Expert Opinion

A biorelevant dissolution stress test device – background and experiences

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Importance of the field: The prediction of the *in vivo* drug release characteristics of modified release (MR) oral dosage forms by *in vitro* dissolution tests is a prerequisite for successful product development.
Areas covered in this review: To improve the predictive power of dissolution testing, the authors recently developed a new dissolution test apparatus that simulates physical conditions of the gastrointestinal (GI) passage of MR dosage forms. The simulation includes pressure force exerted by GI motility, shear stress force generated during phases of GI transport and intermittent contact with intestinal fluids while the dosage form is located in an intestinal air pocket.
What the reader will gain: The article briefly describes selected aspects of GI tract physiology, evolution and goals of dissolution testing as well as the development and use of test devices that are intended to simulate GI tract conditions. The data are discussed in the light of the test results obtained with the new dissolution stress test device developed by the authors' group. Achievements reported from 1986 to 2010 are referred to.
Take home message: The new apparatus was evaluated using extended release (ER) tablets of nifedipine and diclofenac. The dissolution characteristics of some of the tested products were strongly dependent on the test conditions and could be distinctly influenced by the mechanical stress events of biorelevant intensity. Results of these experiments thus indicated that a high sensitivity of dosage forms to GI-specific physical conditions has to be regarded as a major cause of irregularities in the drug release profiles, which may result in fluctuations of the individual drug plasma concentration profiles, as, for example, caused by dose dumping.

Keywords: biorelevant dissolution testing, dissolution stress test device, dose dumping, predictive dissolution testing

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1. Introduction

As orally administered drugs can be absorbed only after having dissolved, the *in vivo* dissolution of pharmaceutical active ingredients (APIs) may critically affect their systemic uptake and thus plays a crucial role in pharmacokinetics. In 1897, Noyes and Whitney published the work 'The rate of solution of solid substances in their own solutions', in which, for the first time, the process of dissolution of solids was described [1]. This was concurrently the beginning of systematic studies of the dissolution behavior of solids. In 1900, Bruner and Tolloczko reported that the dissolution rate of solids can be influenced by several factors, including the physicochemical properties of substances, the nature of the solid form and the surface exposed to the dissolution medium [2]. The authors also noticed that the experimental conditions such as temperature, agitation rate and the construction

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Article highlights.

- Understanding of the gastrointestinal physiology and identification of potential stress factors are prerequisites for rational development of biorelevant drug release tests.
- A realistic simulation of the hydrodynamic and mechanical conditions experienced by modified release dosage forms during gastrointestinal transit is a prerequisite for improving the predictability of their *in vivo* drug release with *in vitro* dissolution results.
- The test system developed by the authors' group facilitates a realistic simulation of the critical mechanical parameters of the gastrointestinal passage of dosage forms.
- The results obtained so far with the dissolution stress test device developed by the authors indicate that the mechanical robustness of the formulation may be an essential factor determining the drug delivery characteristics of modified release formulations.
- The newly introduced stress test procedures can be regarded as a starting point towards a more comprehensive prediction of the conditions that modified release dosage forms meet during gastrointestinal transit.

This box summarizes key points contained in the article.

of the test device may affect the dissolution process [2,3]. Later on this knowledge proved also to be essential for the determination of processes that may influence the dissolution of orally administered drugs as well as solid dosage forms [4]. As a result of these first investigations several test devices, which often differed in terms of their construction and the operating mode, were developed [4]. Almost all of these new devices had a simple construction and provided well-definable conditions by implying continuous exposition of the dosage form to a sufficient amount of dissolution medium. The dissolution medium became an acceptor compartment, consequently determining the API's dissolution rate. The coexistence of several very different test devices as well as test conditions resulted in difficulty with comparing the test results. Therefore, in the 1960s the need to develop standardized test conditions was generally recognized. This resulted in the establishment of the rotating basket apparatus, which in 1970 was introduced as USP Apparatus 1 in the United States Pharmacopeia (USP 18). Further development led to the introduction of more test methods, which were also developed for the testing of dosage forms under well-defined and reproducible conditions. Today, dissolution experiments are typically carried out under highly standardized conditions and in accordance with official guidelines and/or international pharmacopoeias [5-7].

In the last few decades dissolution testing has become a powerful tool for quality control. Furthermore, it can also be applied for determination of the (bio)pharmaceutical equivalence of different formulations, as in the case of the evaluation of minor, post-approval changes in product manufacturing [8,9].

The role of the dissolution test is also dependent on the dissolution characteristics of the products as well as the APIs belonging to a particular class of the biopharmaceutics classification system (BCS), which groups the drugs with regard to their aqueous solubility and intestinal permeability. For generic immediate-release dosage forms (IR) with APIs with good solubility and good permeability as well as good solubility and poor permeability classified to classes I or III of the BCS, the results of dissolution tests can be used as justification for a biowaiver [10].

For IR generics with poorly soluble and good permeability APIs as well as poorly soluble and poorly permeable APIs belonging to BCS classes II and IV, respectively, the dissolution test results cannot waive the bioequivalence studies. Similar to the case of modified release (MR) formulations, the dissolution test results do not waive *in vivo* bioequivalence testing for the approval of solid oral dosage forms independently of the BCS classification of the contained API. In these cases the dissolution testing plays an important role during product development where the *in vitro* dissolution profiles of new formulations are intended to be predictive for the *in vivo* drug release behavior. However, it is often not clear to what extent the results of the dissolution test correlate with the *in vivo* performance of the tested formulations [11,12]. One important factor for an improved predictive power of dissolution testing is to mimic the *in vivo* conditions that are important for the drug release characteristics as realistically as necessary. To elucidate the main factors that affect *in vivo* drug release from oral dosage forms, both mechanical aspects (sometimes also referred as hydrodynamics) and physicochemical aspects of the gastrointestinal (GI) physiology have to be considered [13].

First attempts towards a relevant simulation of *in vivo* conditions were made by including several dissolution media in international pharmacopoeias [6,7]. These dissolution media, such as 0.1 N hydrochloric acid (USP), pH 4.5 acetate buffer (USP) and pH 6.8 phosphate buffer (USP), have model characters for simulating physiological pH conditions in the stomach and small intestine, respectively [7]. Owing to their simple composition, these media are widely applied in routine dissolution testing. Further attempts were made to mimic the enzymatic activity in the different GI sections. This was realized by addition of the digestive enzymes pepsin or pancreatin to the appropriate electrolyte solutions. The corresponding media were introduced into the pharmacopoeias as simulated gastric fluid (SGF) and simulated intestinal fluid (SIF), respectively.

It should be kept in mind that the pharmacopoeial dissolution media reflect only very few aspects of the physicochemical properties of the fluids present in the GI tract. Furthermore, they do not take into account different prandial conditions. Therefore, some more detailed characterization of the GI liquids at various prandial conditions was performed in order to enable a realistic simulation of the physicochemical

properties of GI fluids. This research resulted in several versions of so-called biorelevant dissolution media [14,15]. The work was particularly focused on a realistic simulation of pH, osmolarity, the presence of natural emulsifiers such as bile salts and phospholipids, enzyme activity and the presence of food ingredients and digestive products [15-19]. It was revealed that the composition of the dissolution media can distinctly affect the solubility of drug substances and the dissolution profile of the drugs [18,20-23].

Recently, several attempts were made to simplify the complex composition of biorelevant dissolution media, aimed at their utilization in routine analysis. Adequate simplification of the media was achieved by addition of synthetic surfactants to blank electrolyte solutions of appropriate pH, ionic strength and osmolality in quantities assuring a physiological surface tension. The proposed media provided comparable dissolution profiles for poorly soluble model drugs to those obtained using the established standardized FaSSIF (fasted state small intestinal fluid) and FeSSIF (fed state small intestinal fluid) solutions [24-26]. The use of such simplified biorelevant dissolution media containing adequate concentrations of synthetic surfactants, such as, for example, polysorbate 80, was reported for screening analyses of various tablet and pellet formulations. The discriminatory power of the test methods was distinctly increased in terms of distinguishing between formulations with desired and unwanted *in vivo* drug release characteristics [27,28].

So far, the influence of hydrodynamics, that is, agitation caused by flow of chyme and mechanical stress caused by GI motility acting on the dosage forms in the form of pressure waves, on the release behavior during GI passage is widely accepted but insufficiently understood [29,30]. It has been shown in human studies that the GI passage of dosage forms is characterized by a high variability and discontinuity of the transit conditions. The transport of dosage forms along the GI tract is characterized by a combination of relatively long static phases and events of dynamic transport [31]. During the transport events dosage forms are forced to move for a short period of time with sometimes very high velocities. Very high peak velocities of up to ~ 50 cm/s have been reported to occur during gastric emptying and passage of the ileocecal junction [32,33].

Dynamic and turbulent kinetics of chyme generate hydrodynamical stress and thus shear forces that influence the release profile of drug substances from various dosage forms [34]. During gastric residence the intensity of both types of agitational force of mechanical and hydrodynamical origin are strongly dependent on the prandial conditions. Based on the analysis of images obtained by MRI, the complex movement behavior of the fed stomach could be analyzed. From these data it has been estimated that the movements of the stomach can provoke a local flow of chyme with velocities of up to 12 cm/s [35,36]. Recently, it has also been demonstrated that as a result of the GI motility during GI transit solid dosage forms are exposed to mechanical pressure of up to 300 mbar [29,37,38]. In another MRI study it was observed that water is not equally distributed within the intestinal 'tube' under fasting conditions, but limited to typically 3 – 6 separated fluid pockets containing variable liquid volumes with a median of 12 ml. Moreover, in the same studies it was observed that during GI transit non-disintegrating solid dosage forms are occasionally located in gas-filled sections of the intestines where they are not in contact with fluid [39].

The discontinuity of the GI transit conditions is very likely to have an impact on the drug release and dissolution process and can thus be critical for MR dosage forms, especially for single-unit formulations with modified drug release mechanisms. The release characteristics of extended release (ER) dosage forms typically determine the shape of the *in vivo* concentration profile of the drug [40,41]. Extended release formulations are designed to release drug substances in a controlled and predictable way over the entire dosing interval. They are mostly intended to provide non-fluctuating drug plasma levels within a therapeutic concentration range over a long time period, which typically comes with fewer side effects and an overall improved patient compliance. Furthermore, ER formulations make possible a reduction of the dosing frequency, which may also be beneficial for patient compliance [42,43]. Robust drug delivery behavior is an elementary feature of ER formulations as they usually contain relatively high doses of drug substances, sometimes also with narrow therapeutic index. Particularly for the latter candidates, an overproportionally high *in vivo* drug release from the ER dosage form can result in extraordinarily high systemic drug concentrations, which may be associated with the possibility of dose-related side effects. The release of exaggerated amounts of drug substance from ER formulations within a short time is known as dose dumping and is often a reason for therapeutically undesired drug plasma levels [44-46].

Widely discussed explanations for dose dumping as an unwanted event that is related to the design of MR dosage forms are interactions between the dosage form and the GI fluids, which already in the fasted state show a high inter- and intra-individual variability in their physicochemical properties, such as pH, ionic strength, surface tension, solubilization capability and digestive activity. Food intake is another important factor to consider because it will significantly change the composition and properties of the GI fluids, which (e.g., after intake of a fat-rich meal or ethanol consumption) can result in heavily accelerated drug release. The impact of GI fluid composition on drug release from various MR dosage forms has been studied extensively in the last few years [47,48]. However, so far only a little attention has been paid to the impact of mechanical and hydrodynamical GI-specific stresses on the drug release properties of dosage forms, even if these are of great relevance for both the safety and reliability of MR dosage forms.

The design of the official dissolution test apparatus does not provide the possibility of simulating GI mechanical stress conditions in a meaningful way. In the past only a very few

attempts have been made to develop test devices that are capable of simulating essential physiological stress parameters when performing dissolution tests. Key factors of physical conditions during GI passage that may cause mechanical stresses on dosage forms and that are usually not considered are: the discontinuity of the movement of dosage forms inside the GI tract, the variability of the GI motility and pressure and the intermittent contact of the dosage form with GI fluids [49].

It is very likely that by means of dissolution test methods capable of mimicking the most critical stress conditions occurring during gastrointestinal passage, potential 'dose-dumpers' could be identified before getting into human trials. The use of such, with regard to mechanical stresses, 'biorelevant' test methods would also offer the opportunity to study drug dissolution processes under more realistic conditions. Accordingly, application of such methods in early formulation development would enable identification of undesired drug release behavior without the need to perform Phase I clinical trials. Consequently, such methods might help to reduce considerably the failure risk of bioequivalence studies of both original formulations and generics.

2. Simulation of mechanical conditions of the gastrointestinal tract

2.1 Dissolution devices

The dissolution test devices most relevant for the investigation of solid oral dosage forms are Apparatuses 1 – 4 of the USP and European Pharmacopoeia (Ph. Eur.). These devices represent highly standardized tools for quality control and with appropriate experimental settings also make possible a simulation of the physicochemical conditions in the GI tract. Numerous attempts have been made to provide a more realistic simulation of the mechanical conditions in the GI tract. In most of the cases pharmacopoeial dissolution test devices, especially the paddle apparatus (Apparatus 2) and modifications thereof, have been applied for this purpose.

As an example, polystyrene pellets have been added to the dissolution medium in order to increase the mechanical agitation rate to improve the simulation of the erosive conditions in the human GI tract [50]. A modification that avoids the spontaneous and most probably artefactual agglomeration of undissolved material directly under the stirrer blade in the paddle apparatus is the brush-like crescent-shaped spindle device [51]. This spindle is adapted to the bending radius of the bottom of the standard dissolution vessel [52]. In this way, the strain generated by the spindle during rotational movement is transmitted directly to the dosage form, which is usually placed at the bottom of the vessel. The spontaneous agglomeration of dosage form fragments can also be eliminated by application of the so-called PEAK vessel. Here, the center of the vessel's bottom has a conical shape (peak), which changes the hydrodynamic test conditions, eliminating a zone with poor hydrodynamics at the preferential location of the dosage form in the paddle apparatus [53]. Another strategy towards a more realistic simulation of mechanical conditions is the application of dissolution media with higher viscosities (applied are 20 and 150 mPa s) instead of water (1 mPa s) in order to increase the shear stress forces generated by the media flow provoked by the test conditions. The application of dissolution media with enhanced viscosities results in increased hydrodynamical stress. It could be shown that the dissolution behavior of ER formulations can be strongly influenced by the viscosity of the dissolution medium [54].

USP Apparatus 3 (reciprocating cylinder) has also undergone several modifications. By varying the mesh size of the cylinder bottom, the hydrodynamics of the test can be changed [55]. The addition of agitating elements such as glass beads or disintegration disks to the cylinders results in an increase of the destructive force experienced by the dosage form.

Overall, all of the proposed modifications of the standard devices just roughly simulate the complexity of the conditions as they are present during GI passage. Therefore, more advanced test devices that provide either an improved simulation of selected aspects of GI conditions or the simulation of the whole GI passage have been designed. These devices differ fundamentally in their construction and in the spectrum of physiological stress factors that can be simulated. Most of the newer test devices were initially developed by or for the food industry, with the aim of investigating the digestibility of new food products *in vitro* [56,57]. In addition to food industry applications, the so-called TIM-1 simulator, developed by the Dutch research organization TNO, was also applied successfully to characterizing drug release from various types of oral dosage form [58]. The TIM-1 simulator allows the simulation of conditions as they are present in the stomach and small intestine. In addition, the TIM-2 simulator has been introduced to simulate conditions in the colon. In summary, the two TNO simulators are focused on mimicking physicochemical and enzymatic conditions in the different GI sections. The utility of the two TIM apparatuses for the development and optimization of biopharmaceutical properties of dosage forms has been confirmed empirically [58-60].

A unique opportunity for a realistic simulation of hydrodynamic shear stresses is provided by the rotating beaker apparatus. This device enables the simulation of the shear stress forces that strike the surface of a dosage form in the postprandial stomach [34]. The shear stress forces acting on the dosage form are generated by a laminar flow of dissolution media having well-defined viscosities and Newtonian flow properties. Laminar flow assures the erosion of the outer layers of the dosage form and consequently affects the dissolution process. However, even if this apparatus comes with several unique properties, a realistic simulation of the dynamics and the discontinuity of the flow behavior of the chyme as well as the simulation of mechanical forces acting directly on the surface of the dosage form is difficult to achieve.

2.2 Dissolution stress test

The dissolution stress test device is a test approach that was developed by two of the authors (G Garbacz and W Weitschies) to simulate the impact of physiological mechanical stress that may occur during the GI passage of dosage form. The schematic layout of the device is presented in **Figure 1**. A detailed description is given elsewhere [49]. The dissolution stress test apparatus exposes a dosage form to sequences of agitation including movement and pressure fluctuations alternated with static phases as they typically occur *in vivo*. Moreover, the device enables the simulation of an intermittent contact of the dosage form with the dissolution medium.

The dissolution stress test device consists of a central apparatus axle with six spheres made of steel wire net in which the dosage forms are hosted. Each sphere is divided into two parts. The bottom part is screwed into the central pipe-like axle by a PVC bush and by a profiled nozzle. The central pipe is attached with Teflon handles, placed on the deck plate of the device ~ 3 mm above the top edges of linearly placed standard dissolution vessels in their symmetry plane in such a way that each sphere operates in a separate vessel. The central axis is coupled at one end with a pressure regulation unit by a rotating joint and at the other end with a stepping motor by an Oldham-type disk coupling. Pressure fluctuations are generated by periodic inflation and deflation of the balloons inside the chambers, which are controlled by synchronized switching of solenoid valves. The magnitude of pressure is regulated by a pressure-reducing device. The central axis is driven by a computer-controlled stepping motor that facilitates programmable movement and positioning of the probe chambers with reference to the dissolution medium. This offers the possibility of simulating the interrupted contact of the dosage form with the dissolution media. The test parameters are controlled by custom-made software based on LabView 7.1 (National Instruments corporation, Texas, USA).

Various experiments have been performed with this set up. Owing to the construction of the apparatus, all stress experiments have been performed in 1.2 l of dissolution medium. This volume assures complete immersion of the probe chambers during the rotational movement and the static phases during which the spheres are placed vertically down. The dissolution medium is mixed by a paddle stirrer operated at 100 r.p.m. during the entire test.

The dissolution stress test apparatus has been operated in simplified stress sequences as well as in more complex test programs intended to simulate the mechanical conditions during a fasted GI passage of dosage forms. The stress sequence has been composed of stress events of maximal physiological fortitude applied in a frequency of one or three stress events per hour. Dynamic stress is generated by rotational movement of the central axis at a rate of up to 100 r.p.m. over a period of up to 1 min. The impact of the pressure forces of maximal physiological fortitude is simulated as a sequence of 3 symmetrical pressure fluctuations lasting for 6 s each and having an amplitude of typically 300 mbar. To mimic the mechanical aspects of GI transit under fasting conditions, several test programs have been developed. These are composed of phases of agitation initiated by a rotational movement of the axis of the central apparatus and are intended to simulate events of transport followed by phases of pressure fluctuations mimicking GI tract motility events. During the rotational movement of the axis of the apparatus the dosage form is forced to change its position in the probe chamber. This results in dosage form velocities of up to 60 cm/s, which is in good agreement with velocities determined using a magnetic marker monitoring technique in humans during transport events [31]. High stress phases have been composed as a combination of pressure events of up to 300 mbar fortitude that are followed by 1 min of rotation at 100 r.p.m. The intention of these high stress phases is the simulation of the harsh conditions that may occur during gastric emptying and duodenal passage as well as during passage of tablets through the ileocecal region. Postprandial motility of the stomach has so far been simulated as a simple sequence constituted of rotational movements and pressure fluctuations of biorelevant fortitude [61]. Owing to the known large variability of colonic motility, a realistic simulation of the conditions during colonic passage of dosage form is critical. So far the authors have simulated colon transit as short phases of harsh agitations occurring in intervals of several hours (typically 2 – 4 h). So far the device has been successfully applied for the identification of clinically undesired performances of various single-unit MR dosage forms [49,61-63].

3. Results of the biorelevant dissolution stress test

The stress test apparatus has for the first time been used for the evaluation of Voltaren retard 100 mg ER tablets containing diclofenac sodium [49]. *In vitro* dissolution test profiles generated with the new test apparatus and the paddle apparatus (USP II) were compared and also correlated with drug plasma profiles obtained after the administration of Voltaren tablets to 24 healthy volunteers under fasting conditions. After intake of the Voltaren tablets in the individual plasma concentration–time profiles, typically one to three predominant peaks were observed. However, dissolution tests performed using the paddle apparatus at varying rotational speeds and in different media resulted in almost linear and non-fluctuating release profiles. By contrast, results of dissolution tests performed with the new apparatus revealed that under physiological mechanical conditions the diclofenac release from the ER tablets is extremely variable and depends strongly on the mechanical stress applied to simulated events of transport and motility (**Figure 2**). The dissolution data obtained with the new dissolution stress test device therefore suggest that the diclofenac peaks in plasma observed after administration of the ER diclofenac tablets are most probably caused by the sensitivity of the tablet to events of mechanical

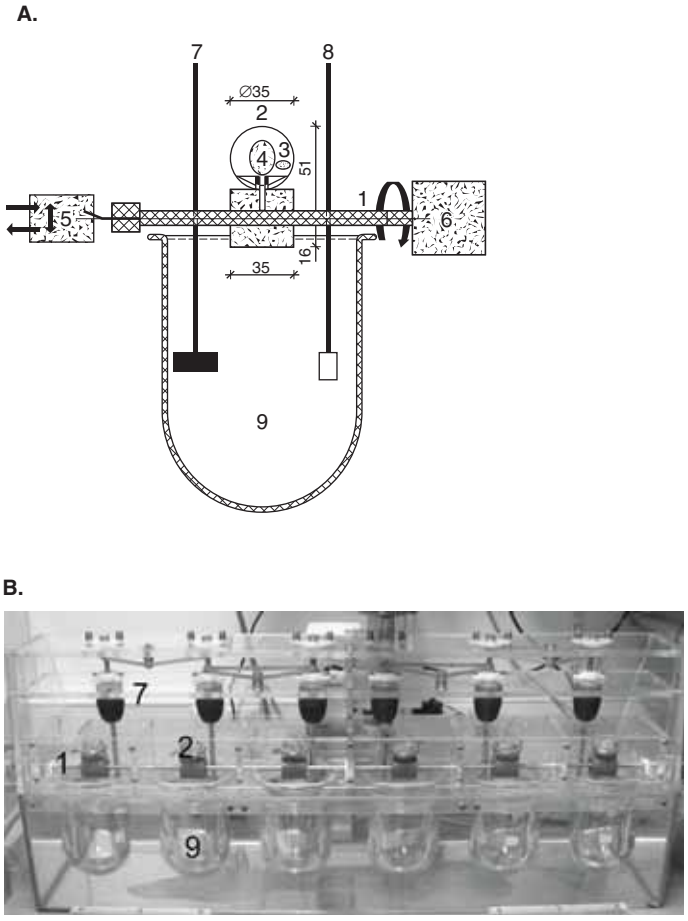

Figure 1. Schematic (A) and photographic (B) representation of the biorelevant dissolution stress test device. 1: central axle (diameter 8 mm); 2: steel netting wire chamber (diameter 35 mm, mesh size 0.5 mm, wire 0.1 mm); 3: dosage form; 4: inflatable balloon; 5: solenoid valve system; 6: stepping motor; 7: stirrer (blade 35 × 15 mm); 8: sampling; 9: standard dissolution vessel.

stress during GI passage. Based on this observation it is hypothesized that dominant peaks in individual diclofenac plasma concentration profiles after administration of the ER tablet product are the result of highly accelerated diclofenac release during biorelevant physical stress events typically representing gastric emptying and passage through the ileocecal region.

In further investigations, the stress test apparatus was applied to investigate the dissolution characteristics of four ER generic formulations of diclofenac sodium 100 mg dose [62]. The tested products were generic formulations of the Voltaren available on the European market that are regarded as bioequivalent with the originator, that is, Voltaren. The investigations were again performed with USP Apparatus 2 and the new biorelevant dissolution stress test device. The test parameters were the same as formerly applied for Voltaren. The tests yielded pronounced differences in the release behavior among the 100 mg diclofenac containing ER generics. The dissolution profiles of the tested formulations were strongly dependent on the test conditions and were distinctly influenced by the mechanical stress events of physiological intensity. Such susceptibility of dosage forms to biorelevant stress may be the main reason for irregularities in drug plasma profiles. Also, pH change from pH 1.0 to pH 6.8 after 1 h of dissolution testing induced further changes in the dissolution profiles of the formulations. The pH-induced changes of the mechanical stability and the dissolution characteristics of the products may be an extra factor inducing variability under *in vivo* conditions. However, as corresponding *in vivo* data are not available the clinical relevance of the results of the generic formulations requires further investigation.

Another series of dissolution studies was performed with nifedipine ER formulations. For patients with cardiovascular diseases treated with nifedipine, it is commonly accepted that ER formulations are the first therapeutic choice in order to avoid unwanted increases in heart rate as they may be caused by steep rises in nifedipine plasma concentrations [64].

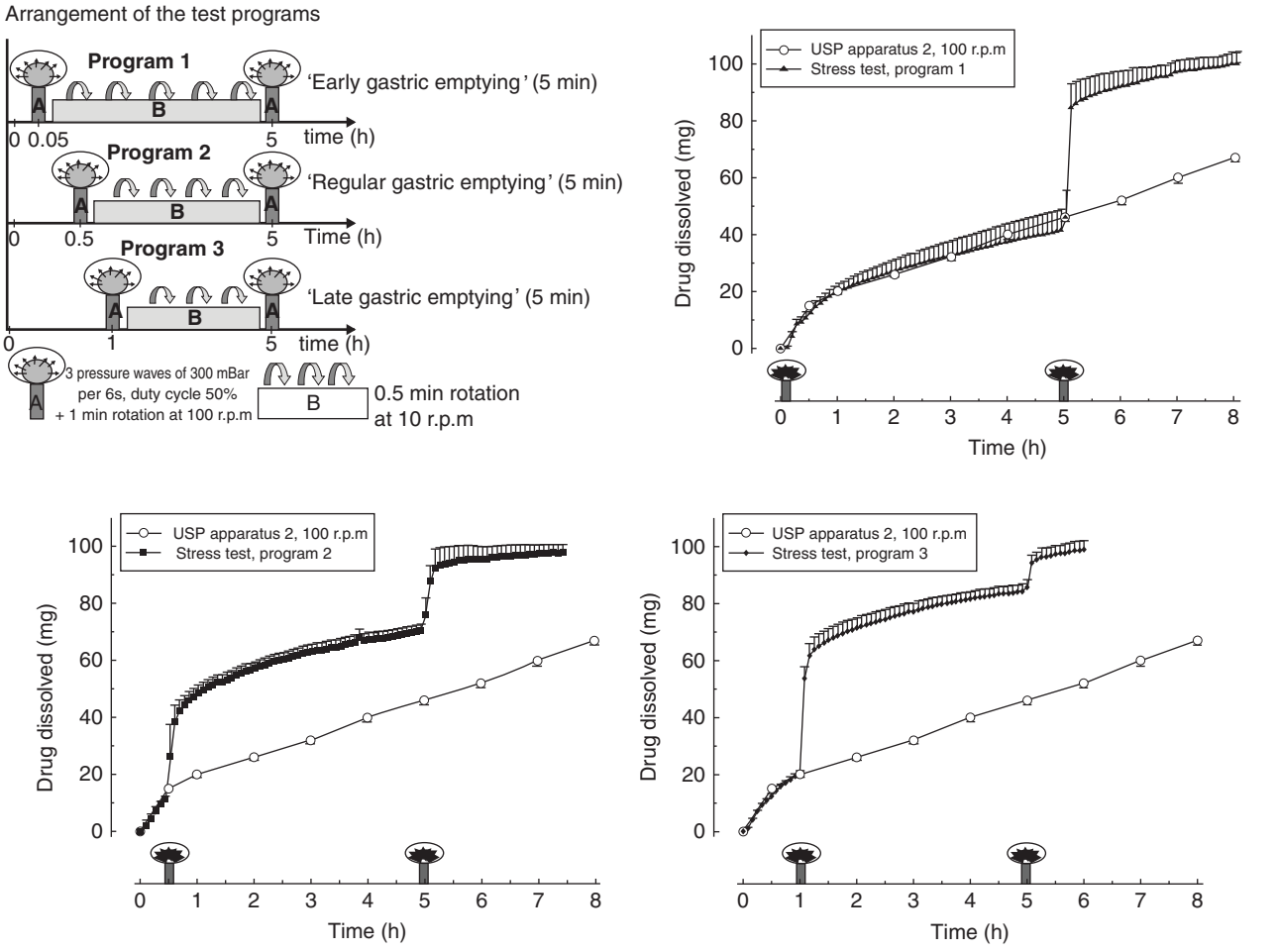

Figure 2. Schematic representation of test programs 1 – 3 and dissolution profiles of Voltaren 100 mg retard tablets obtained in the USP Apparatus 2 at 100 r.p.m. and in the dissolution stress test device under programs 1 – 3. Dissolution medium applied was pH 6.8 phosphate buffer of the USP. Presented are means of n = 6, standard error is indicated by the error bars. A detailed description of the test set up is given elsewhere [49].

Based on these clinical observations, ER formulations can provide their therapeutic superiority only as long as they provide non-fluctuating plasma profiles. The aim of the dissolution studies was thus to compare dissolution experiments carried out on four different nifedipine ER formulations using two established and two new dissolution test methods: the paddle apparatus, the reciprocating cylinder (both according to USP and Ph. Eur.), the rotating beaker apparatus [32] and the dissolution stress test apparatus [61]. At the time of the experiments, all tested nifedipine ER products were marketed in Europe. The pharmacokinetic profiles of Adalat OROS 30 and 60 mg and of Nifedipine Coral 60 mg tablets have been investigated under fasted and fed conditions and described elsewhere [44,46]. The study results demonstrated that the dissolution characteristics of the ER tablets are strongly dependent on the applied test conditions. The dosage form-related food effects reported previously in human bioequivalence studies with Coral 60 mg could be predicted with the two non-compendial dissolution test devices. The lack of mechanical stability and pH-dependent dissolution profiles of Coral tablets 60 mg retard is to the authors' understanding most probably the main reason for the observed food effects. The dissolution profile of Sandoz 40 mg tablets was very sensitive to all applied test conditions, that is, poor mechanical stability of the tablet matrix and a very fast dissolution behavior. The robust drug delivery characteristics of Adalat OROS reported in numerous *in vivo* studies was also observed in all dissolution tests performed in this study.

4. Conclusion

A realistic simulation of the hydrodynamic and mechanical conditions experienced by MR dosage forms during GI transit is a prerequisite for improving the predictability of their *in vivo* drug release with *in vitro* dissolution results. For this purpose, the authors have developed a new biorelevant stress

test device. Using this device the results obtained so far indicate that the mechanical robustness of the formulation may be an essential factor determining the drug delivery characteristics of MR formulations. The newly introduced stress test procedures can be regarded as a starting point towards a more comprehensive prediction of the conditions that MR dosage forms meet during gastrointestinal transit.

5. Expert opinion

Understanding of the GI physiology and identification of potential stress factors are prerequisites for rational development of biorelevant drug release tests. Dissolution test devices enabling a realistic simulation of the mechanical as well as physicochemical factors experienced by dosage forms during GI transit can be realized in many ways. The test system developed by the authors' group facilitates a realistic simulation of the critical mechanical parameters of the GI passage of dosage forms. In comparison with other biorelevant test systems such as TIM-1 and TIM-2, the newly developed dissolution stress test device is characterized by a straightforward design. It is based on a universal probe chamber in the form of a steel wire netting sphere in which the tested dosage form is hosted during the simulation of the GI passage. The biorelevance of the test is realized by appropriate setting of the process parameters. The test enables a realistic simulation of mechanical stress factors such as variable pressure conditions, transport processes as well as intermittent contact of the dosage form with the dissolution medium.

The new stress test device and the test procedures have been developed primarily for the GI transit conditions. So far it has been applied to the investigation of single-unit MR formulations. Single-unit formulations such as ER tablets pass the GI tract in a non-disintegrated form. Therefore, the entire tablet and consequently the residual amount of drug substance in the dosage form are exposed to the physiological stress present in the respective section of the GI tract at one time. Different sections of the GI tract may be of varying impact, especially when the dosage form passes regions of high motoric activity as it is known for pyloric passage during gastric emptying, ileocecal passage during transport from the small into the large intestine, or events of mass movement during colonic passage [29,31,36-38]. In the case of insufficient mechanical stability of ER tablets, the release controlling mechanisms can be affected. This may result in permanent changes of the drug delivery characteristics and can also result in dose dumping. Commonly applied techniques for controlling drug release from oral solid dosage forms include extending the hydration and diffusion of drug molecules in the tablet matrix, modifying the solubility kinetics of the drug, controlling the erosion rate of the dosage form, as well as combinations thereof [65-67]. Using standard dissolution test procedures, the integrity and functionality of the release controlling mechanisms are only characterized under constant and rather gentle conditions.

So far, the extent to which stress events of biorelevant fortitude can influence drug release mechanisms from MR dosage forms has not been investigated. Some insights into the mechanical properties of ER dosage forms within the drug release processes have already been obtained, applying texture analyzers [68-72]. It will be interesting to establish the relationship between the mechanical stability of ER products and their drug release characteristics under biorelevant stress test conditions.

Until now, experiments using the dissolution stress test device were performed using simple dissolution media. This enabled the investigation of the influence of mechanical stresses on the release behavior of single-unit ER dosage forms. However, a realistic simulation of the GI transit conditions requires the application of biorelevant media [15-17]. Moreover, the applied experimental settings used in the experiments performed so far do not simulate the dynamic media changes that are characteristic for the postprandial GI tract. It is well known that digestion products can significantly affect the solubility of drugs [73]. For example, Diakidou *et al.* demonstrated that the *in vivo* drug release behavior of ER tablets containing felodipine, a poorly soluble drug, in the postprandial stomach can be better reproduced when gastric fat digestion is simulated *in vitro* [74]. Therefore, dynamic changes of media conditions will be a task for the future.

As an ultimate goal it would very desirable to answer the question whether oral dosage forms are bioequivalent without the necessity of using human subjects for bioequivalence testing. The authors believe that in the future this might be realized using experimental settings that provide a realistic simulation of the complexity of the *in vivo* conditions by means of a combination of appropriate *in vitro* tests. The prerequisite for the development of such 'bio-predictive' dissolution tests is a profound understanding of the physiological conditions dosage forms are confronted with within the gastrointestinal tract. Such tests will hopefully be suitable for deciding whether two oral drug formulations containing the same drug in the same quantity will be bioequivalent.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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