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The role of individual gastric emptying of pellets in the prediction of diclofenac *in vivo* dissolution

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ABSTRACT

The objective of the present study was to check for the possibility to successfully predict individual *in vivo* dissolution/absorption profiles resulting from fasted administration of a diclofenac extended release pellet formulation. For this purpose dissolution profiles were generated with different dissolution setups using a set of media reflecting pH-conditions in the different segments of the gastrointestinal tract. Since gastric emptying of pellets seemed to be a critical factor for *in vivo* drug release, a set of different gastric residence times was screened in *in vitro* studies. Subsequently, *in vitro* release profiles were first directly compared with the individual *in vivo* absorption profiles and in a second step a mathematical model, which had been developed in a previous study, was applied to calculate predicted individual *in vivo* release profiles based on *in vitro* release profiles and individual gastric emptying. The comparison of predicted individual *in vivo* release profiles and individual *in vivo* absorption profiles showed a high degree of similarity, thus confirming the suitability of a set of different gastric residence times used in *in vitro* drug release testing. Additionally, obtained results indicated that a substantial part of variability of diclofenac absorption profiles can be explained by the variability of pellet gastric emptying kinetics.

1. Introduction

Gastric emptying is a highly regulated process to limit the rate at which food and fluids enter the small intestine. Within this process, the distal stomach, i.e. the antrum and pyloric sphincter, regulate the emptying of gastric contents. The transfer rate of material from the stomach to the duodenum depends heavily on the physical and chemical composition of the gastric contents. As gastric motor responses do not typically differentiate between particles of food and co-ingested drugs, gastric emptying of solid particles is subjected to essentially the same process. Main parameters that determine the gastric emptying of solid particles are their physical size, whether they are administered in the fasted or fed state and, whether they remain intact, can disintegrate to smaller particles, or are digestible. Depending on their diameter and density in the fasted state very fine particles can either be emptied from the stomach with ingested fluid or get held back by the antral sieving mechanism until they are emptied within the last phase of the so called migrating motor complex (MMC), a cyclic motility pattern, which is characteristic for the fasted human stomach [1,2]. Each MMC cycle lasts approximately 80–120 min and, most likely in the third phase, having a duration of ~5-10 min, larger particles are emptied from the stomach by means of forceful contractions of the antrum and simultaneous relaxation of the pylorus. The cut-off size of the "antral sieve" has been discussed frequently but nowadays it is known that the open diameter of the pylorus is closely connected with the contractile forces in the antrum and shows a high inter- and intraindividual variability in both the fasted and the fed state.

For a long time it was thought that gastric emptying of pellets in fasted state follows a very simple scheme and is a fast and complete process. However, recently it became clear that from the fasted stomach pellets can be emptied in a wide time interval lasting from a few minutes up to sometimes even more than 3 or 4 h [3]. Screening the time-profiles of pellet gastric emptying reported in the literature, in some individual profiles a typical pattern, i.e. emptying in a series of boluses, can be observed [4,5]. An explanation for this observation is probably the emptying of certain fractions of pellets during motility phases of consecutive MMC cycles [6].

The composition of physiological fluids in the stomach and upper small intestine differ significantly. Talking about drug release from pellets in the upper gastrointestinal (GI) tract and focusing on the

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variability in gastric residence time, it is likely that, depending on the properties of the drug and/or the formulation the *in vivo* dissolution of pellets can be strongly determined by the residence time of the pellets in the different sections of the upper GI tract. Particularly when dissolution is sensitive to the conditions in stomach and upper small intestine, the release from each fraction of pellets will be dependent on the length of the time interval during which the fraction of pellets is retained in the stomach. Thus, determining *in vitro* dissolution profiles by using a single fixed residence time in simulated gastric fluid will adequately simulate only the *in vivo* dissolution of the fraction of pellets remaining in the stomach for the same time interval. To better predict the *in vivo* release from pellet formulations, it seems to be advisable to take into account the potential time range of gastric emptying and the emptying of boluses when designing the *in vitro* test.

Above mentioned phenomena were implemented in the dissolution experiments using coated pellets (Eudragit® RS coating) for an extended release (ER) of diclofenac sodium (in the following named as diclofenac). Eudragit® RS is a water-insoluble methacrylate polymer which is frequently used in the manufacture of oral coated ER pellet formulations. When getting into contact with aqueous fluids, independent on the medium, Eudragit RS films start to swell allowing fluid to penetrate into the drug loaded pellet core where the drug can dissolve and is subsequently released via the swollen polymer membrane. Diclofenac is a weak acid (pKa 4.0) [7] and has a strongly pH-dependent solubility. Since the drug is poorly soluble in acidic media and solubility increases with increasing pH [8], the solubility of the drug itself can have a significant impact on drug release from the ER pellets.

In the scope of the present work *in vitro* drug dissolution data were linked with the physiological mechanism of individual gastric emptying of pellets with the aim to predict *in vivo* drug dissolution from pellets in the GI tract of an individual. The adequacy of this approach was evaluated by comparing predicted individual *in vivo* dissolution profiles of diclofenac ER pellets with individual absorption profiles obtained from a pharmacokinetic study using the same formulation [9]. In addition, we wanted to estimate how well the *in vivo* variability of diclofenac absorption profiles can be explained by the variability of the gastric emptying of pellets.

2. Materials and methods

2.1. Materials

Diclofenac sodium (lot # 80110508) was purchased from Caesar & Loretz GmbH, Hilden, Germany. All release experiments were performed with Diclofenac-ratiopharm® 100 mg Retardkapseln (lot # J30496, Ratiopharm GmbH, Ulm, Germany) which were obtained by prescription. Each of these capsules was filled with Eudragit RS®-coated pellets containing in total 100 mg of diclofenac sodium (= 93.09 mg diclofenac). All other substances and solvents were of analytical grade and purchased commercially.

2.2. In vitro dissolution testing — selection of test media and residence times

The test set-up in all dissolution experiments was designed to simulate passage through the fasted GI tract. Therefore, the following media were used: simulated gastric fluid (SGF) without pepsin and a pH of 1.8 [10], a slightly pH-modified blank fasted state simulated intestinal fluid (blank FaSSIF [10]) having a pH of 6.8 and simulated colonic fluid (SCoF) pH 5.8 [11].

As one of our objectives was to estimate how good the diclofenac absorption profiles and their variability can be explained by the variability of pellet gastric emptying, a whole set of different gastric residence times (5 min, 20 min, 40 min, 60 min, 100 min, 150 min, or 200 min in SGF) was screened, whereas the small intestinal transit time was the same in all experiments (240 min in Blank FaSSIF). Afterwards, residence in the proximal colon (SCoF) was simulated.

In vitro gastric residence times were set on the basis of pellet gastric emptying profiles for 11 relevant individuals, which were obtained in a previous study [4]. The gastric emptying profiles were divided into a set of time intervals in order to evaluate the duration of exposure of each fraction of pellets to SGF in the *in vitro* experiments. These time intervals were: 0–10 min, 10–30 min, 30–50 min, 50–70 min, 70–130 min, 130–170 min, and 170–230 min. For each of these time intervals a dissolution test was performed. In the dissolution tests the pellets were retained in SGF for a time corresponding to the arithmetic mean of the related time interval, i.e. 5 min, 20 min, 40 min, 60 min, 100 min, 150 min, and 200 min, respectively. The above cited time intervals were set taking into account both the variability in pellet gastric emptying and a minimum number of dissolution tests. The experimental design for each dissolution system thus consisted of 7 tests with varying gastric residence times. As a result, from each apparatus 7 different *in vitro* release profiles were obtained.

2.3. In vitro dissolution testing — test devices and settings

Three different devices were used to perform the *in vitro* experiments: I) the BioDis apparatus (USP/Ph.Eur. apparatus 3), II) a biorelevant stress test device [12] and III) a new glass bead device [13]. The intention of using different devices and different modes of operation was, besides determining the impact of gastric residence and emptying on drug release, to get an estimate on the magnitude of biorelevant *in vivo* stresses influencing the release performance of a pellet formulation.

2.3.1. BioDis (USP/Ph.Eur. apparatus 3) experiments

A CALEVA RRT 8 apparatus (CALEVA Ltd, Dorset, England) was used to perform the experiments. The media temperature was 37 ± 0.5 °C and 200 mL of test medium was used in each vessel. Top and bottom of the reciprocating cylinders were fit with mesh screens having a mesh size of 420 μm and a dip rate of 10 dpm was used in all experiments [14]. Samples were removed at predetermined time points and analyzed at a wavelength of 276 nm by UV-spectrophotometery (U 2000, Hitachi Ltd, Tokyo, Japan). Experiments were run in triplicate and results expressed as mean % (± SD) dissolved at the given sampling time.

2.3.2. Experiments with the biorelevant stress test device

Stress test experiments were performed with a biorelevant stress test apparatus introduced by Garbacz and Weitschies [9,12]. Vessels were filled with 1200 mL of test medium and the medium was agitated with a stirring speed of 100 rpm. A series of experiments was performed a) varying the gastric emptying times corresponding to those used in the other setups used in this study and b) varying the pressure acting on the dosage form during simulated gastric emptying and ileocecal passage. Initial experiments were performed applying a sequence of 3 pressure waves of a duration of 6 s and a pressure of 300 mbar to simulate pyloric or ileocecal passage, respectively. This setting results from maximum *in vivo* pressures that have been measured to act upon monolithic dosage forms during gastric emptying [15]. However, since due to their much smaller size and their spherical shape pellets are assumed to move more freely through the human GI tract, it is likely that they might not be faced with such high pressures when emptied from the stomach and small intestine. Therefore, a set of additional experiments was performed applying lower pressures (200 mbar, 100 mbar, 50 mbar) to find out what might be the relevant stress acting on these small particles. In the final set of experiments no pressure was applied. In addition to simulating mechanical stress during pyloric and ileocecal passage, in all experiments transport episodes were simulated by rotational movements of the basket holding the dosage form. Rotation was initiated every 20 min, the rotational speed was 100 rpm and the duration of each rotational phase was 2 min. All experiments were at least