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Research paper

Predicting in vivo absorption behavior of oral modified release dosage forms containing pH-dependent poorly soluble drugs using a novel pH-adjusted biphasic in vitro dissolution test

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ABSTRACT

The focus of in vitro dissolution testing during early development of modified release (MR) formulations is to provide predictive estimates of drug release in respect to in vivo performance of a drug product. However, there are enormous challenges in MR drug development to establish proper dissolution conditions for a predictive test.

To overcome limitations of dissolution testing at constant pH, a modified USP apparatus 2 was developed, combining biphasic dissolution with a pH-gradient in the aqueous dissolution medium. Quasi sink conditions in the aqueous phase were introduced by the removal of dissolved active via distribution to an organic phase. Results from in vitro drug-release studies and in vivo absorption studies of four MR formulations made by different technologies comprising the pH-dependent poorly soluble drugs, dipyridamole and the investigational drug BIMT 17, indicated that dissolution testing using the biphasic approach enabled an improved forecast of the in vivo behavior and bioavailability of modified release formulations compared to conventional dissolution testing at pH 1, pH 5.5, or pH 6.8.

It can be concluded that the novel pH-adjusted dissolution test might be a useful tool in early drug development to develop, select, and optimize MR prototypes of Biopharmaceutical Classification System (BCS) II compounds.

1. Introduction

In vitro dissolution testing of solid oral dosage forms serves as a very important tool in drug development for selecting and optimizing formulations, studying drug-release mechanisms, ensuring batch-to-batch consistency, monitoring stability, and demonstrating bioequivalence [1]. Additionally, for modified release (MR) development, the focus of dissolution testing in early development is to provide predictive estimates of drug release in respect to in vivo performance of a drug product [2,3]. However, there are enormous challenges in MR drug development to establish proper dissolution test conditions for a predictive in vitro test because of the variability in physiological conditions of the GI tract like pH, intestinal fluids, and transit time. The ideal system for evaluating in vitro drug release of MR dosage forms should be relatively simple, inexpensive, and mirror the physiological environment of the human GI tract, while maintaining some sort of sink conditions throughout the experiment. In general, predictive in vitro dissolution testing during early MR drug development should at least qualitatively reflect in vivo behavior.

USP apparatus 1 (basket) and 2 (paddle) constitute the bulk of compendial dissolution testing in the pharmaceutical industry [4]. But one major limitation of these approaches to forecast the in vivo release profiles of MR dosage forms is that results are typically run in one medium at a time. On one hand, this obviously is in contrast to the changing pH-environment passed during GI transit, and on the other hand, it is often difficult to maintain sink conditions which can be a problem especially for BCS II and maybe BCS IV compounds with very poor solubility [5]. As part of the effort to develop predictive in vitro models that mimic in vivo conditions, biorelevant media are proposed [6–8] and recently updated to simulate pre- and postprandial states in the proximal gut [9]. However, when investigating drug release of MR products, the drug release may even be stronger influenced by consecutive pH changes of the environment compared to biorelevant media. Thus, especially for drugs with pH-dependent solubility, dissolution should be performed with a series of various pH of the media in one experiment [10].

Investigations of physiological pH profiles and transit times along the human GI tract in the fasted and in the fed state have been conducted in several studies [11–16]. Despite a considerable

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variety of reported results, in general, pH in the fasted stomach is expected to be in a range between pH 1.5 and pH 3.0 with a transit time of 0.5 h up to 2 h. In the fasted state, pH should range between pH 5.0 and pH 7.2 in the small intestine and lower compartments with a transit time of 2–5 h for the proximal intestine (duodenum, ileum, and jejunum) and several hours up to days in the colon showing considerable variability in recent studies [17–21]. The variability of pH and transit times may be even higher when regarding studies in the fed state.

In order to establish consecutive pH changes, more advanced methods like USP apparatus 3 (reciprocating cylinder) and USP apparatus 4 (flow-through cell) are proposed [22–24]. They offer the advantage of investigating drug release under various dissolution conditions simulating the GI physiology by the addition of fresh medium.

The flow-through cell is a very flexible method that offers a wide range of opportunities to change pH or composition of the dissolution medium. Though there are some limitations to the application of the flow-through cell, especially concerning very poorly soluble pH-dependent drugs. For instance, high flow rates and large volumes of dissolution media that are not physiologic are required to keep sink conditions. But when high flow rates are used, the method would not be applicable to some complex formulations, as functional excipients like pH-modifying agents would be artificially quickly leached out of the dosage form [25]. The reciprocating cylinder is another alternative to conventional dissolution testing [26]. In a recent study, IVIVC for caffeine-modified release products using BioDis was reported [27]. While leaching of functional excipients should be less pronounced using this method, there might be as well some limitations to maintain sink conditions for very poorly soluble drugs and the drawback of a complex procedure of sampling and technical reliability of automated devices (in our experience) [4,28].

The modification of existing dissolution apparatus is a further approach to improve prediction of in vivo behavior of MR formulations. First proposed by Gibaldi and Feldman [29], the implementation of an additional organic phase was used to maintain sink conditions for poorly water-soluble drugs. A slight modification was used for conducting dissolution tests of lipid-filled soft gelatin capsules [30]. The application of biphasic dissolution systems with constant pH in the aqueous phase was reported for characterization and in vivo prediction of different MR nifedipine products by establishing an in vivo in vitro correlation (IVIVC) [31–33].

The aim of the present study was to set up a new biphasic pH-adjusted dissolution apparatus and evaluate its potential to forecast in vivo performance of early formulation prototypes in a fasted-state pharmacokinetic clinical Phase I study. The model combines consecutive pH changes in an aqueous dissolution medium and a biphasic approach to maintain sink conditions. Therefore, several MR formulations of two weakly basic BCS II compounds [5] with pH-dependent solubility, dipyridamole and BIMT 17, were investigated in vitro and in vivo.

2. Materials and methods

2.1. Materials

Formulations of dipyridamole and BIMT 17, a new investigational drug, were provided by Boehringer-Ingelheim Pharma GmbH & Co. KG (BI), Biberach/Riss, Germany. Pure drug substances for standard curves were supplied by BI; hydroxypropylmethylcellulose capsules were obtained from Shionogi & Co., Ltd. (Osaka, Japan). *n*-Octanol, sodium dihydrogen phosphate, sodium hydroxide pellets, and hydrochloric acid 1 M were purchased from Merck KGaA (Darmstadt, Germany). Cremophor RH 40 was obtained from BASF AG (Ludwigshafen, Germany). All reagents used were of analytical grade.

Physicochemical properties of the pH-dependent poorly soluble compounds dipyridamole and BIMT 17 [34] are presented in Table 1. Four MR formulations of dipyridamole (150 mg per dose) and BIMT 17 (100 mg per dose) were tested, respectively. The selected formulations were based on different release principles manufactured by different technologies, comprising monolithic-coated tablets [35], an extended-release (ER) matrix tablet, and different multiunit pellet formulations (Table 2).

2.2. Methods

2.2.1. pH-adjusted biphasic dissolution system

Drug release from different prototypes was determined using a pH-adjusted biphasic dissolution test system, illustrated in Fig 1. Therefore, a conventional USP 29 apparatus 2 (AT7smart, Sotax AG, Allschwil, Switzerland) was combined with an automated pH titration and controlling device (Titrando 842, Metrohm AG, Herisau, Switzerland). Tests using the modified apparatus were performed in vessels with 500 ml of a sodium dihydrate phosphate-buffered (5 g/l) aqueous phase (lower phase) and 100 ml of *n*-oct-

Table 1
Physicochemical properties and pH-dependent solubility of dipyridamole and BIMT 17.

Compound	Solubility (mg/ml)[a]						Log *P*
	Water	0.1 N HCl	4.0	5.5	6.8	*n*-Octanol	
Dipyridamole	0.03	53.0	0.65	0.022	0.006	>10	>4
BIMT 17	0.008	6.2	0.2	0.005	0.002	>10	>4

[a] Determined experimentally at 37 °C; phosphate-buffered media.

Table 2
MR prototypes of dipyridamole and BIMT 17 used in this study.

Formulation	Dipyridamole	Formulation	BIMT 17
D-1	Spray-layered pellets	B-1	Pellet formulation
D-2	Spray-layered pellets	B-2	ER matrix tablet
D-3	Coated tablet	B-3	Pellet formulation
D-4	Coated tablet	B-4	Pellet formulation

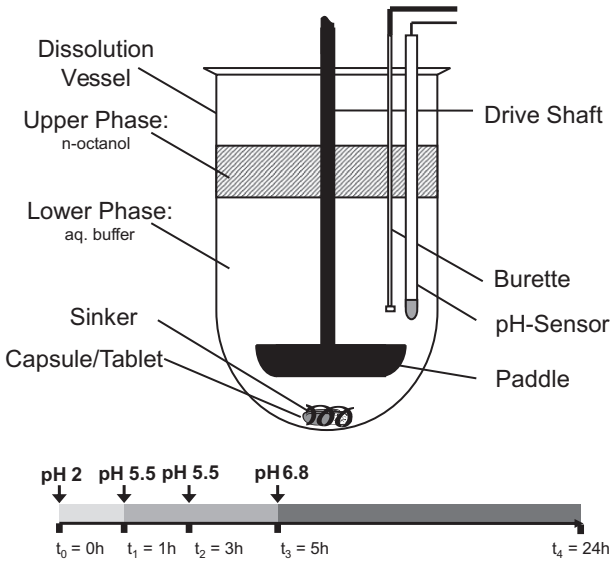

Fig. 1. Schematic diagram of a pH-adjusted biphasic dissolution apparatus comprising two immiscible phases (aqueous and *n*-octanol) and a pH-controller to adjust pH of the aqueous phase according to a simulated physiological pH-gradient.

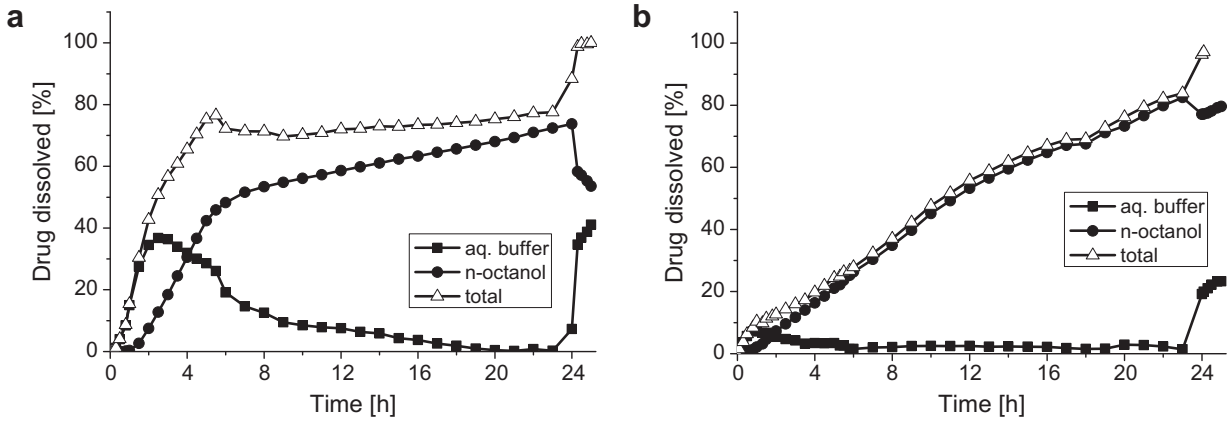

Fig. 2. Dissolution profile of dipyridamole pellets D-2 (a) and BIMT 17 monolithic tablet B-3 (b) in aqueous phase and *n*-octanol adding to a calculated total dissolution profile.

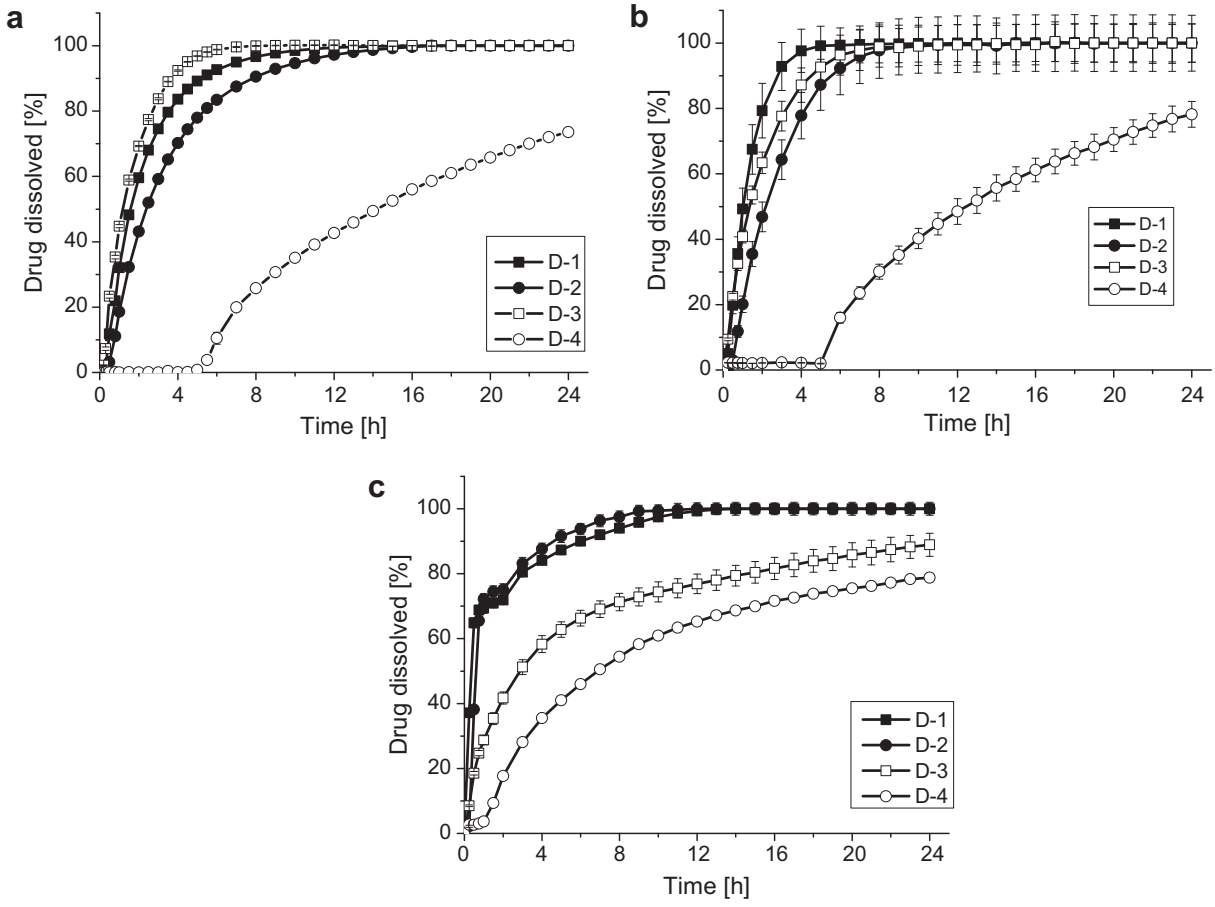

Fig. 3. Dissolution profiles of dipyridamole MR formulations using USP apparatus 1 (basket) at 100 rpm; medium volume 900 ml of (a) 0.1 N hydrochloric acid; (b) pH 5.5 phosphate buffer 0.05 M + 2% Cremophor RH; (c) pH 6.8 phosphate buffer 0.05 M + 2% Cremophor RH; mean ± SD; $n = 3$.

anol (upper phase). A temperature of 37 °C ± 0.5 °C was maintained throughout the experiment, and the stirrer speed of the paddle was set to 50 rpm. Samples were drawn at predetermined intervals from both, aqueous and n-octanol phase. Drug concentration of both phases in the dissolution vessel was monitored simultaneously using a UV diode array spectrophotometer (Agilent 8453, Agilent Technologies GmbH, Waldbronn, Germany). The total amount of released drug was calculated as sum of both fractions released in both *n*-octanol and aqueous buffered medium.

To establish biorelevant pH conditions throughout the test, a sequential pH-gradient was applied in the aqueous phase. The test setup in this study was created to simulate transit through the GI tract in the fasted state with residence times of 1 h in the stomach and 4 h in the small intestine [6,7,11–14,36]. Therefore, at the beginning of the test dissolution was carried out in aqueous media at pH 2 for 1 h. Subsequently, pH was adjusted to pH 5.5 within five minutes using 5 M sodium hydroxide solution. After a total dissolution time of 3 h, the medium was readjusted to pH 5.5.

Finally, after a total dissolution time of 5 h, pH was set to pH 6.8 for the remaining time of the experiment, simulating further intestinal and colonic transit. After 24 h of drug release, finally 10 ml of 4 M hydrochloric acid was added to the medium to examine complete recovery of the drug. The vessels used in this study were equipped with a peak in the centre of the bottom in order to prevent sticking of the drug product to the vessel or lack of hydrodynamic intensity at the vessel bottom and to improve reproducibility. All dosage forms were equipped with a non-compendial sinker made of a coiled wire (3.0 × 1.0 cm) to avoid floating into the upper *n*-octanol layer. Contact between floating pellets and the octanol at the layer interface was observed only sporadically after several hours of drug release, when the density of pellets already had decreased due to swelling and drug release. Transition of pellets to the *n*-octanol was not observed at all. Experiments were performed in triplicate and results expressed as mean percentage dissolved (±SD) at the given sampling time.

2.2.2. Conventional in vitro release studies

Conventional in vitro dissolution studies of dipyridamole and BIMT 17 formulations were carried out in USP apparatus 1 (basket) at 100 rpm using 900 ml of dissolution media at 37 °C ± 0.5 °C in a dissolution apparatus (Sotax AG, Allschwil, Switzerland). Dissolution of dipyridamole formulations was carried out in 0.1 M hydrochloric acid media and in USP 0.05 M sodium phosphate-buffered media at pH 5.5 and pH 6.8, whereas BIMT 17 prototypes were tested at pH 1 and pH 5.5. Cremophor RH 40 (0.5–2%) was added to phosphate-buffered dissolution media of higher pH, in order to guarantee sink conditions. Samples were removed at predetermined time points and analyzed by a diode array UV spectrophotometer (Agilent 8453, Agilent Technologies GmbH, Waldbronn, Germany). Experiments were performed in triplicate and results expressed as mean percentage dissolved (±SD) at the given sampling time.

2.2.3. In vivo absorption study

Individual in vivo plasma concentration vs. time data was obtained from healthy volunteers in the fasted state. The controlled, open-labeled, randomized, single-dose studies to evaluate different prototype formulations were performed in a cross-over design. Dipyridamole formulations were administered to six participants; BIMT 17 formulations were administered to 20 fasted healthy volunteers. Participants had no comedication. Blood samples were withdrawn 5 min before and up to 24 h in the dipyridamole study and up to 96-h post dosing in the BIMT 17 study (data shown up to 48-h post dosing). Blood samples were centrifuged and plasma concentrations analyzed via HPLC. The studies were conducted at the Human Pharmacological Center of Boehringer-Ingelheim following the recommendation of the Declaration of Helsinki. The study protocol was approved by the local ethics committee prior to the beginning of the study. The data of individual plasma concentrations of MR formulations and an IR formulation with the same dose were used to calculate the area under the curve (AUC) of the plasma vs. time profile. The ratio of AUC data of MR formulations compared to AUC data of the IR formulations was plotted in an AUC_{rel} vs. time profile (Figs. 4 and 5).

3. Results and discussion

Dissolution data obtained from the biphasic dissolution test reflect drug concentrations of two compartments, comprising a lower aqueous phase and an upper organic layer of *n*-octanol. In Fig. 2, these dissolution profiles were split to fractions of dissolved drug in the pH-adjusted aqueous phase and in the organic *n*-octanol layer. Drug release of two dosage forms, a pellet formulation (a) and a matrix tablet (b), is displayed in Fig. 2 to exemplarily elucidate the principle of the pH-adjusted biphasic dissolution system. As illustrated by completely different drug concentrations in the aqueous phase, obviously the release mechanism was completely different. So the implementation of a distribution step of dissolved drug to a lipophilic phase combined with pH-adjusted media turned out to be useful to bypass problems with sink conditions and precipitation, which might occur when dissolution of weakly basic drugs at physiological pH is performed.

The choice of *n*-octanol as the organic phase in the biphasic system described in this report was based on its advantageous physical/chemical properties [32,37], like: (1) *n*-octanol is practically insoluble in water (0.05 g/100 g H_2O); (2) *n*-octanol is less dense than water (specific gravity 0.825 at 20 °C), permitting ease of sampling; (3) *n*-octanol possesses low volatility (b.p. = 195 °C) hence, *n*-octanol will not readily evaporate at 37 °C and thus a relatively constant upper phase can be maintained; (4) *n*-octanol possesses rather low viscosity, enabling sampling via conventional tubing and pump; (5) both drugs used in this study, dipyridamole and BIMT 17, are readily soluble in *n*-octanol and possess octanol/water distribution coefficients with log *P* > 4 (Table 1), guaranteeing sink conditions in the *n*-octanol layer. By this means, dissolved drug was distributed to the organic layer, removed from the aqueous dissolution medium, and a quasi sink was obtained throughout the experiment.

The pH-gradient used in the biphasic model was chosen on the basis of aforementioned literature [11–16] with the intention to

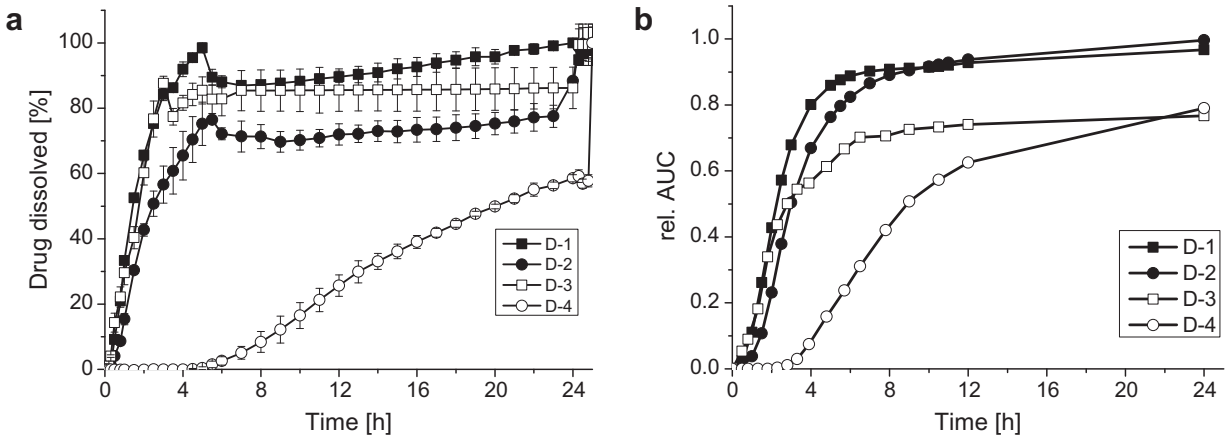

Fig. 4. Dissolution profiles and in vivo absorption of dipyridamole MR formulations (a) biphasic in vitro dissolution; mean ± SD; *n* = 3 (b) in vivo absorption profile.

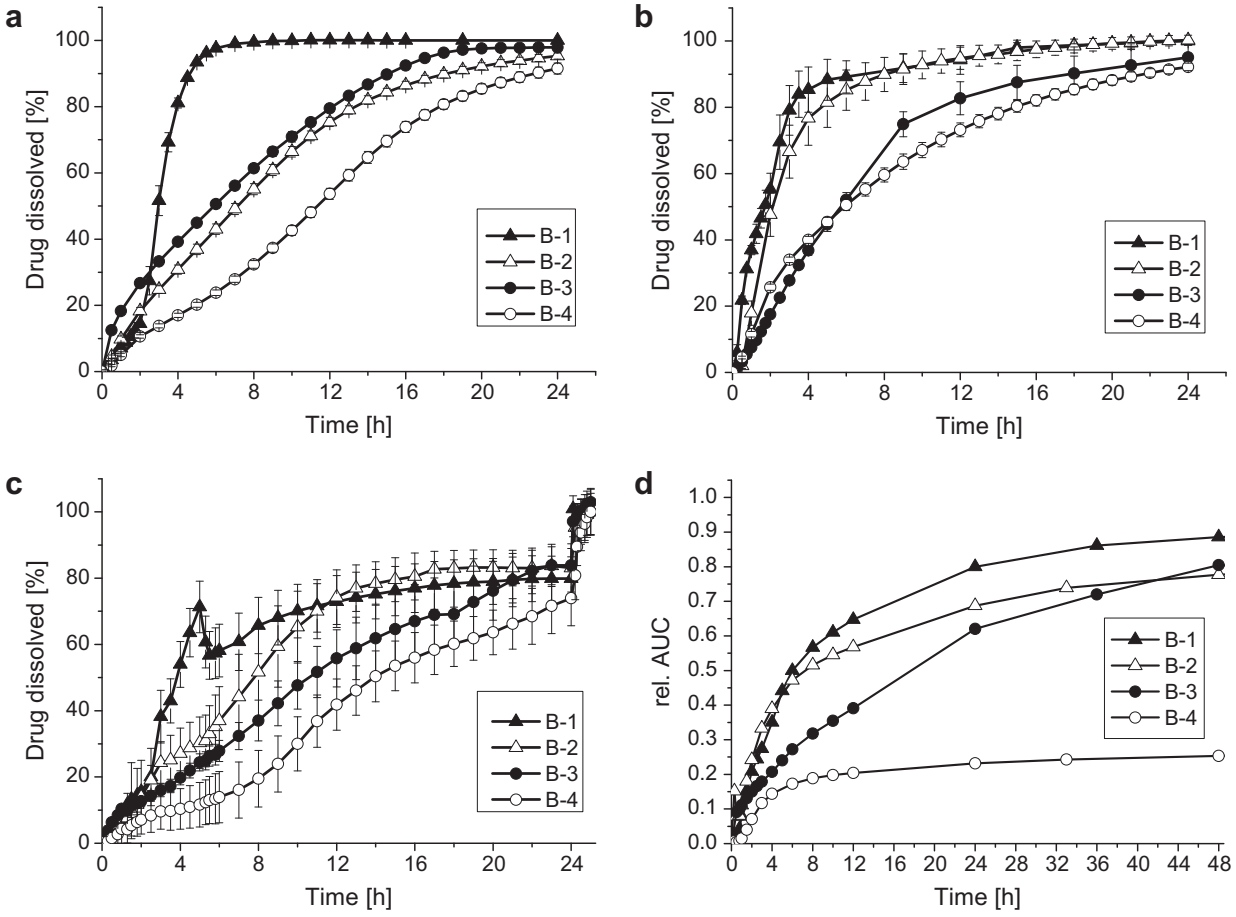

Fig. 5. Dissolution profiles and in vivo absorption kinetic of BIMT 17 MR formulations: (a) 0.1 N hydrochloric acid; USP apparatus 1 (basket), 900 ml, 100 rpm; (b) pH 5.5 phosphate buffer 0.05 M + 0.5% Cremophor RH; USP apparatus 1 (basket), 900 ml, 100 rpm; (c) pH-adjusted biphasic dissolution, paddle 50 rpm; (d) in vivo absorption profile; mean ± SD; $n = 3$.

mimic biorelevant pH conditions and keep the system as simple as possible. But, of course, other or more frequent pH changes and time intervals would be applicable as well. The rotational speed of the paddle equal to or higher than 50 rpm did not significantly affect the release rates or drug distribution between aqueous and *n*-octanol layer (data not shown). Thus, experiments were performed with the paddle rotating at 50 rpm.

In order to further evaluate the new biphasic pH-controlled dissolution apparatus and its potential to predict in vivo performance, several MR formulations of weakly basic dipyridamole and BIMT 17 (Tables 1 and 2) were investigated with conventional and the new pH-adjusted biphasic dissolution model in vitro and compared to in vivo data.

Conventional dissolution studies of dipyridamole formulations at constant pH of the dissolution media are shown in Fig. 3. Both multiparticulate formulations (D-1, D-2) released more than 80% of the drug within the first 6 h in each of the tested media. In contrast, coated tablet formulations (D-3, D-4) tended to show stronger pH-dependent drug release. Formulation D-3 achieved 80% drug release after 2.5 h, 3.5 h, and 16 h at pH 1, pH 5.5, and pH 6.8, respectively. This indicated a considerable slow down of drug release at pH 6.8 and reflected strong pH-dependent drug release of the dosage form. Drug dissolution from formulation D-4 was characterized by a substantial lag time, followed by a rather slow release rate compared to the other formulations. However, the pronounced lag time lasting up to 5 h at pH 1 and pH 5.5 was drastically reduced to only 1 h at pH 6.8. This revealed a change in release kinetics in consequence of higher pH of the dissolution medium.

In general, the tested dipyridamole prototypes showed a homogeneous ranking of drug release at different dissolution media within the same manufacturing technology, but there was no consistent rank–order relationship covering all tested prototypes.

In the pH-adjusted biphasic dissolution test, formulation D-1 achieved complete drug release after 5 h (Fig. 4a). Similar to D-1, formulation D-2 enabled drug release for up to 5 h with 80% drug released. At pH 6.8, there was no additional drug release. Showing the same release kinetic as D-1, the coated tablet D-3 reached up to 90% drug release within 3 h. But, in contrast to pellet formulations D-1 and D-2, drug release had already ceased completely after 3 h. In vitro drug release from slow-releasing tablets D-4 was characterized by 5-h lag time and subsequent drug release of only 50% within the remaining time of the dissolution run at pH 6.8.

Results from a fasted-state single-dose bioavailability study of dipyridamole are shown in Fig. 4b. In vivo absorption of the drug released from pellet formulation D-1 was fast and reflects only slightly sustained drug release. Bioavailability of formulation D-2 was in the same range as for the fast-releasing pellets. However, absorption lag time was nearly doubled to 1 h. While the kinetic of drug absorption of formulations D-1 and D-3 was rather similar, formulation D-3 reflected only limited bioavailability. Drug absorption from D-4 was characterized by an even longer lag time of 3.5 h and in consequence insufficient bioavailability as well.

As shown in Fig. 4, dissolution profiles of dipyridamole formulations using the pH-adjusted biphasic model were in good agreement with in vivo performance. Formulations D-1 and D-3 revealed the same release kinetic within the first hours in vitro. This corre-

sponded well with in vivo data, where both formulations created a very similar absorption kinetic within the first 2 h. The low bioavailability of D-3 could be related to a lack of drug release beyond the initial period of 3 h in the new in vitro drug-release test compared to pellets D-1 where drug release persisted for up to 5 h. This was supported by the performance of formulation D-2, yielding higher bioavailability compared to D-1, while in vitro drug release was only 80% instead of 100% for D-1. But longer lasting drug release in vitro obviously corresponded to higher bioavailability in vivo. The poor in vitro performance of formulation D-4 using the biphasic model was also in good agreement with the results observed in vivo. This formulation was characterized by a large lag time in vivo which was observed as well in vitro, followed by sustained drug release. On this basis, a clear decision to drop this formulation for further development because of poor bioavailability could be made, whereas results of conventional dissolution were ambiguous.

To confirm in vivo predictability of the new pH-adjusted biphasic dissolution system, formulations of a second strongly pH-dependent soluble compound, BIMT 17, were investigated. Three pellet formulations and a monolithic matrix tablet were tested. Using conventional in vitro dissolution, formulation B-1 revealed fast drug release at pH 1 and pH 5.5 with a sigmoid profile at pH 1 (Fig. 5). Drug release from formulation B-2 was more pH-dependent, showing steady and sustained release at pH 1 but fast drug release of more than 80% within 4 h at pH 5.5. The matrix tablet B-3 exhibited a quite pH-independent drug release. In acidic medium as well as in medium of pH 5.5, 40% of the drug was released within 4 h and 80% within 12 h. Finally, formulation B-4 showed the slowest drug release of all tested formulations. In contrast to the other formulations, drug release from B-4 was slower in acidic dissolution medium than at medium of pH 5.5.

In general, dissolution tests of BIMT 17 formulations at constant pH revealed inconsistent ranking of formulations. While Pellet B-1 showed the fastest drug release in all media, a clear rank–order relationship for the additional prototypes covering dissolution at different pH and different manufacturing technologies was not apparent (Fig. 5a and b).

Mean dissolution profiles for BIMT 17 prototypes in the biphasic media are shown in Fig. 5c. Drug release from formulation B-1 displayed a sigmoid release profile characterized by a lag time of 1.5 h and a subsequent pulsed, fast drug release of 50% within 2 h despite the disadvantageous pH value within the dissolution medium (pH 5.5). This was followed by a sharp decrease in drug concentration after 5 h when pH was increased indicating precipitation of dissolved drug in the aqueous phase (Fig. 1). Within the next few hours, precipitated drug redissolved and migrated to the *n*-octanol layer. Formulation B-2 showed the second fastest drug release and slightly sigmoidal release pattern within 5 h followed by a rather steady drug release for the remaining time of the experiment. In contrast, the matrix tablet B-3 provided a rather steady and the most pH-independent drug-release profile in the pH-adjusted test, which was reflected by a steady drug release despite disadvantageous pH of the aqueous media. Formulation B-4 displayed the slowest and least drug release of BIMT 17 formulations. The release profile appeared sigmoid shaped with only 15% drug released within a lag time of 6 h.

Fig. 5d depicts the relative bioavailability of all tested BIMT 17 formulations in a fasted-state single-dose study. The kinetic rank order was led by formulation B-1 with the fastest drug release and the highest bioavailability, followed by pellet B-2 and matrix tablet B-3. Formulation B-4 fell short of the other formulations and reflected insufficient bioavailability.

While the ranking of release profiles obtained from dissolution media at constant pH was inconsistent with their in vivo performance, the release profiles obtained from pH-adjusted biphasic dissolution qualitatively complied with the in vivo performance of the formulations. Thus, the additional value of pH-controlled biphasic dissolution could be confirmed for a second compound.

Formulation B-1 yielded highest bioavailability in vivo and fastest increase in drug absorption corresponding to pulsed drug release after 1.5 h in the biphasic dissolution test. As this pulse was less pronounced at formulation B-2, bioavailability as well as in vitro performance was lower compared to formulation B-1. The matrix tablet B-3 provided the most pH-independent drug-release profile in vitro which was confirmed by a relative steady course of the AUC-profile in vivo. Again, a steady release kinetic in vitro with a reasonable drug release even at unfavorable solubility conditions corresponded to good bioavailability. These observations emphasized the advantage of the pH-adjusted biphasic test to differentiate between formulations exhibiting different principles to get the active dissolved even at a poor solubility environment. Poor in vivo performance of formulation B-4 was not expected on the basis of conventional dissolution testing. However, the dramatic loss of bioavailability of B-4 was caused by insufficient drug release especially within the first hours. This was best reflected by dissolution in the biphasic dissolution test.

Obviously, conventional dissolution testing at various constant pH failed to establish a clear rank order of prototypes in contrast to biphasic dissolution testing (Figs. 3–5). As already seen with dipyridamole formulations, BIMT 17 formulations as well were discriminated stronger regarding unfavorable prototypes indicating slight overretardation using the novel apparatus.

Thus, in this study, conventional dissolution testing without a pH-gradient might be misleading for different MR formulations. The establishment of a dissolution method with a pH-gradient that mimicked physiological in vivo conditions combined with a distribution step to keep sink conditions turned out to be a helpful tool for dissolution testing of MR formulations of pH-dependent poorly soluble drugs that are based on different release principles. With the applied parameters roughly simulating gastrointestinal course of pH and transit times of healthy humans in the fasted state [12–14,36], the new dissolution system might be used as a predictive tool in early formulation development to select the most promising prototypes for a typical fasted-state pharmacokinetic Phase I study.

4. Conclusion

Conventional dissolution testing of MR formulations of pH-dependent poorly soluble drugs revealed limited in vivo predictability. For a comprehensive characterization of in vitro drug release, the implementation of a pH-gradient turned out to be crucial. By the combination of a pH-gradient simulating physiological pH along the GI tract and a distribution step to maintain sink conditions in the dissolution medium, the pH-adjusted biphasic dissolution model enabled an improved characterization of MR formulations of different technologies.

The dissolution results obtained from this method turned out to be qualitatively predictive for the in vivo performance of several formulations of two drugs. Formulations with poor bioavailability could be reliably screened out using the novel apparatus despite ambiguous dissolution data of conventional dissolution testing. This turns the presented model into a powerful and predictive tool to facilitate rational selection of early formulation prototypes.

As the results could be confirmed for two pH-dependent soluble BCS II compounds, the model should be a useful tool during early MR development of other BCS II drugs.

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