recently, it has been shown that dissolution of paracetamol from immediate release formulations with the flow through apparatus is rapid and complete in media simulating the fasted state but it is substantially delayed in media simulating the fed state (24). Dissolution was monitored in milk 3.5% fat (0-90 min, 6 mL/min) (22, 25), followed by FeSSiF (90-180 min, 6 mL/min) (22). Data collected under these conditions adequately reflected the delayed disintegration times of a commercially available paracetamol tablet in fed dogs (24) and in fed humans (26).

3.1.2 Drugs with low solubility (19)

The flow through cell apparatus has been tested for its usefulness in the prediction of food effects on intraluminal dissolution characteristics of poorly soluble compounds and also, since poorly soluble compounds are frequently associated with unproblematic transport through the intestinal mucosa, for its usefulness in the development of correlations between *in vitro* dissolution data and plasma levels.

It has been shown that the improved *in vivo* dissolution of spironolactone particles and troglitazone tablets in the fed small intestine can be correctly predicted with the flow through cell apparatus when physiologically relevant media and flow rates are used (27, 28).

However, Bonlokke et al. (29) have shown that dissolution profiles of carbamazepine particles obtained using the large flow-cell (8) and physiologically relevant media and flow rates (2.5 mL/min) were lower than the *in vivo* dissolution profiles. Authors attributed the discrepancy to the inability of this apparatus to simulate the complex mixing and flow patterns in the normal gastrointestinal tract (29). In accordance with Bonlokke et al. data, Nicolaides et al. (28) also reported that dissolution profiles of another low solubility weak acid (troglitazone) obtained with the large flow-cell, using FaSSiF (22) at 2.5 and 4 mL/min or FeSSiF (22) at 4 and 6 mL/min were lower than *in vivo* absorption profiles (28). These authors also showed that when a troglitazone tablet is initially treated with SGF (0-30 min, 12 mL/min) (30) and then with FaSSiF (30-150 min, 4 mL/min) (22) dissolution is greater in SGF than in FaSSiF; a surprising observation given the ionization and the lipophilicity characteristics of troglitazone. Both the lower *in vitro* profiles compared to *in vivo* profiles and the lower dissolution in media with higher pH and bile salt concentration are attributed to the inadequate simulation of the *in vivo* hydrodynamics; when simulation of conditions in the small intestinal lumen is targeted, the use of physiologically relevant flow rates and the absence of radial loss (absorption) of the drug may lead to non-sink conditions and, therefore, to lower than *in vivo* dissolution profiles (28). In addition, possible sedimentation of particles on the lower sides of the cell (due to its vertical position) may also lead to incomplete *in vitro* dissolution (28).

Sunesen et al. (12) developed *in vitro-in vivo* correlations for danazol hard-gelatin capsules using the flow through cell apparatus, media simulating the intraintestinal composition, and flow rates higher than the physiological, in other words, at least 8 mL/min (12). To compensate for the resulting high (non-physiologically relevant) total fluid volumes, the experiments were extended for 2 hours. It is interesting to note that, with this methodology, point-to-point *in vitro-in vivo* correlations were developed under both fasted and fed conditions; whereas correlations in the fed state were better when lipid digestion products had been included in the relevant release media.

3.2 Extended release dosage forms

Originally, the flow through cell apparatus had been thought to facilitate development of *in vitro-in vivo* correla-

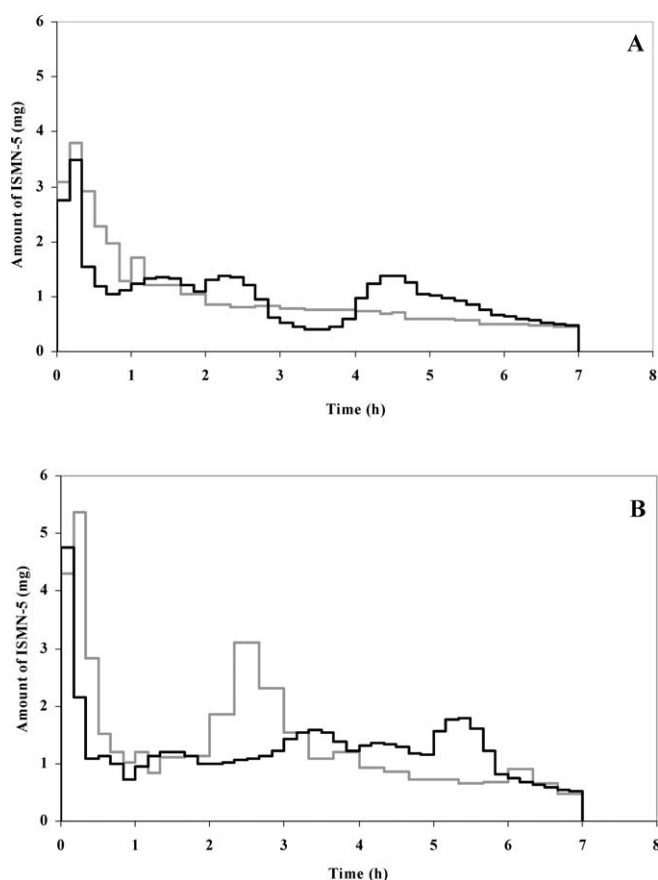


Figure 1. Mean amounts of isosorbide-5-mononitrate (ISMN-5) released *in vitro* (—) and absorbed from the human gastrointestinal tract (---) at 10-minute intervals up to 7 hours after the initiation of each process. (A) Imdur™; (B) osmotic pump. (Reprinted from ref. 33 with permission from Elsevier)

tions for extended release products. Based on the literature data, these correlations are limited, and the data may not be suitable for publication. When Möller and Langenbucher studied release of aminophylline extended release tablets with the paddle and the flow through cell apparatus, they could observe the effect of the pH of the medium on the *in vitro* release only with the flow through cell apparatus (31). Based on the *in vivo* release data, they concluded that the increased inter- and intra-individual variation was due to the pH-dependent release characteristics (31).

Similarly, Emara et al. (32) showed that for ER formulations of vincamine (a compound with pH-dependent dissolution characteristics) the *in vitro* release data with the flow through apparatus could be correlated point-to-point with *in vivo* data only if used as an open system (32). The release was monitored in simulated gastric fluid without enzyme (pH 1.2, 0-1 h and pH 4.5, 1-2 h) and simulated intestinal fluid without enzyme (pH 6.9, 2-4 h and pH 7.5, 4-5 h) at 8 mL/min. It is interesting to note that with the specific experimental setup, sink conditions were maintained throughout the experimental period (32).

Fotaki et al. (33) were able to develop a point-to-point correlation of *in vitro* release data using the flow through

Table 2: Fasted state simulating luminal conditions for the *in vitro* release testing of monolithic extended release dosage forms with the flow-through cell apparatus (33).

Medium	Period (min)	Flow rate (mL/min)
SGF	0–60	8
FaSSIF	60–270	4
SCoF	270–420	4

cell apparatus with the *in vivo* absorption data of two monolithic extended release formulations of a highly soluble - highly permeable compound (isosorbide-5-mononitrate) in fasted state by using physiologically relevant media and physiologically relevant flow rates (Table 2). It is worth noting that in this study *in vitro* release data were also collected in a new medium that simulated the contents of the ascending colon. There are several attempts to simulate the contents of the lower part of the gastrointestinal tract. In the literature, primarily phosphate buffers with pH values of 7 to 7.5 have been proposed for this simulation (34-38). The pH in the first part of the large intestine has been reported to range with time and food intake from 4.8 to 7 (39-44). Furthermore, acetate, propionate and butyrate are the principal organic anions found in colonic contents (45). Based on these data, an acetate buffer with a pH value of 5.8 has been used for simulating the contents of the proximal colon (33). Figure 1 shows that the mean amounts of isosorbide-5-mononitrate released *in vitro* and absorbed in humans every 10 minutes are similar. The same was true for the associated confidence intervals (33). It is interesting to note that, unlike with the immediate release products, the physiologically relevant flow rates did not lead to underestimation of the *in vivo* release from the extended release products of isosorbide-5-mononitrate. This is most likely related to the fact that extended release products are generally less sensitive to changes in agitation intensity.

4. CONCLUDING REMARKS

Literature data suggest that, due to a number of advantages compared to closed systems, the flow through cell apparatus can be used to assess intraluminal disintegration of dosage forms. In addition, raw dissolution data can be directly correlated with appropriate *in vivo* data of poorly soluble compounds and of highly soluble - highly permeable compounds housed in extended release products. The limited use of the flow through cell apparatus, in the evaluation of intraluminal drug release characteristics to date seems to be related to poorly defined optimum operating conditions.

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