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Research Article

The Influence of Simulated Fasted Gastrointestinal pH Profiles on Diclofenac Sodium Dissolution in a Glass-Bead Flow-Through System

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Abstract. High inter- and intra-individual variability in the pH of fluids in the human gastrointestinal (GI) tract has been described in the literature. The aim of this study was to assess the influence of physiological variability in fasted pH profiles of media along the GI tract on diclofenac sodium (DF-Na) dissolution from matrix tablets. Four individual *in vivo* fasted pH profiles were selected from the literature that differed in pH values and transit times from the stomach to the proximal colon. Using a glass-bead device flow-through dissolution system, these pH profiles were simulated *in vitro* using a specific media sequence and considering simulated intestinal buffer capacities corresponding to *in vivo* literature data. Dissolution experiments were then performed in the same system with media sequence following individual pH profiles. In dissolution experiments, where influences of simulated gastric emptying time (GET), gastric pH value, small intestinal transit time, and colonic pH were studied; high influence of gastric pH value and GET on DF-Na dissolution was observed. The effect of variability in pH profiles in the range of individual *in vivo* data on DF-Na dissolution was also clearly observed in experiments, where dissolution studies were performed following three simulated *in vivo* individual pH profiles. The differences in DF-Na release between three individual pH profiles were substantial; they also reflected in simulated plasma concentration profiles and can be attributed to pH dependent diclofenac solubility.

KEY WORDS: gastrointestinal pH profiles; simulation; dissolution; diclofenac sodium; glass-bead flow-through dissolution system.

INTRODUCTION

The composition and properties of fluids in the human gastrointestinal (GI) tract have already been studied by many researchers and continue to be an area of interest for many scientists. In *in vitro* dissolution studies of oral drug delivery systems, physiological parameters, especially characteristics of the upper GI tract fluids are of great importance and should be included in the experimental design. Most frequently GI fluid characteristics are studied after aspiration of the samples using intubation techniques or by less invasive methods, *i.e.*, telemetric capsules.

The majority of studies focusing on the pH value of fluids along the GI tract represent acquired data as location-dependent pH values. In these studies, pH values in different parts of the GI tract are given based either on the position of

the tip of the intubation tube or the location of the telemetric capsule. Instead, some researchers represent their results as time-dependent pH values. In this case, the pH is dependent on the transit time of the telemetric capsule along the whole GI tract. Additionally, significant changes in pH values are expected for transits between certain parts of the GI tract, for example from the stomach to the duodenum or from small to the large intestine, so gastric emptying time (GET) and colon arrival time (CAT) can also be identified.

Median pH values (ranges) reported by one research group, represented as location-dependent data, for the fasted state are: stomach 1.55 (0.95–2.6), proximal small bowel 6.72 (6.15–7.35), terminal small bowel 7.5 (6.8–7.88), cecum 6.05 (5.3–6.55), right colon 5.88 (5.26–6.72), and left colon 6.12 (5.2–7.07) (1). Similar values have been reported by other researchers (2–6). However, high inter-individual and intra-individual variability of pH values in the GI tract has been observed (3). Individual data on GI transit times for fasted individuals from different studies were evaluated, and values for 114 measurements were reported: mean GET was 48 min, mean small intestinal transit time (SITT) 220 min, and mean CAT was 269 min (7). Additionally,

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data on retention time at the ileocecal junction (ICJ) were also reviewed in the same study and were reported to be variable with median value 43 min (7).

Another parameter of GI tract fluids that might also be very important is buffer capacity but this is even less studied than pH values. Due to a paucity of data, different methods of collecting samples, and differences in methods for buffer capacity determination, only approximate values of buffer capacity of the GI fluids for healthy fasted individuals can be summarized from the literature: small intestine 1.7–13 mmol/L/pH (8–12), ascending colon 10.3–21.4 mmol/L/pH (11,13). Additionally, researchers also measured buffer capacities of the fluids throughout the upper GI tract (up to mid/distal jejunum) after application of 800 mg ibuprofen immediate release tablet, and the reported average value was 2.26 mmol/L/pH (range 0.26–6.32 mmol/L/pH) (14).

Diclofenac is a weakly acidic BCS class II drug with pKa value around 4 and log *P* value 4.75 (15,16). The solubility of diclofenac is pH-dependent and increases with increasing pH value of the media (15). Due to the low pH value in the stomach incomplete dissolution and/or immediate precipitation of diclofenac can occur, as it was demonstrated in a recent *in vivo* study using diclofenac potassium immediate release tablets (17).

The purpose of this study was to predict the influence of the highly variable *in vivo* fasted pH values and GI transit times on diclofenac sodium (DF-Na) release from HPMC matrix tablets using an *in vitro* flow-through dissolution model reflecting dosage form passage through the GI tract. The dissolution model was established in order to follow physiological pH values to which the dosage form is exposed after administration and *in vivo* intestinal buffer capacities. The influence of the variability of particular GI parameters (GET, gastric pH value, SITT, and colonic pH value) on DF-Na dissolution was first studied. Next, dissolution studies were performed in media sequence characterizing three different individual *in vivo* pH profiles, and the effect of inter-individual variability on DF-Na dissolution was also studied. Based on these results, plasma profiles were additionally simulated to estimate the effect of the GI tract luminal pH variability on predicted DF-Na plasma concentrations.

MATERIALS AND METHODS

Materials

Disodium hydrogen phosphate (Na_2HPO_4), citric acid monohydrate ($C_6H_8O_7 \cdot H_2O$), trisodium phosphate dodecahydrate ($Na_3PO_4 \cdot 12H_2O$), and Titrisol® concentrates for the preparation of 1 M HCl and 1 M NaOH solutions were purchased from Merck KGaA (Germany). DF-Na was purchased from Sigma-Aldrich (Germany), hydroxypropyl methylcellulose (HPMC) was manufactured by Shin-Etsu (Metolose 90SH-4000SR, Japan) and kindly donated by Harke Pharma (Germany). Lactose monohydrate ($C_{12}H_{22}O_{11} \cdot H_2O$) was purchased from Caesar & Loretz GmbH (Germany), and magnesium stearate was purchased from Lex (Slovenia).

Readings of *In Vivo* Fasted GI pH Profiles from Graphs in Literature

Literature data on individual pH profiles in GI tract are most frequently presented in the form of graphs showing time-dependent *in vivo* measured human GI pH values with marked gastric emptying and colon arrival. Articles with the fasted individual *in vivo* pH profiles of the human GI tract luminal content were searched in the literature, and pH values were read from graphs using Engauge Digitizer software (18). pH values were read from graphs as precise as possible, which depended also from graph quality and fluctuations of the *in vivo* pH values (*i.e.*, where the pH changed extensively in a shorter time period it was sometimes difficult to determine the exact pH value).

Preparation of Tablets

Matrix tablets consisted of 25% DF-Na, 35% HPMC, 39.5% lactose monohydrate, and 0.5% magnesium stearate. The tablet mixture was thoroughly manually mixed, and tablets were then compressed using a Kilian SP300 instrumented single punch (IMA Kilian, Germany) at the Faculty of Pharmacy, University of Ljubljana, Slovenia, with 12 mm flat-faced punches. Tablet mass was set at approximately 400 mg, and tablet hardness was 100–110 N (Vanderkamp VK200, Varian, USA).

The Glass-Bead Device Flow-Through Dissolution System

The glass-bead device flow-through dissolution system was designed by our group at the Faculty of Pharmacy, University of Ljubljana, Slovenia, constructed by Merel d.o.o., Slovenia and is in details described elsewhere (19). A schematic presentation of the system is shown in Fig. 1. The flow-through system consisted of a peristaltic pump (Masterflex L/S standard digital pump system, Masterflex L/S 4-channel 8-roller cartridge pump head and Masterflex L/S small cartridges, Cole-Parmer, USA) which pumped the medium through two tubes (Masterflex microbore silicone (platinum-cured) two-stop tubes (0.89 mm i.d., length 38 cm), extended with Cole-Parmer PTFE tube (1.59 mm i.d., 22 cm on each end of the silicone tube), both Cole-Parmer, USA). The flow-rate was adjusted to 2 mL/min. One tube supplied fresh medium into the working vessel, and the other tube pumped the sample from the working vessel into the sample collecting cylinder. The second tube, which was dipped in the medium in the working vessel, allowed pumping the sample from the working vessel into the cylinder and had a 500 μm pore size mesh placed to prevent larger particles from entering the tube. A magnetic bar and 25 g of glass beads (1 mm diameter) were placed in the working vessel. The volume of the medium in the working vessel was maintained at 40 mL, and the stirring rate of the magnetic stirrer was set to 50 rpm. The temperature in the working vessel was maintained at 37 °C.

Dissolution Media

For the simulation of gastric fluids, hydrochloric acid solutions of different concentrations (2, 20, 30, or 50 mM
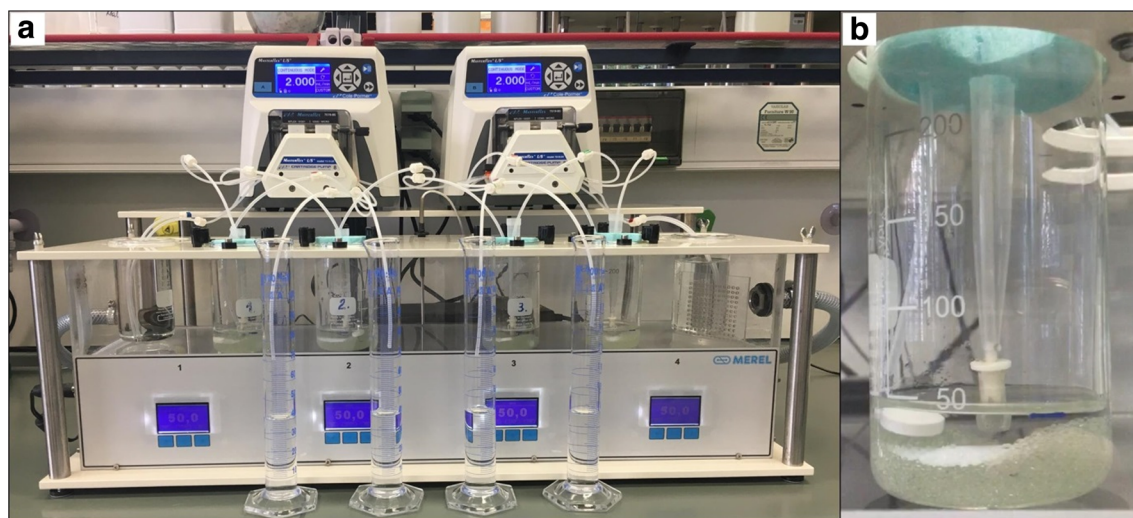
Fig. 1. A configuration of the glass-bead device flow-through system with four working vessels (**a**) and a figure of a working vessel with glass beads, magnetic bar, and tablet (**b**)

HCl) were used to simulate the *in vivo* gastric pH values. The passage from the stomach to duodenum was simulated by addition of a Na_3PO_4 solution of different concentrations (0.12, 0.16, 0.2, 0.28 M Na_3PO_4) or undiluted McIlvaine buffer (MB) pH 5.6 to achieve the desired fast pH increase. For the simulation of small and large intestinal fluids, different dilutions of MBs with different pH values were used. The dilutions of the MBs were experimentally determined in such way that the buffer capacity of the diluted MBs corresponded to the physiological range of intestinal buffer capacities (8–13). Undiluted MBs are composed of 0.2 M Na_2HPO_4 and 0.1 M citric acid in different volumetric ratios based on the required pH value (20). MBs and their dilutions were selected as dissolution media due to the possibility to achieve a wide range of pH values with required buffer capacity.

Determination of Buffer Capacities of Dissolution Media

Buffer capacities were determined at 37 °C using titration with 0.1 M HCl which was added in increments into a beaker with stirred selected medium until a final pH change of approximately 0.2 pH units was detected. Buffer capacities of in-flow media were additionally determined by titration with 0.1 M NaOH.

Buffer capacities were first determined for all media used for the simulation of intestinal fluids. Furthermore, buffer capacity was measured also during the simulation of intestinal pH profiles (tablet not present) to demonstrate that the buffer capacity was in the required range also after delivering a sequence of media (with different pH values) into the working vessel. For that purpose, media pumped out of the working vessel were collected during different chosen time intervals (depending on the media change), and buffer capacity of these media mixtures was then determined using the same method as described above.
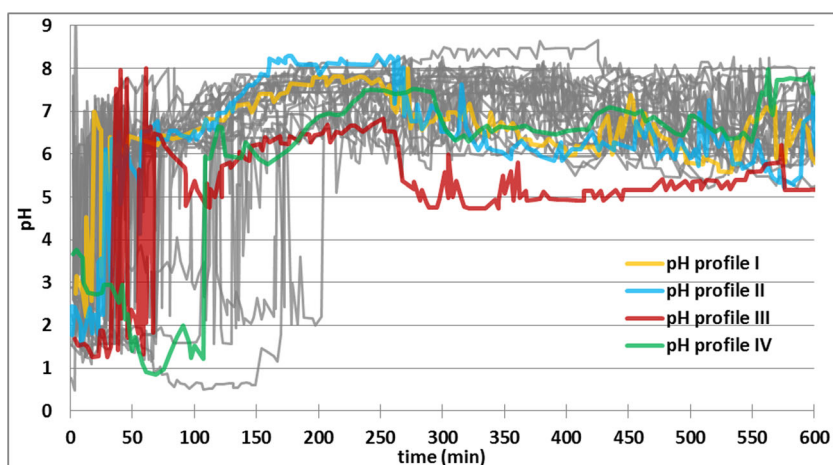
In vitro Simulation of pH Profiles

Four individual fasted *in vivo* pH profiles (marked as pH profiles I, II, III, IV) were selected from the literature (4,6)

and simulated *in vitro*. pH profile I (selected from (6)) was selected since we estimated that it represented approximate median values of transit times as well as pH values throughout the GI tract according to fasted individual *in vivo* GI pH profiles found in the literature (3,4,6,21) and shown in Fig. 2. Furthermore, pH profiles I-L, Ia, Ia-L, Ib, and Ic were not simulations of actual *in vivo* pH profiles but were created based on possible variations in pH profiles that were expected to influence DF-Na dissolution and are modifications of the pH profile I. The different variables that were separately changed in these pH profiles are represented in Table I.

The other three pH profiles, pH profiles II, III (both from (6)), and pH profile IV (from (4)), were selected from literature since they represented fasted individual *in vivo* pH profiles that differed greatly between each other. These profiles were simulated as closely as possible to the actual *in vivo* determined pH profiles.

pH profiles were simulated using the above described flow-through system by subsequent changing of the in-flow media. The tablets, used later in the dissolution studies, were not present in the system during the pH profile determination. For simulation of the pH profile I, the exact sequence of media delivered into the working vessel is presented in Table II. During the determination of the suitable media sequence for pH profile simulation, the pH meter electrode was dipped into the medium in the working vessel, and pH was measured continuously. Measured time-dependent pH values were depicted, and the achieved pH profile could then be compared with the corresponding *in vivo* pH profile read from a graph in the literature. In Fig. 3, simulated pH profile I using the specific media sequence described in Table II and the corresponding *in vivo* pH profile read from the literature are represented. Similar media sequences were also used for simulations of other pH profiles. Variability of simulated pH profiles was very low (RSD was lower than 1% in most cases except during the fast increase in pH value simulating passage from the stomach to duodenum where RSD was maximally 6.4%) and is thus not shown in figures.

Fig. 2. The highly variable individual *in vivo* pH profiles read from data on graphs found in the literature (3,4,6,21). pH profiles used for *in vitro* simulation in the present study are marked with yellow, blue, red, and green color (4,6). Gray curves represent other individual *in vivo* pH profiles, found in the literature, that were not simulated in this study

Dissolution Studies and Sample Analysis

Dissolution studies were performed using the glass-bead device flow-through dissolution system presented above. The conditions were the same as in the pH profile simulation experiments (described above), except that the pH electrode was not present in the working vessel. Before the dissolution experiment, tablets were weighed. The experiment began when the tablet was placed in the working vessel, and the peristaltic pump was switched on. Samples were collected at 20 min intervals in cylinders with 40 mL of 0.1 M NaOH solution, thus the total volume of the sample, diluted with NaOH, was 80 mL. The sample was then filtered through a 0.45 μm regenerated cellulose membrane filter, and the absorbance of the filtrate at 276 nm was measured using a UV-Vis spectrophotometer (Agilent 8453, USA). If needed, samples were additionally diluted. The calibration curve was linear ($R^2 = 0.9999$) in the concentration range 0.698–65.400 mg/L.
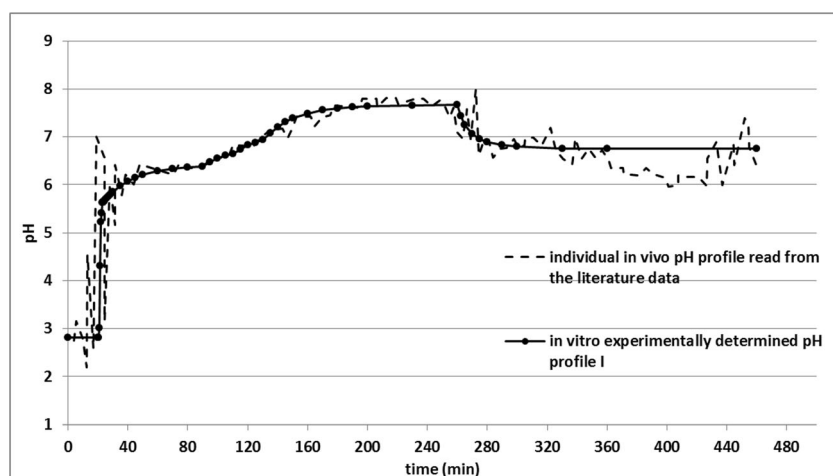
Simulation of Plasma Concentration Profiles

Based on the dissolution profiles in media sequence simulating *in vivo* pH profiles II, III, and IV, DF-Na plasma concentration profiles (C_p (t)) were simulated using two-compartment disposition model, which is represented by the following equation:

$$C_p(t) = A_1 \times e^{-\lambda_1 \times t} + A_2 \times e^{-\lambda_2 \times t} \tag{1}$$

Table II. Time Intervals of Medium Delivery Into the Working Vessel and Media Used for the Simulation of pH Profile I

Time interval of medium delivery (min)	Medium used	Simulated fluid/part of the GI tract
0–20	2 mM HCl	Gastric fluid
20–22	Undiluted MB pH 5.6	Passage from the stomach to duodenum, marked by a fast pH increase
22–90	15-Times diluted MB pH 6.4	Medium in the proximal part of the small intestine
90–110	A mixture of 15-times diluted MB pH 6.4 and 15-times diluted MB pH 7.7 in a volumetric ratio of 3:1	Slow pH increase in the small intestine
110–130	A mixture of 15-times diluted MB pH 6.4 and 15-times diluted MB pH 7.7 in a volumetric ratio of 1:1	Further slow pH increase in the small intestine
130–260	15-Times diluted MB pH 7.7	Medium in the distal small intestine
260–480	4-Times diluted MB pH 6.75	Medium in the proximal colon

MB McIlvaine buffer, *GI* gastrointestinal

Table I. Chosen Parameters for the Simulation of the pH Profile I and Variations of These Parameters (italic) Used in the Simulation of Modified pH Profiles I-L, Ia, Ia-L, Ib, and Ic

Label of the simulated pH profile	Simulated GET (min)	Approximate pH value of the simulated gastric fluid	Simulated SITT (min)	pH value of the simulated fluid of the proximal colon
I	20	2.8	240	6.75
Ia	*120*	2.8	240	6.75
Ib	20	2.8	*155*	6.75
Ic	20	2.8	240	*5.1*
I-L	20	*1.5*	240	6.75
Ia-L	*120*	*1.5*	240	6.75

Fig. 3. Comparison of *in vitro* experimentally determined pH profile I (solid line) with the corresponding individual *in vivo* pH profile depicted from data read from graph found in the literature (dashed line) (6)

A1 and A2 represent dose-corrected intercepts on the ordinate axis for two exponential segments. Hybrid first-order rate constants are represented by λ_1 and λ_2. The simulation model is identical to the model used in a study (22). NONMEM software version 7.2.0 and subroutine ADVAN3 with TRANS5 were used for the simulation. One thousand subproblems were simulated for each experiment. Median, 2.5th, and 97.5th percentiles were calculated for all time points in each dissolution experiment. Detailed information about the simulation model and parameters used are provided in our previous study (23).

RESULTS AND DISCUSSION

Dissolution studies are commonly performed using a standard pharmacopoeial dissolution apparatus and simple medium with fixed pH value or a system of two subsequently used media simulating dosage form passage from the stomach (usually simulated by HCl solution) to the small intestine (usually simulated by phosphate buffer pH 6.8) (24,25). Researchers also use media sequence with different pH values and media that simulates physiological conditions more closely, *i.e.*, biorelevant media containing bile components (26) or bicarbonate buffers (27,28). The need for dissolution studies using media with suitable pH and buffer capacity according to the physiological conditions has been described before (29), and in a recent study (30) both, physiological bicarbonate buffer and individual GI pH profiles simulation were already included in a dissolution evaluation of mesalazine formulations.

Simulation of pH Profiles Using Glass-Bead Device Flow-Through System

Articles with the included graphical presentation of the individual *in vivo* human fasted GI pH profiles were examined, and numerical values for each pH profile were read from the figures in these articles (3,4,6,21). All individual pH profiles were then depicted (Fig. 2), and four *in vivo* pH

profiles (colored pH profiles in Fig. 2) were selected for *in vitro* simulation. Using the glass-bead device flow-through system, the pH profiles along the GI tract, *i.e.*, from the stomach to the proximal part of colon, were then simulated by delivering a specific sequence of media into the working vessel. The glass-bead device flow-through dissolution system used in this study enabled us to consider multiple physiological conditions during the dissolution study. The advantages of this flow-through system have already been described before (19). The parameters used in this study, the volume in the working vessel (40 mL), and the flow-rate (2 mL/min) simulate conditions in a fasted stomach. A certain amount of glass beads was added to the working vessel. They were stirred by a magnetic bar thus enabling specific movement of the glass bead layer and of the tablet. The glass-bead device was a part of the flow-through system where media were easily changed, and the composition of the medium in working vessel was controlled by the in-flow medium. Furthermore, in order to increase similarity to physiological conditions, the buffer capacity of the intestinal media was considered as well. Gastric medium was represented by HCl solution, pH was then increased to simulate the passage to duodenum, and from this point on, buffer capacities were adjusted using different concentrations of in-flow buffers. In all performed experiments, buffer capacities of the media simulating the small intestine content were in the range between 3 and 12 mmol/L/pH and for the simulated media of the proximal part of the colon 9–23 mmol/L/pH. These values are close to literature data on physiologic values of the buffer capacities (8–13).

The Influence of Different Variations in pH Profile on DF-Na Dissolution

Using the simulated *in vivo* pH profile I and its modifications, different gastric pH values, GET, SITT, and proximal colon pH values were simulated in separate experiments, and the influence of these variations on DF-Na dissolution from HPMC matrix tablets was studied. DF-Na was selected as a model drug due to its physicochemical
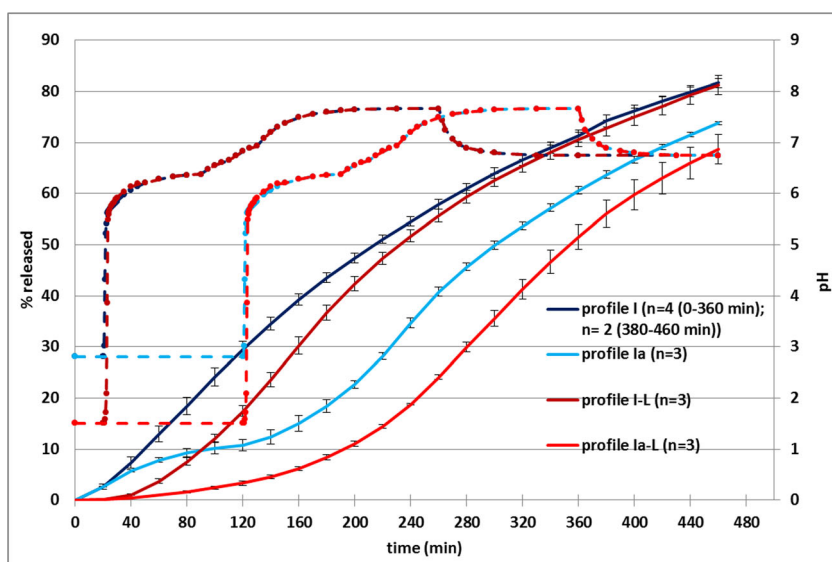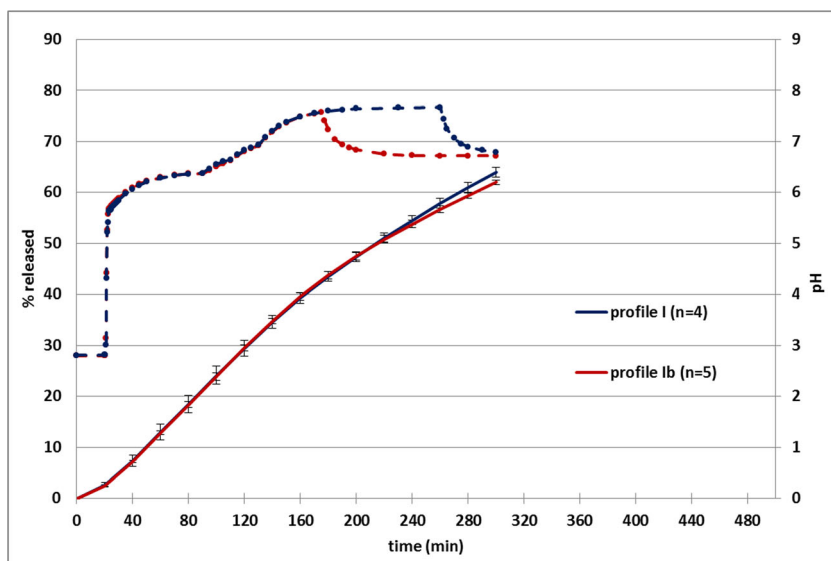
Fig. 4. The influence of variability of simulated gastric pH value and GET on DF-Na *in vitro* dissolution. Simulated pH profiles (dashed lines) and corresponding average dissolution curves for DF-Na tablets (full lines) are depicted by the same color. The number of parallels is written in brackets in legend. For dissolution curves, standard deviations are also represented. The labels of pH profiles are described in Table I and in the text

properties, especially its pH-dependent solubility. An effect of changes in the pH of the media on DF-Na dissolution was thus expected.
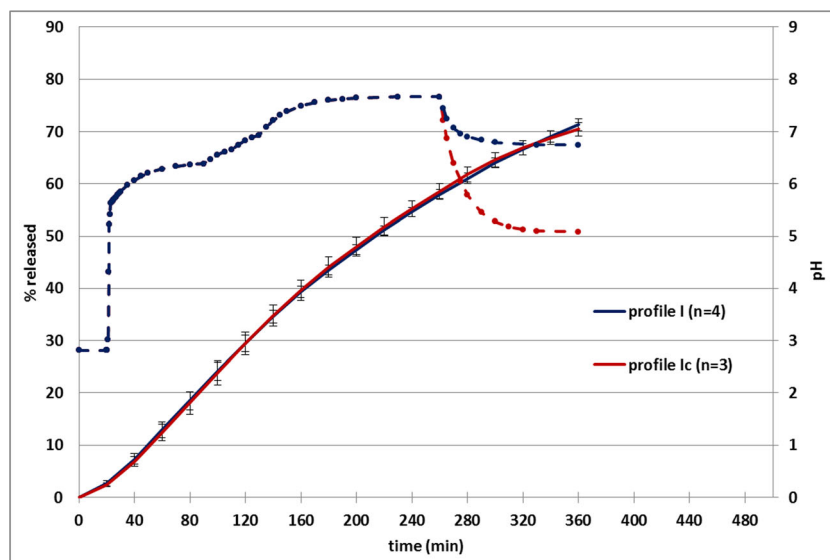
The Influence of Simulated Gastric pH Value and GET on DF-Na Dissolution

Median fasted gastric pH values are reported to be between 1 and 2 (31,32). However, much higher fluctuations of pH values have been recorded (6). High interindividual variability was also shown for GET of non-

disintegrating tablets determined in different studies, which ranged from 0 to 192 min (7). The influence of simulated gastric pH and GET on DF-Na dissolution from HPMC matrix tablets has previously been studied by our group (23). Despite the different dissolution methods used, compared to the previous study, similar results were observed in this work. Longer retention in acidic medium or lower acidic pH produced a longer lag time until the beginning of faster release as can be seen in Fig. 4. The reason for that effect might be the formation of poorly soluble non-ionized diclofenac in the acidic medium.

Fig. 5. The influence of variability of simulated SITT on DF-Na *in vitro* dissolution. Simulated pH profiles (dashed lines) and corresponding average dissolution curves for DF-Na tablets (full lines) are depicted by the same color. The number of parallels is written in brackets in legend. For dissolution curves, standard deviations are also represented

Fig. 6. The influence of variability of simulated colonic pH value on DF-Na *in vitro* dissolution. Simulated pH profiles (dashed lines) and corresponding average dissolution curves for DF-Na tablets (full lines) are depicted by the same color. The number of parallels is written in brackets in legend. For dissolution curves, standard deviations are also represented

Researchers also showed that in acidic medium, intramolecular cyclization of diclofenac can occur (33), and the presence of different diclofenac hydrate forms is possible (34,35) which can additionally lower drug solubility in acidic medium. During dissolution experiment, part of DF-Na might dissolve in acidic medium and precipitate in the form of acid. Very small particles might be pumped out of the vessel to the NaOH solution and dissolve. Thus, the determined percentage of drug released in acidic medium, which is very low, may be partly attributed also to these precipitated particles.

The Influence of Simulated SITT on DF-Na Dissolution

In contrast to GET, SITT is supposed to be less variable *in vivo* (36); however, some studies also report large interindividual variability (37). Since the small intestine is the main absorption site for many drugs, SITT and its variability are of great importance. Thus, the influence of simulated SITT on DF-Na dissolution was also studied in this work. The slow increase of pH values along the small intestine can be seen from *in vivo* pH profiles in Fig. 2 (3,4,6,21). However, in distal parts of the small intestine, pH values remain almost constant for a certain time
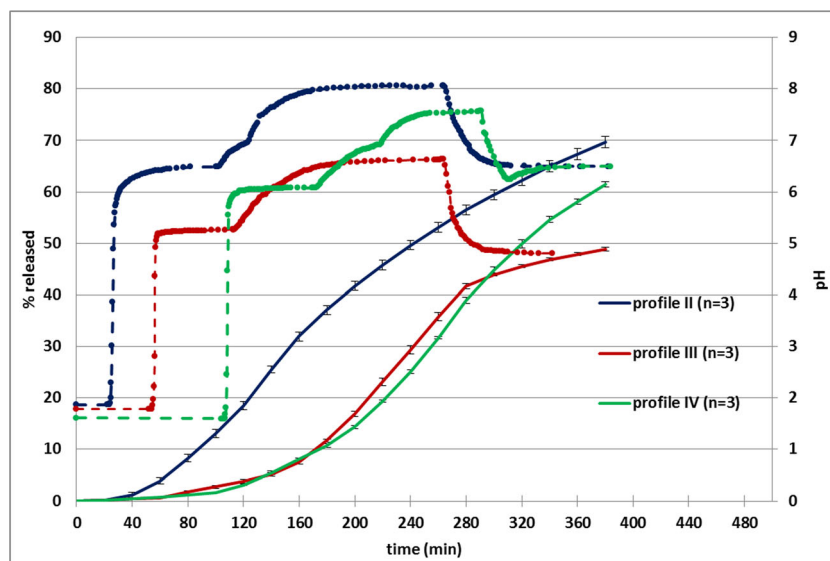
Fig. 7. Simulated individual pH profiles (dashed lines) and average dissolution curves for DF-Na tablets (full lines). Corresponding profiles are depicted by the same color. The number of parallels is written in brackets in legend. For dissolution curves, standard deviations are also represented

period until the pH drop is observed, indicating the passage to the cecum. It is assumed that before passage to the cecum, the dosage form might be retained at the ICJ for a certain time period (7).

SITT of the pH profile I (6) was simulated to be 240 min. A constant pH value for the last 90 min of the SITT might at least partly correspond to the tablet retention at the ICJ. Median SITT reported in literature is 215 min and can range from 60 to 544 min (7). Retention time at the ICJ is also variable with median value 43 min (7). The pH profile I thus represents an example of SITT that is close to median SITT value with possible retention at the ICJ. Shorter SITT (155 min) was also simulated in such a way that the last part with a constant pH was shortened from 90 to 5 min which might correspond to earlier passage through ileocecal junction, *i.e.*, eventually shorter ICJ retention time (Fig. 5). The difference in observed release profiles when different SITT were studied was small with a slight decline of the release curve at shorter SITT compared to longer SITT. Slightly slower release in the case of shorter SITT was a consequence of lower pH of the simulated colonic medium compared to pH of the simulated terminal small intestinal medium. Small differences were expected as both pH values (7.70 and 6.75) are few pH units higher than the pKa value of diclofenac, and low solubility of unionized form cannot influence strongly. It is important to note that the influence of SITT on dissolution is only one aspect; another is its influence on the time available for absorption which is extremely important for drugs absorbed only in the small intestine.

### The Influence of Simulated Colonic pH Value on DF-Na Dissolution

After the passage from distal parts of the small intestine to the proximal colon, a pH drop in the range from approximately 0.5 to 2.5 pH units is usually observed (38). In our study, two different proximal colonic pH values, namely pH 6.75 (pH profile I) and pH 5.1 (pH profile Ic), were simulated. The difference in DF-Na release following pH profiles with different

colonic pH values was not observed (Fig. 6). Higher differences might be expected to be expressed if there would be larger amount of drug still present in the tablet and thus the dissolution would continue for a longer period of time after pH change.

The Influence of Individual *In Vivo* Fasted GI pH Profiles

The Influence of Individual In Vivo pH Profiles on DF-Na Dissolution

To study the influence of physiological variability in fasted GI pH profiles on DF-Na release, a series of dissolution studies following specific media sequence simulating three different *in vivo* individual fasted GI pH profiles (4,6) was performed. These are the pH profiles II, III, and IV marked on Fig. 2, which differ from each other in all previously tested variables, *i.e.*, GET, SITT, and pH values in the stomach, small intestine, and proximal colon. In Fig. 7, dissolution results obtained under the conditions of simulated individual pH profiles are represented. A similar influence of previously discussed parameters was also observed in these dissolution studies. Characteristics of pH profile II are the shortest gastric residence time and the highest pH in the small intestine which are translated into a greater percentage of dissolved DF-Na. Additionally, in the dissolution experiment following pH profile III, the slope of drug release curve decreased after passage to cecum was simulated. Although the influence of the colonic pH value was low in previously described experiments (pH profiles I and Ic on Fig. 6), it appears that when different variables are combined and the amount of remaining drug in the tablet at the time of the pH change is higher, the lower pH value of the colon also influences DF-Na release. Thus, dissolution profiles (Fig. 7) corresponding to simulated extreme pH profiles of the GI tract media differ significantly and are results of the influence of the combination of different variables.
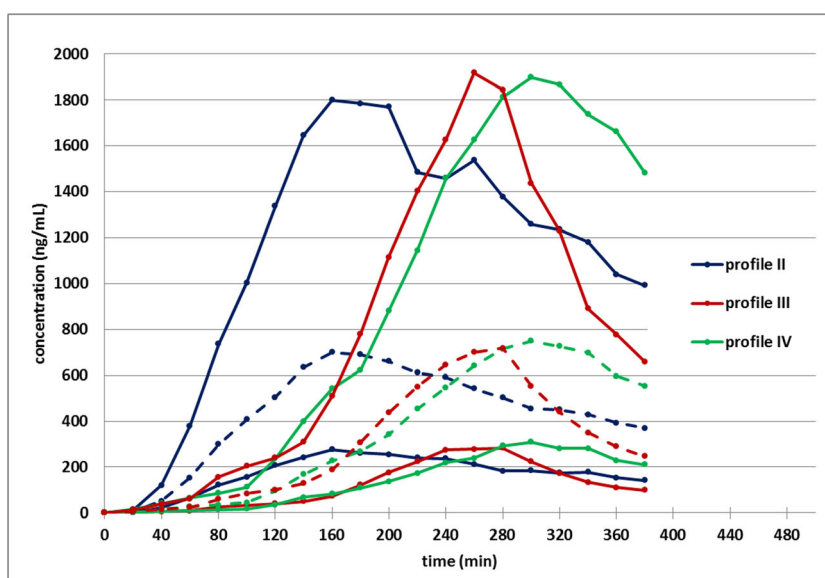
Fig. 8. Simulated plasma profiles for DF-Na dissolution in media sequence following individual pH profiles; 95% prediction interval is represented with solid lines limited by 2.5th percentile and 97.5th percentile. Median values are represented by dashed lines

The Influence of Individual In Vivo pH Profiles on Simulated DF-Na Plasma Profiles

Based on the differences in DF-Na release results obtained from dissolution studies described above and since DF-Na is a BSC class II drug (39), plasma concentration profiles were simulated and are represented in Fig. 8. The maximum plasma concentrations reached were similar for all three pH profiles. However, the time needed to reach the maximum plasma concentration was different. The shortest time was obtained for pH profile II which had the shortest gastric residence time, the highest simulated pH value throughout the GI tract and consequently the highest dissolution profile in the study. The decrease in drug release that occurred in profile III after simulated passage to the lower pH value of colon was also reflected in plasma profiles as a fast decrease in plasma concentrations after maximum plasma concentration was reached. Thus, higher pH in the proximal colon produces a further higher release of DF-Na which maintains higher (simulated) plasma concentrations for a longer period of time, under the supposition that diclofenac is absorbed also from the colon. Absorption of diclofenac from colon was shown in a research where DF-Na was administered directly in the colon by the aid of colonoscopy (40).

In general, high inter- and intra-individual variability in pH profiles along the GI tract is thus expected to produce also high variability in plasma profiles of DF-Na. If the pH of the liquids in the lumen of GI tract would be the most important parameter that influences DF-Na dissolution *in vivo*, then the described differences in simulated plasma profiles might also be expected in *in vivo* plasma profiles. However, there are many other conditions in the GI tract that vary and might also influence the dissolution, but were not included in the present study, for example, the presence of bile components. Thus, the pH values in the lumen of the GI tract are expected to influence DF-Na dissolution and consequently plasma profiles in the direction described in the present work also *in vivo*, but the extent to which this influence is expressed *in vivo* cannot be predicted as there are also other parameters which might have an important impact.

CONCLUSION

A flow-through dissolution system for the simulation of individual fasted pH profiles of GI tract media to which a dosage form is exposed after oral administration was established. High variability in measured dissolution profiles and in simulated plasma profiles of a model drug, diclofenac sodium, as a consequence of variability in simulated pH profiles, was observed. The variability was attributed to the solubility of the model drug which is highly pH dependent in pH ranges corresponding to those of media in the lumen of GI tract.

FUNDING INFORMATION

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