

Predictive Dissolution Testing – Concepts and Challenges



To date the question of the equivalence and the pharmacokinetic reliability of solid oral dosage forms can in most cases be answered only in clinical trials. However, with the increasing number of both *in vitro* test systems capable of mimicking selected aspects of human gastrointestinal (GI) physiology and various *in silico* tools and pharmacokinetic models applied to translate *in vitro* release data into plasma profiles, it is likely that at some point the equivalence and the pharmacokinetic safety of oral dosage forms might be answered without the need to use human subjects for bioequivalence testing, but using an appropriate *in vitro* test design. From our point of view, both questions may not be answered with a single *in vitro* test but a set of *in vitro* experiments with experimental settings that provide a realistic simulation of the complexity of the *in vivo* conditions. Developing predictive *in vitro* test systems for solid oral dosage forms which are capable of a realistic simulation of gastrointestinal transit conditions is still a challenge. Such predictive dissolution tests should be suitable to assess the robustness and reliability of the formulation, as well as to answer the question whether two oral drug formulations containing the same dose of the same drug will be bioequivalent. A prerequisite for developing predictive dissolution tests is detailed information on the physiological conditions a dosage form is confronted with during GI passage, as well as the implementation of such information in the rational development of both test systems and methodologies.

The GI passage of dosage forms is characterised by a high variability of the physicochemical properties of the GI content, as well as by a discontinuous transit with changing dynamic conditions. The impact of GI fluid composition on drug release has been extensively investigated

within the last years^{1,2}. It has been identified that there is a high inter- and intraindividual variability in the physicochemical properties (e.g. pH, ionic strength, surface tension), the solubilisation capacity and the digestive activity of GI fluids³⁻⁵. It is also well known that food intake can result in a significant change in the composition and the properties of the GI fluids, which in turn (e.g. after intake of high caloric meal or ethanol consumption) can result in meaningful changes of the dissolution behaviour of oral dosage forms⁵. However, to date only a little attention has been paid to the impact of mechanical stresses like pressure and hydrodynamics on the drug delivery characteristics of solid oral dosage forms. However, such impacts are likely to be of great relevance for the pharmacokinetic safety and reliability of at least oral modified release (MR) formulations.

In numerous human studies it has been shown that the GI passage of dosage forms is characterised by highly variable and discontinuous transit conditions. The transport of dosage forms along the GI tract is a result of alternating static phases of relatively long duration and events of dynamic transport^{6,7}. During GI transport events, dosage forms are temporarily handled with high velocities which can particularly be measured during gastric emptying and passage through the ileocecal junction. Recently, it has also been recognised that during GI transit, solid dosage forms are exposed to mechanical pressures resulting from typical GI motility events. Maximum pressures were registered in the regions of pyloric and ileocecal sphincters⁸⁻¹⁰. In addition to the transit conditions, the volume of fluid available in the GI lumen can have a significant impact on drug release. Data derived by magnetic resonance imaging (MRI) demonstrated that under fasting conditions liquids are not equally

distributed along the intestinal “tube” but limited to typically three to six discrete fluid pockets. In accordance with this observation, it could be shown that during GI transit, non-disintegrating solid dosage forms are not in continuous contact with GI fluids but are occasionally located in empty or gas-filled sections of the intestines¹¹.

With all this background information, it becomes clear that the design of standard dissolution methods does not provide for a realistic simulation of the GI-specific stress conditions. In the last decades the pharmacopoeial dissolution test apparatuses became powerful instruments for standardised dissolution methods used in quality control. Since these apparatuses fall short in simulating biorelevant stresses, their applicability in establishing test methods predictive of the *in vivo* performance of solid oral dosage forms is often limited. To better simulate the impact of *in vivo* hydrodynamics and mechanical stress on drug release, we developed a “biorelevant dissolution stress test device” capable of simulating the essential physiological stress parameters, such as the discontinuous movement of dosage forms in the GI tract, the variability of GI motility and pressure waves as well as the intermittent contact of the dosage form with GI fluids¹².

Dissolution Stress Test Device

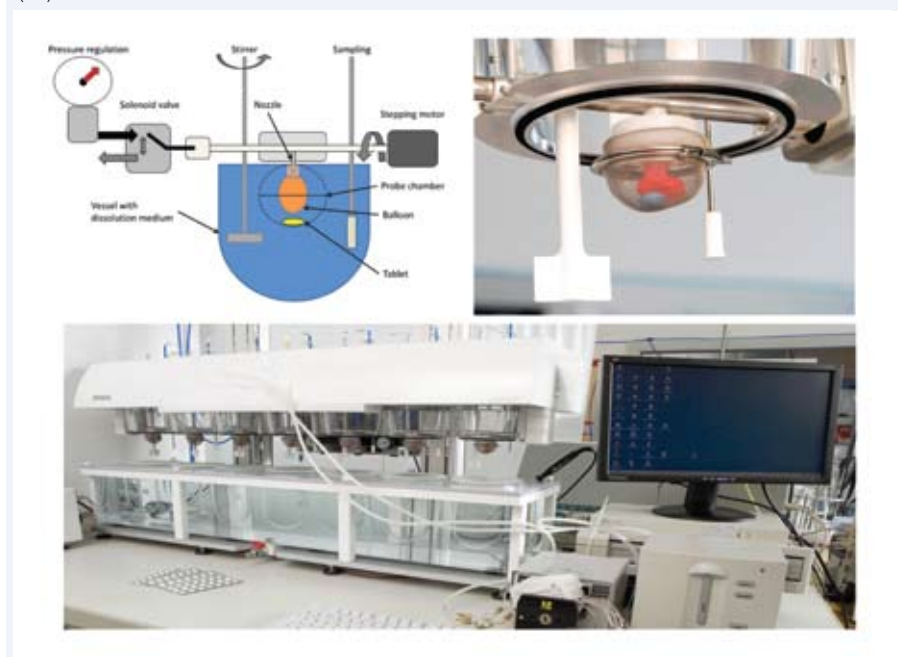
The dissolution stress test device was first introduced by G. Garbacz and W. Weitschies¹². In the meantime, the prototype of the apparatus has been technically upgraded and translated into a professional version manufactured by ERWEKA GmbH, Heusenstamm, Germany. The apparatus aims to simulate the dimensions of physiological mechanical stress that may occur during the GI passage of a solid dosage form. For this objective, the

dissolution stress test apparatus exposes a dosage form to sequences of agitation including movement and pressure fluctuations alternated with static phases as observed *in vivo*. Moreover, the device enables the simulation of an intermittent contact of the dosage form with the dissolution medium. The device is illustrated in Figure 1 and a more detailed description can be taken from references¹²⁻¹⁴.

are controlled by synchronised switching of valves, and the pressure can be regulated by a pressure-reducing device. The central axis is driven by the stepping motor, which is computer-controlled and thus enables a programmable movement and positioning of the probe chambers in and outside of the dissolution vessel, resulting in immersion in the medium or in contact with air. This offers the possibility to simulate the interrupted

hour. In the first set of experiments, dynamic stress with velocities of up to 100rpm and lasting over a period of one minute was generated by the rotational movement of the central axis. In the second set of experiments, pressure forces of maximal physiological fortitude were simulated by a sequence of three symmetrical pressure fluctuations with fortitudes of up to 300mbar and a duration of 6s each. Subsequent experiments were focussed on mimicking the variations of the mechanical parameters affecting orally applied dosage forms during their GI transit under fasting conditions. Several test programmes were developed to cover a whole range of such variations. These test programmes are composed of phases of agitation initiated by a rotational movement of the central axis intended to simulate events of transport which are followed by phases of pressure fluctuations mimicking motility events in the GI tract. During the rotational movement of the central axis, the dosage form is forced to move with velocities of up to 60cm/s which are in good agreement with those determined in an *in vivo* study examining transport events in humans with a magnetic marker monitoring technique^{17,12,16}. Phases of high stress are composed of pressure events with pressures of up to 300mbar which are followed by one minute of rotation with a velocity of 100rpm. Such phases of high stress are intended to simulate the harsh conditions which may occur during gastric emptying and duodenal passage, as well as during passage of tablets through the ileocecal junction. The motility of the postprandial GI tract, particularly that of the stomach, has so far been simulated as a simple sequence of rotational movements and pressure fluctuations of biorelevant fortitude^{12,13,17}. The test algorithms for simulating the dynamics and the variability of postprandial conditions are currently under development. Due to the known large variability of colonic motility, a realistic simulation of the conditions during colonic passage of dosage form is hardly possible. So far we simulated colonic transit by means of short phases of harsh agitations occurring in intervals of several hours (typically two to four hours).

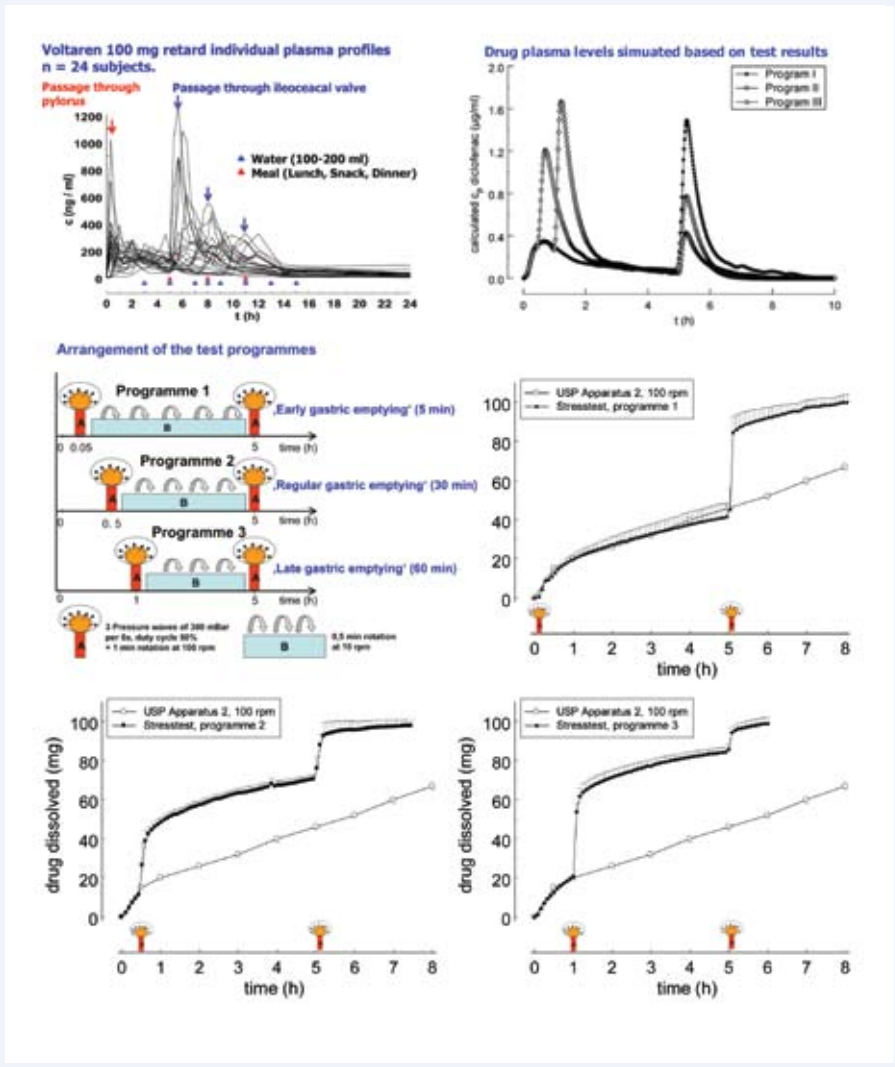
Figure 1: Biorelevant dissolution stress test device: schematic representation, construction detail, and photographic representation of the test setup with flow through UV Vis spectrophotometer (14).



Briefly, the dissolution stress test device consists of a central apparatus axle with seven spheres (probe chambers) made of a stainless steel wire netting in which the dosage forms are hosted throughout the test. Each sphere is divided into two parts. The bottom part is screwed into the central pipe-like axle by a bush and a nozzle. In the working mode the central pipe is placed on the deck plate of the device about 3mm above the top edges of a row of seven standard dissolution vessels in their symmetry plane. Consequently, each sphere operates in a separate vessel. On one end the central axis itself is coupled to a pressure regulation device, and on the other end a stepping motor is attached. Pressure waves are generated by periodic inflation and deflation of the balloons located inside the probe chambers. These balloons

contact of the dosage form with GI fluid. All test parameters are controlled by custom-made software. The dissolution medium (1160-1200mL) is mixed by a separate paddle stirrer operated at 100rpm during the entire test. To date various experiments have been performed with this setup¹⁵. In these experiments the dissolution stress test apparatus was operated in simplified stress sequences as well as in more complex test programmes intended to simulate the mechanical forces acting on a dosage form during fasted GI passage. In the simplified experiments, the focus of the experiments was to examine the impact of a single parameter on drug release. Various stress sequences were applied. These were composed of stress events of maximal physiological fortitude applied in a frequency of one or three stress events per

Figure 2: Results of the BE studies of Voltaren 100mg retard tablets; the *in silico* simulation of the drug plasma levels obtained from the measurement data; schematic representation of the test programmes 1 to 3 and dissolution profiles of Voltaren 100mg retard tablets obtained in the USP apparatus 2 at 100rpm, and in the dissolution stress test device under programmes 1 to 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. Detailed description of the test setup is given elsewhere¹².



To date the device has been successfully applied for the identification of clinically undesired performance of various single-unit modified release (MR) formulations¹⁴. Results of drug release experiments of Voltaren 100mg retard performed with the novel apparatus clearly indicated that under physiological mechanical conditions, diclofenac release from the extended release (ER) tablets is highly variable, and strongly depends on the mechanical stress events of transport and motility¹². The study results helped to explain the irregular plasma peaks of diclofenac obtained in a fasted state *in vivo* study with Voltaren ER tablets. These irregularities, which could not be explained with any

of the pharmacopoeial dissolution methods, are most likely caused by the sensitivity of the tablet to events of mechanical stresses during GI passage, which can particularly be measured during gastric emptying and ileocecal passage. By simulating a range of different gastric residence times combined with varying pressures and transport events in the dissolution stress test device and subsequent translation of the resulting *in vitro* profiles into theoretical plasma profiles, a whole set of characteristic profiles was obtained. Similar to the plasma profiles obtained from the *in vivo* study, the theoretical profiles showed significant differences in both the maximum plasma concentration

and the time at which this concentration could be measured. The applicability of the novel device and the test protocol used in the Voltaren experiments was confirmed in further experiments where it was applied to screen for the interchangeability of generic ER formulations of diclofenac sodium 100mg¹⁷. The tested products were generic formulations of the original Voltaren retard formulation and regarded as bioequivalent. However, test results indicated pronounced differences in the release behaviour of the two generic formulations. As already observed for Voltaren retard, dissolution of the generic formulations was strongly dependent on the test conditions, and when applying mechanical stress of physiological intensity the different formulations were not affected in equal measure. From our point of view, such susceptibility of dosage forms to biorelevant stress might be the main reason for irregularities often seen in drug plasma profiles. However, since for these generic formulations corresponding *in vivo* data were not available, the clinical relevance of the results requires further investigation¹⁴. Another series of dissolution studies was performed with nifedipine ER formulations in order to clarify the reason for the dosage form-related food effects for Coral 60mg retard tablets reported in a previously performed human bioequivalence study¹³. Results from experiments with the dissolution stress test device indicated the lack of mechanical stability and a pH-dependent dissolution behaviour of Coral 60mg retard tablets. These factors are thus likely to be the explanation for the food effects observed *in vivo*. Overall, test results and experiences obtained to date suggest that the biorelevant dissolution stress test device is a useful tool for the identification of undesired biopharmaceutical properties of MR products like “dose dumping” and could therefore become an important tool for the successful identification of reliable and safe drug delivery characteristics¹³. To optimise the biorelevant dissolution stress test device with respect to better estimating the

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in vivo performance of MR after both fasted and fed state administration, further developmental steps aiming at the improvement of the test protocols are needed. Until now, little attention has been paid to the volume and composition of the dissolution medium. For many MR formulations one can assume that drug release should not be affected by the composition of GI fluids or the dissolution medium, respectively. For this reason, in early experiments performed with the dissolution test device, the main criterion for selecting dissolution media was to assure sink conditions rather than simulating the composition of the different GI fluids in detail. Thus, the composition of the media did not always take into account the whole set of fluid parameters, i.e. physiological pH, ionic strength, surface tension, solubilising capacity, osmolality, ionic strength etc. that might be relevant for drug release. For future experiments, these aspects also need to be considered where necessary.

Whereas many MR formulations contain highly soluble drugs, and for such formulations drug release is often not that much affected by the volume of test medium applied in the experiments, the use of a non-physiological large volume is prohibitive for biorelevant dissolution testing of immediate release (IR) dosage forms, particularly when simulating fasting conditions. In order to extend the applicability of the biorelevant dissolution stress test device to IR dosage forms, we implemented modifications in order to reduce the media volumes towards volumes representative for physiological conditions. Moreover, recently we established test programmes that are intended to simulate the extremes of physiological conditions experienced by the dosage form after fasted intake, and reflect so-called edge parameters of physiological emptying patterns of liquids as well as for the mechanical stresses.

We are convinced that with the biorelevant dissolution stress test setup or other methods capable of mimicking the most critical (stress) conditions occurring during gastro-



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intestinal passage, formulations with undesired drug delivery characteristics can be identified. Since the use of biorelevant test methods offers the opportunity to study drug dissolution under more realistic conditions, application of such methods in early formulation development will enable identification of formulations with unfavourable release characteristics without the need to perform Phase I clinical trials. Consequently, our methods might help to considerably reduce the failure risk of bioequivalence studies. They might also help to reduce the risks for the volunteers involved in studies of both original formulations and generics and will finally bring us a step closer to a predictive dissolution testing.

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