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Research paper

Irregular absorption profiles observed from diclofenac extended release tablets can be predicted using a dissolution test apparatus that mimics *in vivo* physical stresses

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ABSTRACT

The prediction of the *in vivo* drug release characteristics of modified release oral dosage forms by *in vitro* dissolution tests is a prerequisite for successful product development. A novel dissolution test apparatus that mimics the physical conditions experienced by an oral formulation during gastrointestinal transit was developed. This included the simulation of pressure forces exerted by gut wall motility, shear forces generated during propagation, and loss of water contact when the dosage form is located in an intestinal air pocket. The new apparatus was evaluated using a diclofenac extended release (ER) tablet. The *in vitro* dissolution profiles were compared between the novel test apparatus and a conventional dissolution apparatus (USP II). These data were compared with the profiles of plasma concentration versus time that were obtained after the administration of an ER tablet to 24 healthy volunteers under fasting conditions. Multiple peaks were observed in individual plasma concentration–time profiles after the intake of the reference ER tablet. Standard dissolution testing showed typical characteristics of an almost continuous release for this formulation; however, dissolution testing with the novel apparatus suggested that the diclofenac release from the ER tablets would be extremely variable and dependent on the applied stress. The data suggest that the observed multiple peaks of plasma concentration after dosing of the ER diclofenac tablets are most probably caused by sensitivity to physical stress events during gastrointestinal transit.

1. Introduction

Dissolution testing is a prerequisite for the optimisation of dosage forms and for batch quality control. It is commonly performed using a pharmacopeial apparatus under highly standardized conditions. However, the predictive value of the *in vitro* dissolution profile with regard to the variability in the individual *in vivo* dissolution characteristics is often poor. This is most critical for the prediction of *in vivo* dissolution profiles for extended release (ER) products [1].

It is well recognized that the temperature, and the composition of the dissolution media, specifically the pH, ionic strength, buffer capacity as well as the presence of surfactants such as bile salts and/or the presence of digestive enzymes (e.g., pancreatic enzymes) may greatly influence the characteristics of release from immediate release and extended release dosage forms [2–4]. For this reason, many attempts have been made to adapt *in vitro* dissolution media closer to real physiological conditions in order to improve the predictability of *in vivo* dissolution of drugs in a series of various dosage forms [5–8]. The starting point for the composition of simulated gastrointestinal fluids is based on the results of the analytical characterization of human gastrointestinal contents [9,10]. Accordingly, the application of simulated gastrointestinal fluids, also defined as 'biorelevant dissolution media', has gained increasing attention in pharmacopeial monographs including the United States Pharmacopeia.

In contrast, there are fewer studies available in the literature where hydrodynamic or mechanical conditions have been simulated to be closer to physiological conditions in order to evaluate the physical robustness of formulation principles in the gastroin-

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testinal tract [11,13,14]. This does not represent a lack of interest, and still non-pharmacopeial variants of dissolution simulators are appearing. They vary in complexity from complicated devices such as the TIM simulator [14] to simple agitation systems including improvements for mixing in an USP dissolution apparatus 2 fitted with a crescent-shaped spindle [12]. Computer models based on images obtained with magnetic resonance imaging (MRI) and wall movements of the stomach have been used to predict the erosion of matrices [15,16]. In spite of these innovations, the slow speed of progress may be explained by the sketchy experimental database describing the mechanical and hydrodynamic forces generated by the smooth muscle throughout the gastrointestinal tract. Imaging techniques which provide data on the conditions that dosage forms meet during the transit through the gastrointestinal tract are becoming available [17,18] and provide interesting insights which run counter to common assumptions. For example, it has been demonstrated in a recent MRI study that non-disintegrating dosage forms are not consistently in contact with fluid during their passage through the small and large bowel [18]. Furthermore, the real time imaging of gastrointestinal transport of dosage forms reveals that movement of the formulation in the stomach as well as in the small and the large bowel is extremely discontinuous. Gastrointestinal transport of solid dosage forms is typified by consecutive phases of rest or slow propagation of highly variable duration and typically brief motility events with velocity spikes of greater than 50 cm/s [17,19]. This observation is in agreement with the characteristics of intestinal propulsion of chyme, as movement of chyme involves periods of slow transit that alternate with bursts of rapid flow [20]. Therefore, the discontinuity of peristaltic effects applied along the intestine and bowel can be regarded as distinguishing features of gastrointestinal transit.

Following these observations, we have designed a novel dissolution apparatus that provides the simulation of disregarded parameters which may be important for hydrodynamic and mechanical stress under *in vivo* conditions. First, a discontinuous movement of the dosage form within the gastrointestinal tract can be generated. The second feature is the possibility to mimic the agitation caused by GI pressure waves as observed *in vivo*. Finally, an interrupted contact of the dosage form with the intestinal fluid can also be simulated.

It was the aim of the study to evaluate the developed dissolution test device as a tool for the understanding of the behaviour of an extended release formulation of diclofenac that exhibited characteristic plasma peaks in a clinical trial.

2. Materials and methods

2.1. Clinical study protocol

Extended release (ER) tablets based on HPMC (Voltaren Retard Retarddragées, Novartis Pharma GmbH, Germany) containing 100 mg of diclofenac sodium were used in these studies. The investigational product served as one of two reference medications in a standard bioequivalence study in which a new extended release dosage form of diclofenac was tested. The second reference (Diclofenac-ratiopharm 100 mg Retardkapseln, Ratiopharm, Germany) and the test formulation were multiple unit preparations (pellets). The controlled, randomized, four-period cross-over study, with a washout period of at least seven days, was performed in 24 healthy subjects (11 females, 13 males, age 21–31 years, body weight 50–93 kg, body mass index 19–27 kg/m^2) who had given a written consent before inclusion. The size of the sample was chosen to ensure a power of 80% for the $AUC_{0-\infty}$ variability in standard bioequivalence decisions [21]. All subjects were carriers of wild-type alleles of *CYP2C9* type. They were ascertained to be of good health by means of histories, physical examinations, routine clinical chemical and hematological screenings. Three volunteers were smokers of less than 10 cigarettes per day. Alcohol intake in all subjects was less than 25 g per day. The subjects were HBV and HIV negative and free of drugs, took no medication except hormonal contraceptives and abstained from alcohol during the whole study. The study protocol was approved by the local ethics committee.

The volunteers were admitted at the clinical research unit in the evening prior to the pharmacokinetic study day. After overnight fasting for at least 12 h, the study medication was administered with 240 ml tap water (room temperature). Subjects were requested to remain in upright position (standing or sitting) for the following 5 h after administration. Venous blood samples (3 ml) were collected before dosing and every 20 min up to 10 h, then 11, 12, 14, 16 and 24 h after drug administration. Blood was centrifuged at 2000g for 10 min. The serum was transferred into polypropylene tubes and stored below −20 °C until quantitative drug assay.

Intake of food and beverages was standardized during in-house confinement. Tap water was served 3 h (200 ml), 5 h (200 ml), 7 h (100 ml), 9 h (200 ml), 11 h (100 ml), 13 h (200 ml) and 15 h (200 ml) after administration of the study medication. Additionally, the volunteers received 100 ml of a coffee substitute at 8 h post administration and 100 ml of peppermint tea at 11 h post administration. Standardized meals were served at 5 h (noodle soup, chicken with rice and mixed vegetables, 200 g fruit yoghurt), at 8 h (cake) and at 11 h (bread, margarine, cheese, sliced salami, vegetables) after administration of the study medication. On all pharmacokinetic study days, the volunteers were requested to eat the same individual amount of food at lunch, tea time and dinner.

2.2. Analysis of serum samples

Diclofenac in serum was quantified after liquid extraction using a HPLC method with UV-detection at 280 nm. Briefly, 0.5 ml serum was mixed with 0.025 ml internal standard solution (5 μg/ml niflumic acid) and 1 ml acetonitrile. After centrifugation, the supernatant was separated, acidified with 0.5 ml diluted phosphoric acid and extracted with 5 ml diethylether. The organic layer was dried under a gentle air stream at 40 °C. The residue was dissolved in 125 μl mobile phase of which 50 μl were injected for chromatography. The HPLC system consisted of the autosampler AS-4000, the pump L-6200, the diode array detector L-4500, the chromatography data station L-6000 (Merck-Hitachi, Tokyo, Japan), the column thermostate Mitu jetstream (W.O. electronics, Langenzersdorf, Austria) and the degasser Degasys (Uniflows, Tokyo, Japan). The HPLC system was equipped with the analytical column LiChroSper®100 RP-18e, 5 μm filled in EcoCart® 125-3 cartridge system (Merck, Darmstadt, Germany). The mobile phase consisted of 30% purified water adjusted with phosphoric acid to pH 3.0, 50% acetonitrile and 20% methanol. The chromatograms were evaluated with the internal standard method using peak-height ratios for calculation. The assay was validated between the concentrations 0.005 and 2.0 μg/ml of diclofenac. The calibration curves were linear in this range and were therefore evaluated using linear regression analysis weighted by $1/x$ (x = concentration). The recovery rates of the drug from serum at 0.025, 0.1 and 1.0 μg ml were 109%, 91.6% and 99.7%, respectively. The recovery of 125 ng/ml niflumic acid was 88.4%. Within-day accuracy ranged from −5.7% to 1.1% of the nominal concentrations, and precision was between 1.6% and 8.6% of the mean concentrations. The respective between-day quality data were: accuracy −4.7% to −1.0% of the nominal values; precision 5.5–13.4% of means.

2.3. Standard dissolution tests

The release behaviour of Voltaren Retard was examined using apparatus 2 of the USP (paddle apparatus, PT-DT 7, PharmaTest, Hainburg, Germany). Dissolution of diclofenac was determined in 0.1 N hydrochloric acid, pH 1, phosphate buffer, pH 4.5, R Ph.Eur. and phosphate buffer, pH 6.8, USP each time at a rotational speed of 100 rpm. In addition, the release in phosphate buffer, pH 6.8, USP was investigated at 50 rpm. Each test was executed in 1000 ml of dissolution media at 37.0 ± 0.5 °C. The samples for analyses had a volume of 5 ml. The withdrawn volume was replaced with the according by tempered buffer solution immediately after sampling and considered in the calculation. During the dissolution experiments with hydrochloric acid and phosphate buffer, pH 4.5, samples were taken after 0.5, 1, 2, 3 and 4 h. The samples were mixed with 1 ml of 1 N sodium hydroxide to obtain a pH of about 12. Samples from phosphate buffer, pH 6.8, were taken after 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 23 and 24 h. The solutions were filtered through a pore filter, 0.22 μm (Millex GP membrane filter unit), and absorption was measured at 276 nm (UV 1602, Shimadzu, Germany).

The determination of the amount of drug remaining in the tablets was carried out for experiments performed with USP phosphate buffer, pH 6.8, as dissolution medium. After 24 h the remaining parts of the tablets were separated from the dissolution medium and transferred into glass flasks filled with 300 ml of pure buffer solution, then suspended by magnetic stirrer at 300 rpm for 2 h. The samples were pre-treated, and the drug was measured as described above.

2.4. Novel stress test apparatus

The novel dissolution stress test device exposes the dosage forms to an arbitrary sequence of movements, pressure waves and phases of rest as they may occur under *in vivo* conditions. The device consists of a central pipe (axle), with six steel netting spheres (chambers) of 35 mm diameter where the dosage forms are hosted. Each chamber is divided into two parts. The bottom part is screwed onto a steel central pipe by a PVC bush and by a profiled nozzle. The central pipe is attached by teflon handles, placed on the deck plate of the device very closely (3 mm) above the top edges of linearly placed standard dissolution vessels in their symmetry plane. Each sphere operates in a separate vessel. The central axle is coupled at one end to a pressure regulation unit by a rotating joint and on the other end to a stepping motor (Fig. 1).

Pressure waves are generated by a pulsatile inflation and deflation of balloons inside the chambers that are tightly attached to the nozzles. The inflation and deflation is controlled by synchronised switching of solenoid valves (ASCO G262C022, ASCO Jucomatic, Germany). The pressure is regulated by a computer-controlled pressure-reducing device (Norgren R16-200-R30D, Germany). The central axle is driven by a computer-controlled stepping motor (St. 5818M1008, optocoupler SMC 32C, Nanotec, Germany). The movement of the central axis, the pressure amplitudes, the synchronisation of the pressure waves and the sampling are software-controlled (LabView 7.1, National Instruments, USA).

All experiments with the stress test device were carried out in 1150 ml phosphate buffer, pH 6.8, (USP). This volume assures the complete immersion of the steel wire netting sphere in the dissolution medium during the phases of the rest when the spheres are placed vertically down. During each rotation the spheres are for 50% of the time immersed in the medium and for 50% of the time in the air. The medium was homogenised using a steel paddle stirrer (size of the stirrer blade was 15 mm by 35 mm) operated at a rotational speed of 100 rpm.

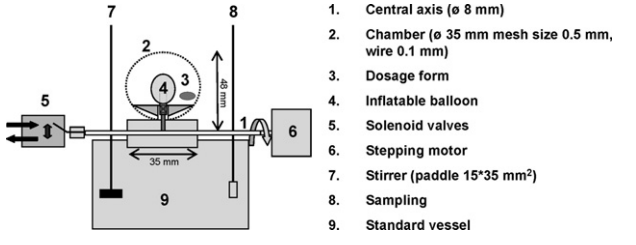

Fig. 1. Schematic representation of the dissolution stress test device.

2.5. Investigation of tablet movement during rotation

The tablet movement during the rotations of the sphere was investigated using the magnet tracking system MTS 1000 (STL Systemtechnik Ludwig, Konstanz, Germany). For this purpose, a non-magnetic sphere was prepared with identical dimensions to the steel netting wire spheres used in the dissolution stress device. This sphere was fitted to an elongated stepping motor axle in order to avoid magnetic noise generated by the motor. In order to obtain a detectable magnetic signal from the tablets, two small permanent magnets (IBS DE153, IBS Magnet Germany, diameter 1.5 mm, length 3 mm) were press fitted into the tablets via a small drill hole (diameter 1.6 mm). The localization data were recorded at a sampling rate of 100 Hz and evaluated using software based on Axum 5.0.

2.6. Dissolution experiments with the stress test apparatus

Two primary types of physical stress can be applied by the developed dissolution stress test device: rotational movement where the chamber passes during each rotation through the air–water interface and secondly, a simulated peristaltic 'squeeze'. In a first set of dissolution experiments, the impact of these two primary stress types was investigated using two homogenous sequences (Table 1). Sequence 1 consisted of three consecutive pressure waves (300 mbar) with a duration of 6 s each and a duty cycle of 50% that were repeated every 20 min. Sequence 2 consisted of a phase of 1 min rotation of the chambers at a rate of 100 rpm, repeated every 20 min.

For the simulation of gastrointestinal transit three test programs were used (Table 1). These programs were a combination of phases of agitation initiated by rotational movement of the central axle simulating events of transport, and phases of pressure waves simulating episodes of high gastrointestinal motility. The first event was identical in all three programs. It consisted of three symmetrical pressure waves of 300 mbar lasting 6 s each (i.e., an element of sequence 1) followed by 1 min of rotation at 100 rpm (i.e., an element of sequence 2). This agitation phase was intended to simulate the harsh conditions that may occur

Table 1
Sequences and test programs used for the dissolution stress experiments

	Pressure (3 cycles of 300 mbar, duration 18 s)	Rotation 100 rpm (duration 1 min)	Rotation 10 rpm (duration 0.5 min)
Sequence 1	Every 20 min	Not applied	Not applied
Sequence 2	not applied	Every 20 min	Not applied
Program I	At 5 min	At 5 min*	Every 10 min
	At 5 h	At 5 h*	(starting after 15 min)
Program II	At 30 min	At 30 min*	Every 10 min
	At 5 h	At 5 h*	(starting after 40 min)
Program III	At 60 min	At 60 min*	Every 10 min
	At 5 h	At 5 h*	(starting after 70 min)

* Following pressure cycles.

during gastric emptying and duodenal passage of tablets after administration under fasting conditions. The agitation phase was initiated after 0.05 h in program I ('rapid' gastric emptying), after 0.5 h in program II ('regular' gastric emptying) and after 1 h in program III ('late' gastric emptying). In all three programs, small intestinal transport was simulated as a sequence consisting of 0.5 min rotation at 10 rpm followed by 9.5 min of rest with the tablet submersed in the dissolution medium. After 5 h, 'colon arrival' was simulated, using the identical conditions as for gastric emptying (3 pressure waves of 300 mbar lasting 6 s each followed by 1 min rotation at 100 rpm). These stress phases attempted to mimic the passage through the ileocecal junction, a region that is characterized by strong motor activity and high pressure gradients [22].

The determination of the dissolved drug was carried out using a spectrophotometer (UV 1602, Shimadzu, Germany) equipped with multi-cell positioner by means of a closed flow-through system. Samples were taken by a peristaltic pump (IPC-N 16, Ismatec, Germany) at a flow rate of 10 ml/min in a five minute-long pump period (three minutes of pump time and two minutes of rest) and filtered through a glass filter (20 μm, Jena Glas, Germany) under isothermal conditions. The filtered medium was fed into a quartz flow-trough cell (light path 2 mm, Hellma, Germany). The absorption was measured in intervals of 5 min in a differential mode at 276 nm (signal) and 450 nm (reference). Data were recorded with commercial software (UV-Probe, Shimadzu, Germany). The volume of the dissolution medium was measured for each vessel immediately after finishing the experiments. It was assumed that the loss of dissolution medium (the observed maximum was 5%) was caused by the evaporation and had a linear character. The proportional decrease in the volume of dissolution media was taken into consideration for each of the measurement points.

Plasma concentration–time profiles were calculated (Axum 5.0) in steps of one minute from the obtained in vitro release profiles applying published microconstants ($k_a = 0.0482\ min^{-1}$, $k_{10} = 0.1842\ min^{-1}$, $k_{12} = 0.0029\ min^{-1}$, $k_{21} = 0.0242\ min^{-1}$) for diclofenac [23].

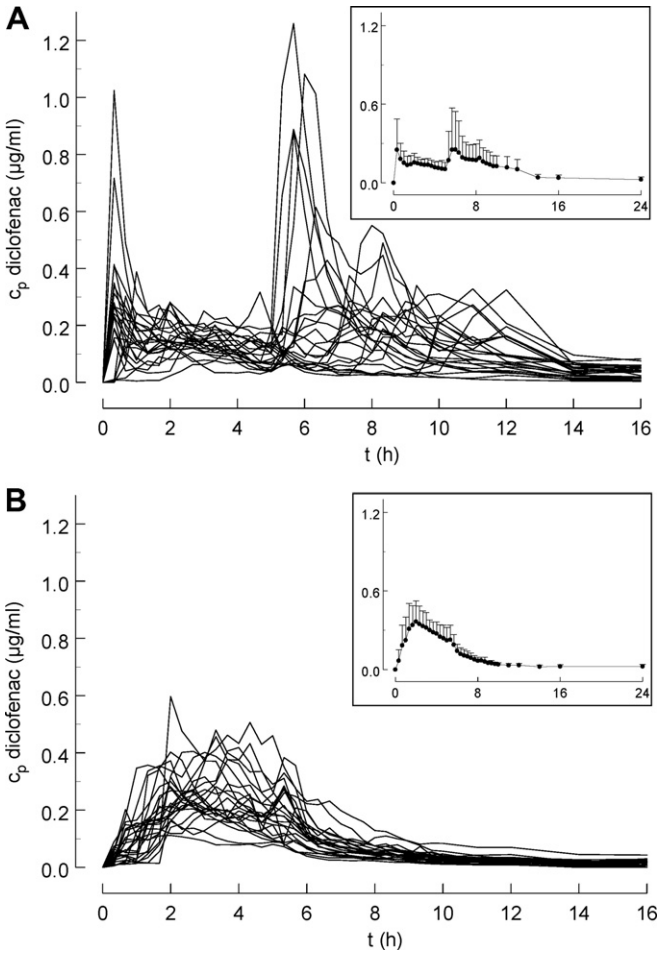

Fig. 2. Individual diclofenac plasma concentration profiles obtained after the administration of 100 mg diclofenac in the form of ER formulations under fasting conditions ($n = 24$). In the insets the means and standard deviations are shown. (A) Voltaren retard ER tablets; (B) Diclofenac-ratiopharm ER pellets.

3. Results

3.1. Clinical study

After intake of the ER tablet, the individual plasma concentration–time profiles strongly fluctuated (Fig. 2A). Plasma concentration peaks were most frequently observed in the individual profiles within 0.33–1 h and 5–9 h after ingestion. Some profiles showed late peaks between 9 and 12 h after administration. The AUC was 2254 ng h/ml, C_{max} was 441 ng/ml and the half-life was 1.46 h (geometric means). The arithmetic mean (± standard deviation) of t_{max} was 4.45 ± 3.51 h, and the median of t_{max} was 5.5 h (range: 0.33–11.00 h). Such strong variability in the plasma concentration–time profiles was not observed following the administration of both pellet formulations. Furthermore, plasma concentration peaks later than 5 h after the administration were not observed. For illustration, the individual plasma concentration–time profiles obtained after administration of Diclofenac-ratiopharm Retardkapseln are shown in Fig. 2B.

3.2. Standard dissolution test

The dissolution profiles of the tablets obtained using USP apparatus 2 (paddle) at different pH values and varying rotational speeds are shown in Fig. 3. Due to the very poor solubility of diclofenac in the acidic media, the dissolution is pH-dependent with minimal diclofenac dissolved in 0.1 N hydrochloric acid, pH 1, and very slow release in buffer of pH 4.5. At pH 6.8, the ER tablets provided regular dissolution profiles with approximately 70% drug dissolved after 12 h and 90% after 24 h at both rotational rates. The total recovery was between 95% and 103% (calculated as the sum of dissolved drug and drug found in the tablet after 24 h).

3.3. Dissolution stress test

The release profiles obtained after continuous repetition (every 20 min) of pressure episodes (sequence 1) or transport episodes (sequence 2) are shown in Fig. 4A and B. Both types of physical stress significantly affected the dissolution behaviour and resulted in a rapid liberation of typically 10–20% of the drug immediately following the stress phase. The response to the pressure waves (sequence 1, Fig. 4A) was more homogeneous compared to the rotational movement (sequence 2, Fig. 4B).

The dissolution profiles that were obtained using the three dissolution test programs are shown in the Fig. 4C–E. The later the first stress phase was applied, the higher was the related burst of release. This indicates that the influence of the stress phase on the release profile increases with increasing water uptake of the tablets. The rather mild conditions simulating stresses during small intestinal transit yielded release rates of about 2–5 mg/h. This is lower than the release rate of approximately 6 mg/h that was observed with the standard paddle apparatus at 50 or

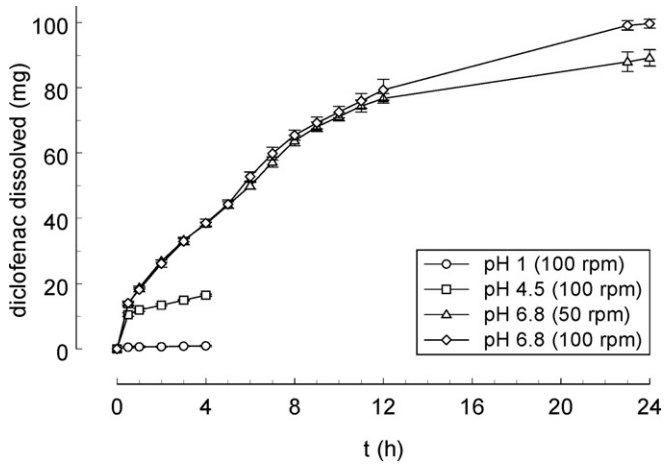

Fig. 3. Diclofenac release profiles under varying conventional dissolution test conditions (paddle, mean ± SD, $n = 6$) obtained from Voltaren retard 100 mg ER tablets.

100 rpm during the first 12 h (Fig. 3). The second stress phase that was applied after 5 h of dissolution testing provoked almost complete drug release. This observation corroborates the interpretation that the effect of physical stress on these tablets increased with swelling time.

3.4. Tablet movement in the dissolution stress test apparatus

A typical tablet movement during one minute of rotation at 100 rpm is shown in Fig. 5A. During the rotational phases the tablets are located at the outer rim of the chamber for most of the time. However, sometimes irregular movements are observed. The measured tablet velocity was in the range of 25–40 cm/s with a mean of 30 cm/s. This is somewhat below the track speed of 42 cm/s calculated for a tablet that is permanently located at the outer rim.

4. Discussion

After oral administration of diclofenac, two or more peaks in the plasma concentration–time profiles are commonly observed [23–27]. Different explanations have been offered for this phenomenon, such as pH-dependent dissolution [27], formation of a poorly soluble diclofenac tetrahydrate [28], bile-dependent intestinal absorption [29], enterohepatic recirculation [30], or multiple, separated absorption windows along the gastrointestinal tract [31]. Interestingly, the occurrence of multiple peaks in the individual plasma concentration profiles depends on the dosage form. The typical diclofenac dosage form is the enteric-coated tablet. Here, the individual plasma profile is usually characterized by one single peak concentration [23,26]. However, the time of the appearance of the peak is highly variable. This phenomenon can be attributed to the well known dispersion in gastric emptying times for solids in combination with the high variability of intestinal passage time of enteric-coated tablets until disintegration [32]. After administration of IR formulations or even solutions of diclofenac to fasting subjects, multiple peaks in the individual plasma concentration–time profiles are common [23,26]. However, in the case of a high initial peak concentration, further peaks are not observed [33]. In our opinion, the second and other late peaks most likely reflect the emptying behaviour of the stomach in the interdigestive phase for the part of diclofenac that had precipitated under the acidic conditions within the stomach. This explanation is in accordance with pharmacokinetic data reported after dosing of diclofenac as an IR formulation and after direct application into the stomach [34,35].

In the case of ER products, the occurrence of multiple peaks in the individual plasma concentration–time profiles is formulation-dependent [34]. This was also observed in our study (Fig. 2A and B). In principle, multiple peaks in the individual plasma concentration–time profiles after dosing of ER products may be caused by several mechanisms including prolonged gastric retention of the dosage form [36] and pH changes when the formulation enters the caecum [37]. Another problematic mechanism is the breakup of the formulation principle (dose dumping). Dissolution of diclofenac is poor under the acidic conditions present in an empty stomach. For this reason, and also because a fasted protocol was used in our study, an accumulation of diclofenac in the stomach that is due to a prolonged residence time of the tablets seems improbable.

It is proposed that the irregular absorption profiles observed in the individual plasma concentration–time profiles result from peristaltic stress events that occurred during gastrointestinal transit causing irregular release. It is notable that in some individuals, prominent peaks are observed within the first hour whereas most of the individuals show peak concentrations later than 5 h after ingestion. A possible explanation for the early plasma concentration peaks is the rapid drug release from the ER tablets due to high physical stress applied to the tablets during gastric emptying in these individuals. In most subjects, peak plasma concentrations were observed between 5 and 6 h after ingestion of the tablet, shortly after the first meal was served. It is known that food intake induces the onward movement of material which has accumulated at the end of the ileum into the colon, a phenomenon termed the gastro-ileocecal reflex [18,38,39]. Ileocecal passage is associated with a high pressure event [22]. In treatment of diseases of the bowel, release at the terminal ileum or rupture of device may be a desired property as it leads to increased dispersion in the caecum [40]. The next predominant time period for the appearance of plasma peaks started after 8 h. This is the time point when the subjects received the next meal.

In order to test the hypothesis that the tested ER tablet is susceptible to harsh physical conditions occurring during key segments of gastrointestinal transit, we developed a novel dissolution test apparatus that enables the simulation of relevant physical stress. In principle, such a dissolution test device can be constructed in many different ways. We intended to have permanent exact control over the rotary motion of the apparatus as well as the possibility to simulate the influence of intraluminal pressure waves. Moreover, it was a requirement that the novel device should offer a possibility to control the location of the dosage form with respect to contact with fluid.

A system that was based on steel netting wire spheres as housing for the tablets attached to the bottom part to a central tubular axle was constructed in our laboratories. The device features several novel components for drug dissolution testing. First, the tested dosage form is subject to a predetermined pattern of movements, as well as phases of rest, in order to simulate phases of transport and of relative rest during gastrointestinal transit. Second, the apparatus offers the possibility to apply a controlled pressure with respect to intensity and duration. Third, contact of the dosage forms with the dissolution medium is not constant and can be interrupted during the analysis by appropriate positioning of the central axle. The movement of the test product, leaving and re-entering the aqueous phase, corresponds to the *in vivo* situation. Under fasted conditions, the small intestine is partially collapsed or can be seen to contain gas; water exists predominately in the form of pockets rather than a continuous phase filling the intestinal tube [18].

To simulate physical conditions during gastric emptying and ileocecal passage, a pressure of 300 mbar and a rotational rate of

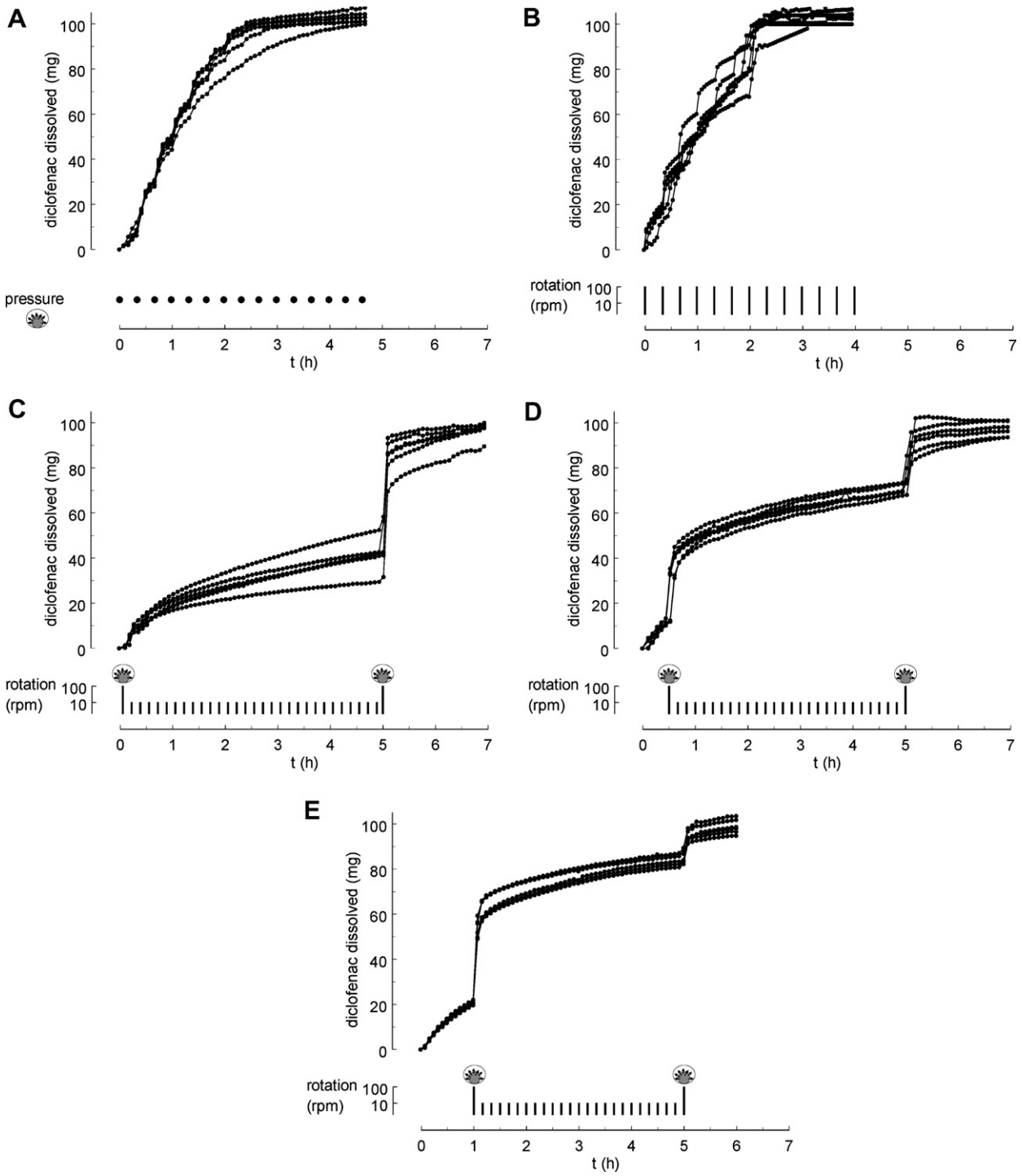

Fig. 4. Diclofenac release profiles obtained from Voltaren retard 100 mg ER tablets in phosphate buffer, pH 6.8 (USP), using the dissolution stress test apparatus under varying conditions ($n = 6$). (A) Sequence 1. (B) Sequence 2. (C) Program I. (D) Program II. (E) Program III.

100 rpm were chosen. The figure of 300 mbar represents an average value for pressures generated during the phase III activity ('housekeeping waves') of the Interdigestive Migrating Motor Complex (IMMC) [41]. The value chosen is in good accordance with pressures registered with a wireless pressure sensitive capsule during gastric emptying [42]. It is somewhat high compared to pressure values measured in the ileocecal region [22]. The applied rotational rate of 100 rpm results in a velocity of the tablet in the range of 25–40 cm/s as determined in this study. We confirm that this is a realistic value for tablet velocities as measured for short periods during gastric emptying and duodenal passage [17,19]. Comparable data are not available for the velocities at the ileocecal junction. However, as ileocecal passage is described as jet propulsion [22], it can be assumed that such velocities will also be possible during passage of the ileocecal valve. The plasma concentration–time profiles calculated from the mean release profiles that were obtained using the three stress test programs are in good accordance with the measured plasma concentration–time profiles (Figs. 6 and 2). This indicates that the observed peaks in the plasma concentration–time profiles are most probably caused

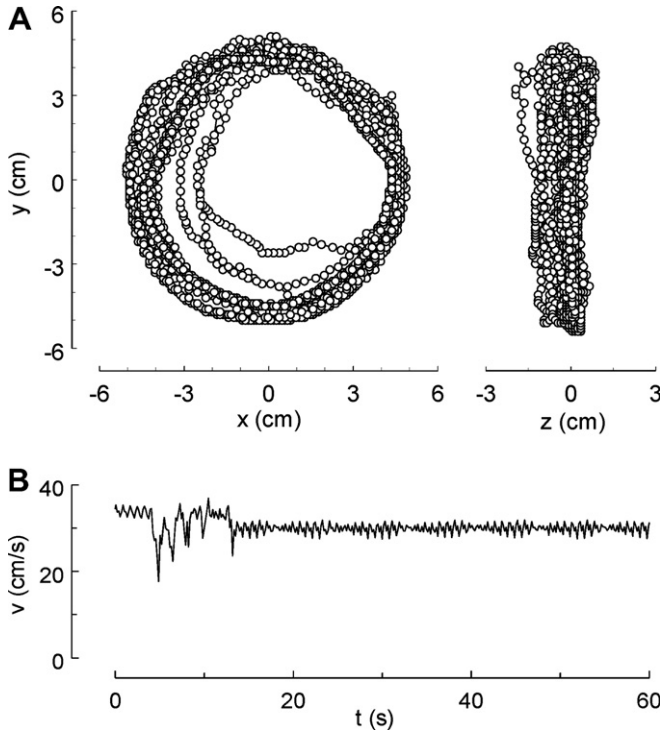

Fig. 5. Movement of a magnetically labelled Voltaren retard 100 mg ER tablet in the dissolution stress test apparatus for 1 min at 100 rpm. (A) Localisation plot in x–y plane (right) and z–y-plane (left). (B) Velocity profile.

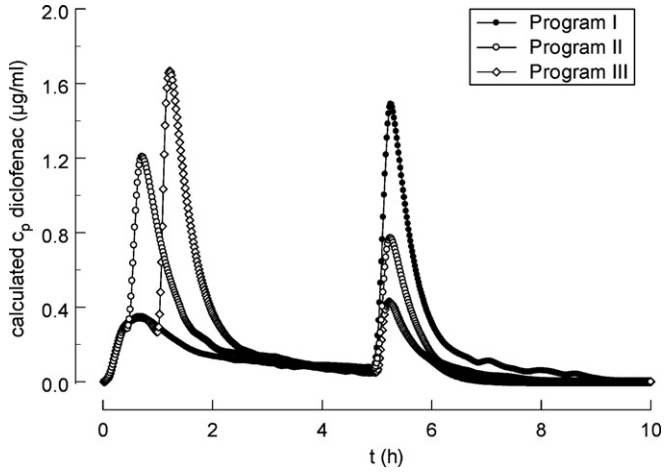

Fig. 6. Predicted plasma concentration–time profiles calculated from the mean diclofenac release profiles obtained using the programs I, III and III.

by events of rapid drug release characterized as dose dumping. The data show that such dose dumping events can be predicted by applying physical stress conditions that are known to be possible at least during gastric emptying and ileocecal movement. Therefore, we consider that the presented principle is a feasible approach for mimicking the harsh conditions that solid dosage forms may meet during GI passage. Work comparing the postprandial situation in the stomach when the dosage form is contained within chyme will be a useful direction to pursue in the future.

5. Conclusions

Using a novel dissolution test apparatus that mimics physical stress conditions during gastrointestinal passage, we propose that multiple peaks in individual diclofenac plasma concentration profiles after dosing on an ER tablet product would be caused by a strongly accelerated drug release during biorelevant physical stress events. The ER tablets that were tested show rapid drug release characterized as dose dumping under the conditions that are known to be possible at least during gastric emptying and ileocecal movement. In further investigations, the stress test apparatus will be applied to data derived from *in vivo* transit measurements obtained under fed conditions in order to simulate the temporal pattern and the strength of the applied physical stress, in biorelevant dissolution media.

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