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Research paper

Magnetic Marker Monitoring: High resolution real-time tracking of oral solid dosage forms in the gastrointestinal tract

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ABSTRACT

Knowledge about the performance of dosage forms in the gastrointestinal tract is essential for the development of new oral delivery systems, as well as for the choice of the optimal formulation technology. Magnetic Marker Monitoring (MMM) is an imaging technology for the investigation of the behaviour of solid oral dosage forms within the gastrointestinal tract, which is based on the labelling of solid dosage forms as a magnetic dipole and determination of the location, orientation and strength of the dipole after oral administration using measurement equipment and localization methods that are established in biomagnetism. MMM enables the investigation of the performance of solid dosage forms in the gastrointestinal tract with a temporal resolution in the range of a few milliseconds and a spatial resolution in 3D in the range of some millimetres. Thereby, MMM provides real-time tracking of dosage forms in the gastrointestinal tract. MMM is also suitable for the determination of dosage form disintegration and for quantitative measurement of in vivo drug release in case of appropriate extended release dosage forms like hydrogel-forming matrix tablets. The combination of MMM with pharmacokinetic measurements (pharmacomagnetography) enables the determination of in vitro–in vivo correlations (IVIC) and the delineation of absorption sites in the gastrointestinal tract.

1. Introduction

The oral route is still by far the most common way used for the administration of pharmacologically active substances. This is mainly due to the ease of administration and the general acceptance by the patients. Furthermore, the gastrointestinal tract is the natural site for the uptake of all essential substances with exception of oxygen that is absorbed via the lung. As food and beverages are typically contaminated with micro-organisms, the gastrointestinal tract is very tolerant towards most bacteria and fungi. Consequently, the microbiological requirements on orally administered drugs are relatively low as long as no pathogens are involved. Another important advantage of the oral route of administration is the possibility to administer dry products without the need for dissolution prior to use and without serious safety aspects in terms of particle size as it is the case for injectables. Among the orally administered dry products tablets and hard capsules that are filled with powders, granules or pellets play a predominant role. These products can be manufactured in high numbers at reasonable costs. Taken together, orally applicable dosage forms are very convenient for most patients, and fortunately also the cheapest way of pharmacotherapy.

With the upcoming great success of industrially manufactured solid oral dosage forms as early as in the 1950s the observation was made that two tablets containing the same amount of the same drug substance must not necessarily provide identical therapeutic effects and can also result in different adverse events. Based on this observation, disintegration test methods and somewhat later dissolution test apparatuses and procedures were developed in order to determine parameters that were recognized to be of major relevance for the performance of the product in the gastrointestinal tract. However, with the development of the generic industry it became obvious that the in vitro test procedures being available at that time were not capable to predict the performance of solid oral dosage forms to such a degree that is was acceptable with respect to efficacy and safety. As a consequence, in the 1980s the concept of bioequivalence testing was developed [1].

Despite the fact that we have in the meantime an impressive number of analytical procedures and methods to characterize solid oral dosage forms, we are still not generally able to predict

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whether two solid dosage forms of the same drug substance will be bioequivalent or not. This holds even true if they contain the same excipients.

With respect to the experiences gained by bioequivalence testing, scientists realized that a rational development of solid oral dosage forms requires a profound understanding of their fate and behaviour in the gastrointestinal tract. First attempts to gain information about the in vivo behaviour were made using X-raying [2] and further methods with sometimes almost heroic character like the so-called Jo-Jo-technique [3], where tablets with an attached band were swallowed and later withdrawn from the stomach in order to determine the temporal course of in vivo disintegration. A major breakthrough was achieved when gamma scintigraphy was introduced as a very effective method for the investigation of the behaviour of dosage forms in the gastrointestinal tract and later also for other routes of administration like pulmonary, nasal or even ophthalmic. This work was mainly pioneered by Wilson, Hardy and colleagues at the University of Nottingham [4] and by Digenis and colleagues at the University of Kentucky [5].

Subsequently, gamma scintigraphy became the Gold standard for the investigation of the behaviour of dosage forms within the human body. A major advantage of gamma scintigraphy is the broad availability of the imaging technique. The required imaging equipment as well as the data evaluation methods are essential tools in nuclear medicine and therefore easily accessible. Furthermore, gamma scintigraphy can be applied to solid, liquid and semi-solid dosage forms as it is based on the addition of trace amounts of the γ-emitting radioisotopes technetium-99 m, indium-111 or samarium-153. The latter is of major relevance for the labelling of solid oral dosage forms as it can be derived by neutron activation from the non-radioactive isotope samarium-152 [6]. Gamma scintigraphy provides planar images with a spatial resolution in the range of a few centimetres. In case of typical radiation doses that are applied in human volunteers studies the temporal resolution is in the range of a minute [7]. Significant drawbacks of gamma scintigraphy are the ethical problem that healthy subjects become exposed to radiation without having any personal benefit with respect to medical treatment or diagnosis, as well as the limited temporal and spatial resolution. A direct comparison of the application of gamma scintigraphy and Magnetic Marker Monitoring (here also referred as Magnetic Moment Imaging) has been performed recently [8].

In order to overcome such ethical and technical restrictions that are associated with the use of radioisotopes, in the beginning of 1990s we started to develop an alternative method for the investigation of the behaviour of solid dosage forms in the gastrointestinal tract, which is based on the labelling of the dosage as a magnetic dipole by means of incorporation of trace amounts of ferromagnetic particles, recording of the magnetic dipole field using biomagnetic measurement equipment and data evaluation applying techniques established in magnetic source imaging (MSI). This method is known as Magnetic Marker Monitoring (MMM) or Magnetic Moment Imaging (MMI) [8,9]. During the last 10 years MMM has been applied for the determination of the performance of disintegrating and non-disintegrating solid dosage forms like tablets, capsules and pellets in the gastrointestinal tract, as well as for the determination of the in vivo drug release from modified release products like enteric-coated tablets and enhanced release tablets. Many details on data acquisition devices and techniques as well as the procedures developed for data evaluation have already been reviewed [10]. Therefore, in this review only limited attention will be turned to technical aspects of MMM. The main focus will be given to the application of MMM for the investigation of the gastrointestinal transit behaviour of dosage forms, as well as the in vivo determination of their drug release properties in combination with the pharmacokinetic outcome, an aspect that is often referred as "pharmacoscintigraphy" in case of the application of gamma scintigraphy [11] and in analogy that can be referred as "pharmacomagnetography".

2. Labelling of solid dosage forms as a magnetic dipole

Magnetic labelling of solid dosage forms in order to generate a stable magnetic dipole is usually achieved by the incorporation of small amounts of the black ferrimagnetic iron oxide magnetite (Fe_3O_4) that is a well accepted colourant for food and pharmaceutical products (E172, 21CFR73.1200, 21CFR73.200). Alternatively, the red iron oxide maghemite (γ-Fe_2O_3) can be applied. Maghemite is also ferrimagnetic with a remanent magnetization, which is well comparable to magnetite. Both magnetic colour pigments are not absorbed from the gastrointestinal tract as they are insoluble in gastrointestinal fluids. Magnetite in pharmaceutical quality has a particle diameter of about 200–500 nm (Fig. 1). In order to generate a magnetic dipole, the magnetic orientations of the individual magnetic particles have to be aligned. This is achieved by a magnetization process of the dosage form prior to administration. For this purpose, either strong bar magnets or electro magnets can be used. With respect to the coercivity of iron oxides field strengths of at least 0.6 T should be reached during the magnetization process. The net magnetic moment that generates the dipole field measured in MMM is a superposition of the aligned magnetization of individual particles. Any process that disturbs the alignment of the magnetic particles reduces the net magnetization. The decrease in magnetization due to particle loss or particle reorientation can be used for the determination of the disintegration of dosage forms and in case of extended release formulations for the determination of drug release profiles. This is illustrated in Fig. 2. Besides this beneficial effect, the required alignment of the particles' magnetizations limits the applicability of MMM to solid preparations as in liquids the magnetic particles are freely movable and already rotational diffusion leads to an significant decline of the net magnetization (relaxation) within viscosity dependent short time spans [10].

The quantity of iron oxide applied for labelling depends on the sensitivity of the measurement device and the aims of the study. Using highly sophisticated biomagnetic measurement equipment,

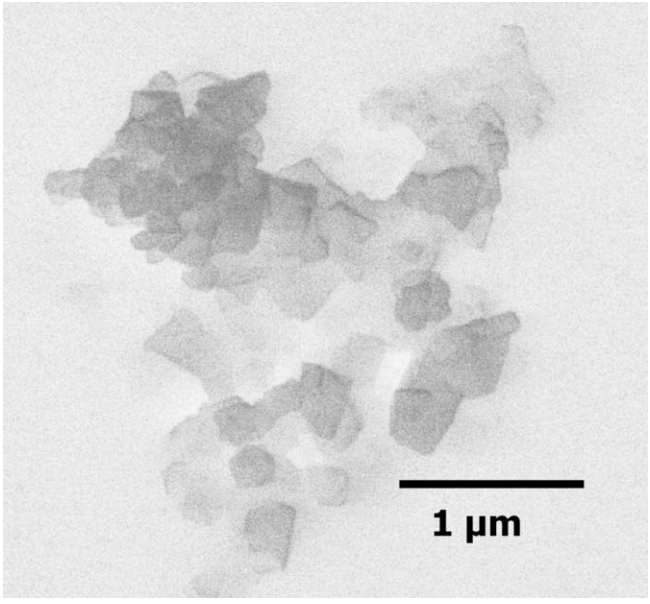

Fig. 1. Electron micrograph of black iron oxide used for the magnetic labelling of solid dosage forms.

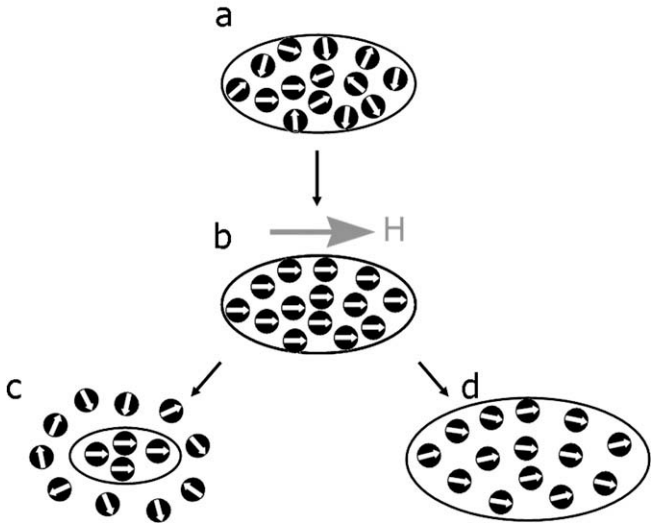

Fig. 2. Principle of magnetic labelling of solid dosage forms as a magnetic dipole and effects of disintegration, erosion and swelling. (a) After incorporation into the matrix, the magnetic orientations of the individual black iron oxide magnetic particles are randomly distributed (or the individual particles are even not magnetized). The dosage form has no net magnetic moment. (b) After magnetization in a sufficiently strong magnetic field H the magnetic orientations of the particles are aligned. The dosage form generates a net dipolar field. (c) Magnetic particles released due to disintegration or erosion of the dosage form are randomly orientated as they are freely movable in the surrounding environment. The net magnetic moment of the dosage form decreases. (d) Swelling of the dosage form results also in a loss of alignment of the magnetic particles and thereby a decrease in the net magnetic moment of the dosage form [41].

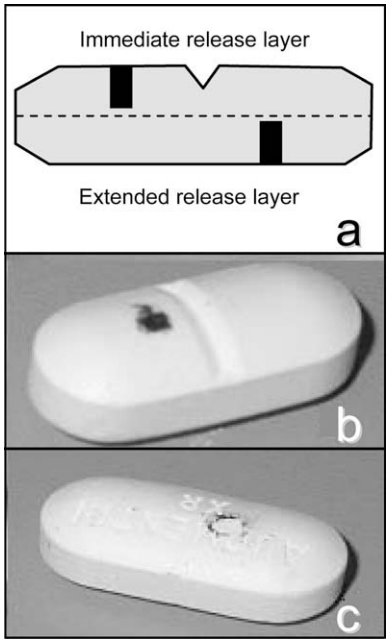

Fig. 3. Magnetically labelled dual layer tablet (Augmentin XR). (a) Schematic representation of the two layers and the arrangement of the bore holes. (b) Photograph of the immediate release layer with the bore hole that is filled with about 5 mg iron oxide. (c) Photograph of the extended release layer with the bore hole that is filled with about 5 mg iron oxide and closed with magnesium stearate [42].

it is possible to detect dosage forms that are labelled as a magnetic dipole with amounts starting at about 0.1 mg of magnetite with an acceptable precision (Fig. 4). The labelling of dosage forms with such very trace amounts of about 0.1–0.2 mg of magnetite has successfully been applied for the monitoring of the fate and behaviour of individual particles in the range of a millimetre or below [12]. For transit studies, employing typical single unit dosage forms like tablets or capsules about 1–3 mg iron oxide have been proven to be optimal in our typical experimental setup. In case of studies where the temporal profile of the decline of the magnetic moment is of interest – thus representing long-lasting drug release from extended release formulations – we prefer amounts of magnetite between 3 mg and 10 mg. Such amounts of magnetite have also been useful in case of studies where a high magnetic contamination caused by other instruments is present during the investigation, e.g. when catheters with pressure sensors are additionally applied for simultaneous manometry [13].

Incorporation of the iron oxide that is required for magnetic labelling can be achieved in different ways depending on the product and the accessibility of the production process. Tablets can be labelled by addition of the iron oxide to the powder mixture or the granulate that is used for tabletting. Alternatively, tablets can also be labelled by drilling a small bore hole (diameter typically 1 mm) into the tablets along their short or long axis and subsequent filling of a suitable amount of iron oxide into the bore hole (Fig. 3). In case of modified release formulations like enteric-coated tablets or matrix formulations, the drill-hole can effectively be closed by using either some biocompatible glue like butyl cyanoacrylate or magnesium stearate. Hard capsules can magnetically be labelled by addition of the magnetic iron oxide to the filling. However, in this case the capsules have to be filled completely, in order to avoid the disorientation of particles with aligned magnetic orientation – as it was achieved during the magnetization process – due to particle movement in the powder matrix.

3. Biomagnetic measurement technique and localization procedure

The measurement setup and the localization procedure have been described in detail elsewhere [10]. The magnetic fields generated by dosage forms that are magnetically marked by the incorporation of about 0.1–10 mg iron oxide are very weak. Therefore, we apply measurement equipment that is based on superconducting quantum interference devices (SQUIDs) as the most sensitive magnetic flux sensors that are available [14,15]. In order to avoid disturbances caused by environmental magnetic fields like the earth's magnetic field the measurements are performed in a magnetically shielded environment, so-called magnetically shielded rooms [16].

After the volunteers ingested the magnetically labelled dosage form, components of the magnetic dipolar field are continuously measured whilst the subject is in either supine or upright (usually sitting) position. The typical data sampling frequency is 250 Hz. The location, orientation and strength of the dipole are reconstructed from the measured field components applying the Levenberg–Marquardt algorithm [17,18].

The accuracy of the localization results depends on several factors such as the sensitivity, arrangement and number of magnetic sensors, the distance between the sensors and the magnetically labelled dosage form, as well as the strength of the dipole, i.e. the amount of magnetite used for labelling. This is illustrated in Fig. 4, where results from phantom measurements for two magnetically marked capsules labelled with either 1.3 mg or 0.13 mg of magnetite are shown. The experimental description of the phantom experiments is given elsewhere [19]. The comparison shows that the capsule with 0.13 mg magnetite can be followed with a sufficiently high accuracy in the range of some millimetres, as long as the capsule is located beneath the measurement device. The capsule labelled with 1.3 mg of magnetite can be localized with a very high precision in the range of 1 mm in the three dimensions x, y and z under all tested conditions.

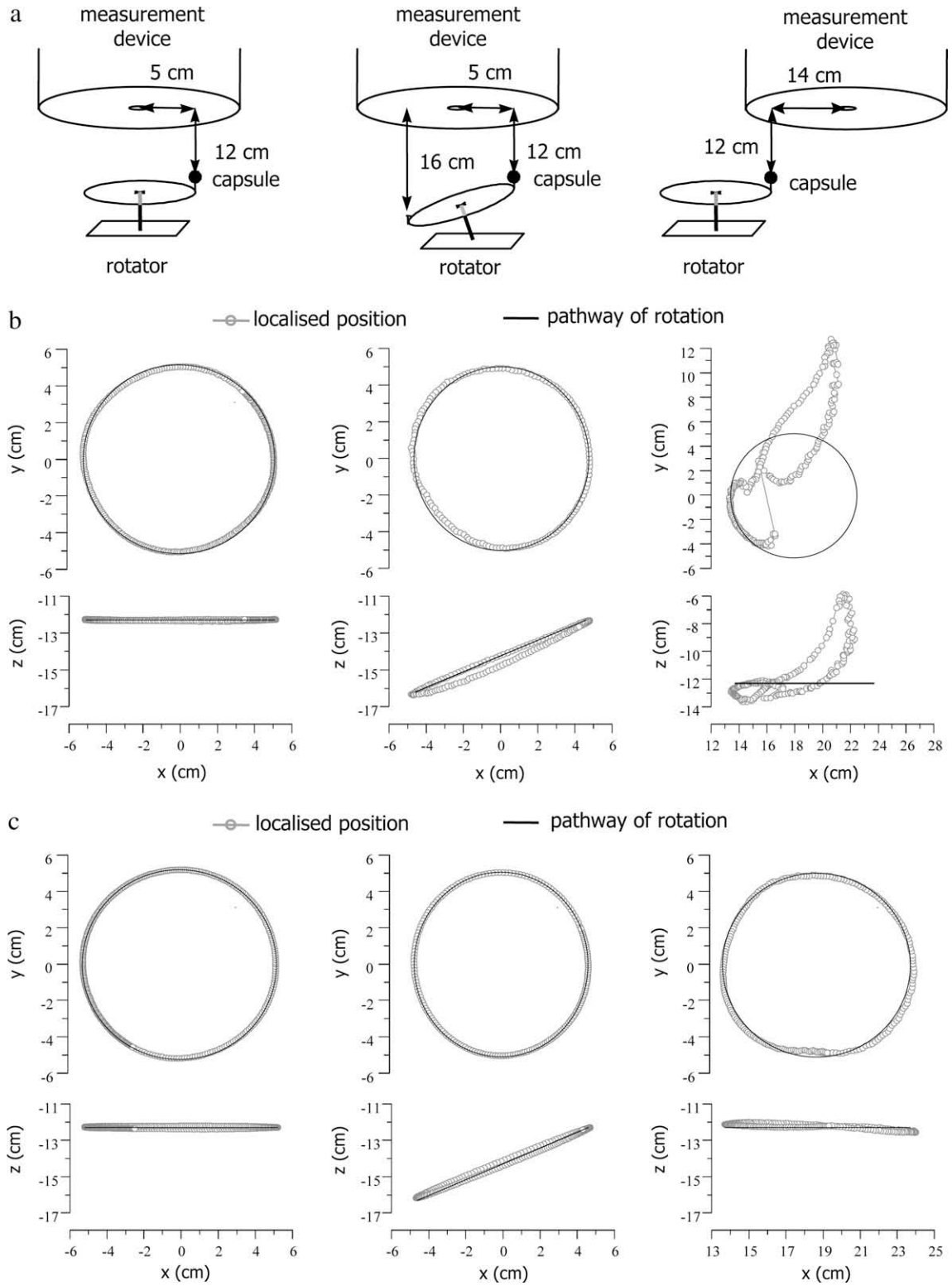

Fig. 4. Accuracy of magnetic maker localization [19]. (a) Experimental setup schemes for phantom experiments with a non-magnetic rotating disk. (b) Localizations (temporal resolution 20 ms) in an *x*–*y* plane and in an *x*–*z* plane for one rotation of a capsule labelled with 0.13 mg black iron oxide. (c) Localizations (temporal resolution 20 ms) in an *x*–*y* plane and in an *x*–*z* plane for one rotation of a capsule labelled with 0.13 mg black iron oxide.

4. Alternative measurement equipments

In the meantime, other imaging equipments and procedures have been developed for the localization of solid magnetic objects in the gastrointestinal tract that are also based on the detection of a magnetic dipole [8,20–23]. All of these closely related measurement devices and arrangements avoid the application of the extremely sensitive but expensive biomagnetic measurement equipment and can be operated in regular environment without the necessity of magnetic shielding that is also very elaborate.

However, application of magnetic measurement equipments that are less sensitive than biomagnetic measurement devices and that are operated in unshielded environment requires magnetic markers with essentially stronger dipolar magnetic moments compared to those applied using biomagnetic measurement equipment. For example, the magnet used by Stathopoulos et al. for the recording of gastrointestinal passage had a magnetic moment of 200 mA m^2 [21]. In contrast, the dipolar magnetic moment obtained after labelling of a solid dosage form with 1 mg of magnetite and subsequent magnetization is typically in the range of 5–10 μA m^2, depending on the iron oxide used and the geometry of the dosage form.

At the current stage of development, the tracking of real dosage forms that are labelled with trace amounts (i.e. some milligrams) of magnetic material is not possible with these alternative methods. However, for the investigation of gastrointestinal physiology, the interplay between gastrointestinal physiology and model dosage forms or for clinical purposes in the field of gastroenterology such alternative methods might also be very useful considering the reduced financial and technical effort making them more practicable in clinical environments and for medical diagnostics than biomagnetic measurement technique.

However, it should be kept in mind that the application of strong permanent magnets as marker is hampered by the disadvantage that the presence of a second magnetic or magnetizable object in the gastrointestinal has to be strictly excluded. This limitation has been learned during the last years by severe injuries including death that have been observed in cases where children had swallowed magnetic toys [24]. With respect to such serious risks that have been observed after swallowing of strong permanent magnets, it seems essential to our opinion that at least in volunteer studies the swallowed marker is not a non-disintegrating strong permanent magnet and that the swallowed object does not disintegrate into a few sizable parts with remaining attracting magnetic forces.

5. Characterisation of gastrointestinal transit by MMM

Besides esophageal transport, gastrointestinal transit is characterized by phases of relative rest that are intermitted by episodes of transport. The frequency and duration of the transport episodes as well as the velocity reached by solid dosage forms during these events are to our experiences highly variable. This very high discontinuity has also been observed for the transport of chyme [25,26].

The high temporal and spatial resolution of MMM provides detailed insights into gastrointestinal transit pathways in 3D. An example is given in Fig. 5, where the passage of a non-disintegrating capsule through the stomach of a healthy male subject in four repeated experiments is shown (experimental details are given in [43]). Although in this case the total gastric residence times are comparable with 24 min, 20 min, 14 min and 25 min, the intragastric location of the capsules during their gastric residence differs remarkably. Whilst the proximal stomach (area of the fundus) was the main site of capsule residence in experiments 1 and 2, the capsules passed the proximal stomach immediately after stomach arrival with passage times through the area of the fundus below 1 s in experiment 3 and about 3 s in experiment 4, respectively. With respect to the rather low myoelectric activity in the fundus and the occurrence of strong contractions in the antrum of the stomach such obviously erratic behaviour concerning the first site of intragastric dosage form disposition is highly susceptible to affect the in vivo disintegration rate of dosage forms.

The very high discontinuity of gastrointestinal transport is illustrated in Fig. 6. Here, the velocities of capsule movement in the

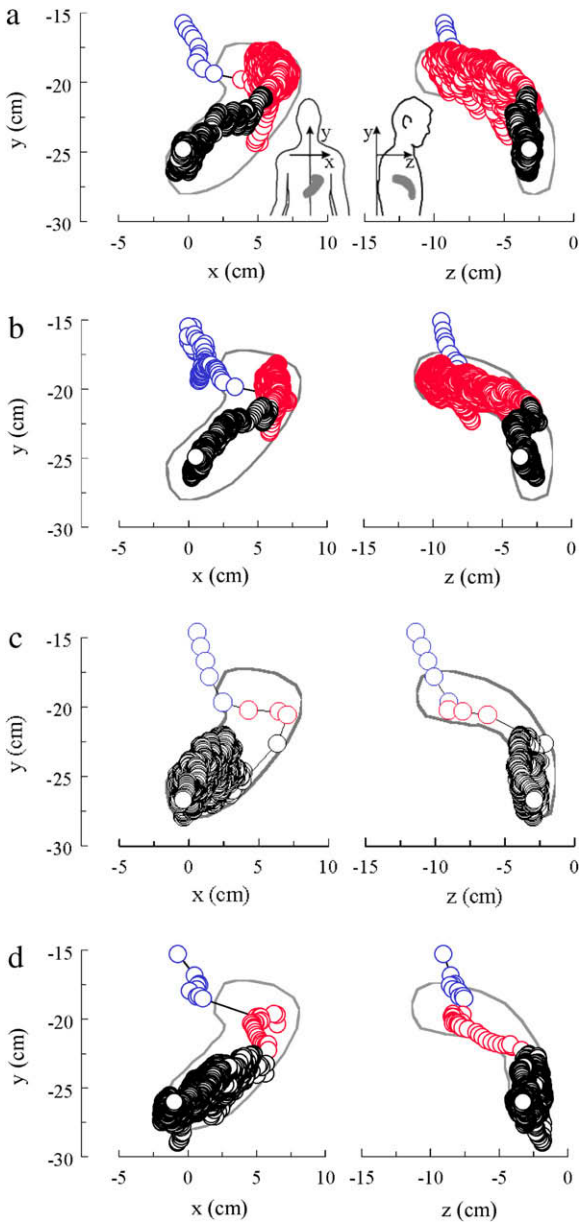

Fig. 5. Passages of a non-disintegrating capsule through the stomach monitored in four repeated experiments in a volunteer. Each circle represents a position localized in steps of 100 ms: ○ passage through the terminal part of the esophagus into the stomach; ○ passage through the proximal stomach (fundus) and ○ passage through the distal stomach (corpus/antrum). (a) Experiment 1 (gastric emptying time: 24 min), (b) Experiment 2 (gastric emptying time: 20 min), (c) Experiment 3 (gastric emptying time: 14 min) and (d) Experiment 4 (gastric emptying time: 25 min) [43].

stomach and the small intestine until arrival in the colon are shown as they were observed in experiment 2 and experiment 3 of the in previously mentioned study [43]. Typically, gastric emptying as well as transit through the ileocecal region is associated with velocities spikes of up to about 50 cm/s. Small intestinal passage is characterized by phases of relative rest that are intermitted by short episodes of either slow or rapid transport. In case of duodenal transport, we have observed in several cases of rapid retrograde transport, so-called retropulsions [27]. Such retropulsions are characteristic for phase III activities of the interdigestive-migrating motor complex (IMMC) and result in mixing of duodenal contents with gastric juice [28]. In one case, we observed even that an enteric-coated tablet re-entered the stomach shortly after gas-

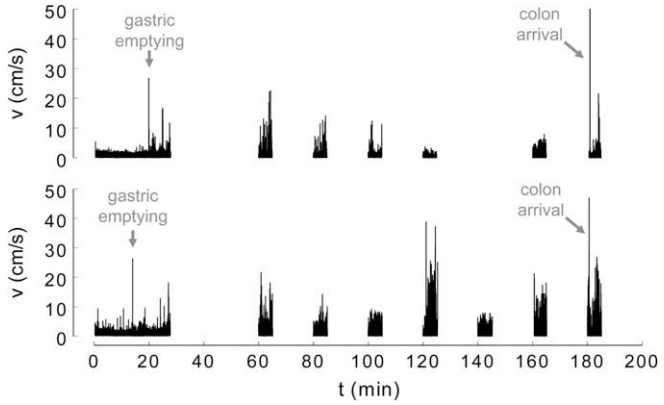

Fig. 6. Velocities of non-disintegrating capsules determined during sequences of their passage through the stomach (0–20 min after ingestion), the small intestine (20–180 min) and arrival in the colon (181–185 min). Calculated from the data of experiment 2 (top) and experiment 3 (bottom) presented in [43].

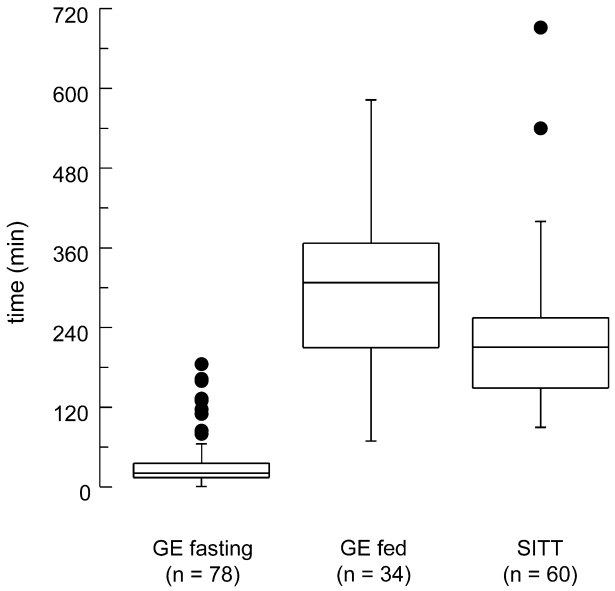

Fig. 7. Box plot of time points of gastric emptying (GE) under fasting and fed conditions as well as small intestinal transit times (SITT, calculated as difference between the time point of arrival in colon and gastric emptying) of non-disintegrating capsules and tablets with a diameter of at least 5 mm as determined in several MMM studies.

tric emptying during such a reflux event. We have never identified retrograde transport of solid dosage forms in the jejunum or the ileum. Furthermore, we have never observed retropulsion of a dosage form from the colon into the small intestine.

Typical distances passed during a transport event in the small intestine are in the range of 10–20 cm. Until now, we were not able to distinguish distinct patterns or frequencies that are characteristic for the occurrence of transport events in the small intestine. However, in most cases the transit velocities as well as the distances passed over one episode of transport tend to decrease from the proximal small intestine to the distal small intestine. Nevertheless, we have also observed cases of rapid and far ranging movement in the more distal small intestine. The two examples shown in Fig. 6 illustrate this observation. In experiment 2, movement velocity of the capsule decreases with increasing small intestinal transit time whilst in experiment 3 the highest capsule velocity was observed in the measurement interval lasting from 120 min to 125 min after intake of the capsule, i.e. after about 100 min of small intestinal transit.

Findings from a survey of our MMM investigations of gastric and small intestinal transit of non-disintegrating capsules and tablets with a diameter of at least 5 mm in healthy volunteers under fasting and fed intake conditions are summarized in Fig. 7. After intake under fasting conditions (at least 8 h without food ingestion prior to administration), gastric emptying (GE fasting) of single unit dosage forms occurred within a broad time range lasting from 1 min to 185 min with a median of 21 min and a mean of 37 min. Intake of single unit dosage forms together with a meal or shortly (within 30 min) after a meal (containing in our studies typically about 500 kcal but sometimes also 1000 kcal) resulted in markedly delayed gastric emptying (GE meal) with a range between 69 min and 583 min with a median of 302 min and a mean of 308 min. The transit times through the small intestine (small intestinal transit times = SITT) were between 90 min and 692 min, with a median of 221 min and a mean of 211 min. These values are in quite good accordance with data reported from studies applying gamma scintigraphy [29].

However, gastric residence times of single unit dosage forms after intake together with a meal are also not independent from the timing of the next meal. In the presented analysis, gastric emptying times have only been enclosed when the dosage form had left the stomach before the next meal was served. If gastric emptying had not occurred before serving of the next meal, a further prolongation of gastric residence resulted. Therefore, the data presented in Fig. 7 represent only gastric emptying times that were observed without intake of further meals before the dosage form had left the stomach. With respect to "real life" this is a rather unrealistic condition. Under regular food intake behaviour consisting of typically three to four meals per day (breakfast, lunch, eventually a snack in the afternoon, dinner), we would not expect gastric emptying of a non-disintegrating single unit dosage form with a diameter above 5 mm during daytime in the vast majority of cases. Furthermore, small intestinal transit times are also affected by the eating behaviour. Food intake stimulates transport of indigestible material from the terminal small intestine into the colon, a mechanism that is known as gastro-ileal or gastro-ileocecal reflex [30,31]. This effect is probably the more pronounced the longer the fasting period before meal intake lasted.

In human clinical bioavailability studies, the first meal after dosage form administration under fasting conditions is typically served after 4 h. Taken together with typical gastric emptying times, this fits nicely to the usually observed small intestinal transit times of 2–4 h [29]. This interpretation that the typical food intake scheme in bioavailability studies serves as a major determinant of small intestinal transit times of dosage forms is corroborated by a finding that we made in a clinical study applying magnetic resonance imaging (MRI). Here, we observed that in cases of no meal served for 7 h post-dose the dosage forms were still located in the terminal small intestine in the majority of the investigated subjects (9 out of 12). In contrast, eating of a meal 6 h post-dose induced translocation of the dosage forms into the colon in all subjects [31]. This understanding of the impact of timing of meal intake relative to dosage from administration on small intestinal transit time is corroborated by observations reported in a recently published study [32].

Transit of dosage forms through the colon is also extremely variable and depends on several factors like the time point of dosage form administration and meal intake. There is an ongoing debate on the possible influence of size, shape and density of dosage forms on colonic transit times. However, from scintigraphic and radiological data, it seems likely that small particles like pellets have prolonged colonic residence times compared to large single unit dosage forms [33,34]. A possible explanation for this observation is that small particles become often trapped in the haustral folds

of the colon, whereas the solid units are more likely to become propelled forward.

To our experiences, transit through the large bowel seems to be mainly determined by colonic mass transport, a phenomenon that is also inducible by food intake [35,36]. During the last years, we have recognized that in measurement sequences performed during 15–60 min after intake of a meal colonic transport events often occur. Such food intake related colonic transport episodes may cover transport distances of up to 50% of total colon length. They can be seen for large single units but also for small particles as it is demonstrated in the example shown in Fig. 8. Here, the transport of a magnetically labelled particle with a diameter of about 1 mm is shown. The particle passed the ascending colon and the transverse colon in one continuous movement that started about 23 min after lunch and lasted for 1.63 min.

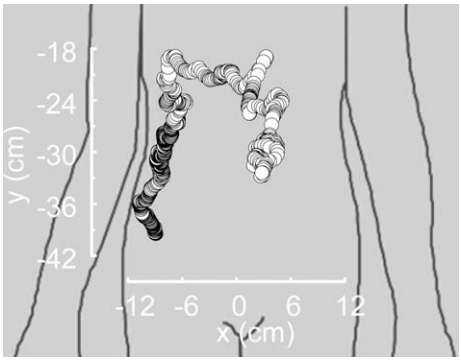

Fig. 8. Mass transport of a magnetically labelled particle in a healthy volunteer from the proximal colon ascendens over a distance of more than 50 cm to the beginning descending colon within 1.63 s. The mass transport started 264 min after ingestion of the particle. Lunch was eaten 23 min before. The temporal resolution is 1 s, i.e. every circle represents one localization in steps of 1 s. Experimental details are given in [12].

6. Pharmacomagnetography

Magnetic labelling of dosage forms by the incorporation of particulate magnetic material and subsequent magnetization in order to create a magnetic dipole has the unique advantage that the strength of the dipole (that means the magnetic moment) is a function of the number of magnetic particles with aligned magnetic orientations as it is illustrated in Fig. 2. Release of magnetic particles from the dosage form causes a decrease in its magnetic moment. The released particles do not contribute anymore to the measured signal. This is an essential difference – and advantage for the intended investigation – to gamma scintigraphy, where a quantitative determination of release of radioactive label from the dosage form is very difficult to achieve. As the released magnetic particles do not generate a background signal, the temporal course of the magnetic moment can be taken as a direct measure for the disintegration of the magnetically labelled dosage form or in case of extended release preparations for drug release. For the determination of in vivo drug release profiles, a stable correlation function between the temporal course of the development of the magnetic moment and drug dissolution is required. Such correlation functions between the magnetic strength of the dosage form and drug release can be established applying appropriate in vitro experimental settings [9,12,19,27,41,42].

The dependence of the measured signal on the integrity of the dosage form can be used for the determination of the in vivo disintegration behaviour of dosage forms that are intended to provide site specific drug delivery properties; for example, enteric-coated tablets containing locally acting drug substances for the therapy of inflammatory bowel diseases, as well as new excipients or new formulations that are suspected to be resistant towards gastric juice [12]. Further typical applications are investigation on the cause of food effects, the delineation of absorption sites, the determination of in vivo release profiles of extended release formulations and the establishment of in vitro–in vivo correlations (IVIVC) [27,42]. This can also be achieved on an individualised basis. Furthermore, data obtained by pharmacomagnetography can be used for the development of dynamic pharmacokinetic models describing the transport and absorption properties of different segments of the gastrointestinal tract [37].

An example for the potential of the combination of MMM with pharmacokinetics is the determination of the origin of the complex food effect of an extended release formulation of amoxicillin and clavulanic acid. In the prescribing information of the extended release bilayer tablet, Augmentin XR (Fig. 3) that contains 562.5 mg amoxicillin and 62.5 mg clavulanic acid in the immediate release and 437.5 mg amoxicillin in the modified release layer [38] the following advice is given: "... *Augmentin XR is optimally administered at the start of a standardized meal. Absorption of amoxicillin is decreased in the fasted state. Augmentin XR is not recommended to be taken with a high fat meal, because clavanulate absorption is decreased.*" (prescribing information Augmentin XR, GSK, AX:L9, December 2006). In order to clarify the underlying mechanisms for this complex intake recommendation, we performed a MMM study with these tablets after magnetic labelling of both layers (Fig. 2). Thereby, we obtained information about the disintegration of the immediate release layer and the extended release layer that, according to in vitro investigations nicely, correlated with the release profile [42].

The combined analyses of the localization data and the plasma concentration profiles showed that the reduced bioavailability of amoxicillin under fasting conditions is due to early gastric emptying of the tablets in combination with poor absorption of amoxicillin from deeper parts of the small intestine. The decreased bioavailability of clavulanic acid after tablet intake following a high fat meal is due to a prolonged gastric residence of clavulanic acid that is caused by the initial intragastric tablet deposition after ingestion in the fundus of the stomach and the resulting poor mixing. An essential aspect of this finding is illustrated in Fig. 9, where the effect of early gastric emptying on the absorption of amoxicillin is demonstrated for one subject under the three intake conditions that were investigated: fasting, at the beginning of a meal and after a meal. Despite the comparable drug release performance of the tablets as indicated by the temporal development of the magnetic moments (first decrease in magnetic moment indicates drug release from the immediate release layer and second decrease indicates drug release from the extended release layer), the resulting plasma concentration profiles are essentially different. This is mainly due to the gastrointestinal location of the tablet at the time point of drug release. In case of tablet intake under fasting conditions, the tablet (that means the remaining extended release layer of the tablet) was emptied after a gastric residence time of 14 min from the stomach. Accordingly, drug release from the extended release layer took place in the distal part of the small intestine after about 150 min of small intestinal transit. As it can be seen from the plasma concentration profile (Fig. 9, top), the released amoxicillin was not absorbed from such distal parts of the small intestine. In case of tablet intake after the meal, the tablet disintegration of both parts of the tablet took place in the proximal part of the stomach (i.e. the fundus of the stomach), resulting in a delayed appearance of amoxicillin in plasma due to the time that was required for the released amoxicillin to pass the stomach (Fig. 9, bottom). In contrast, release of amoxicillin in the distal stomach as provoked by tablet intake at the start of the meal resulted in a fast absorption (Fig. 9, middle).

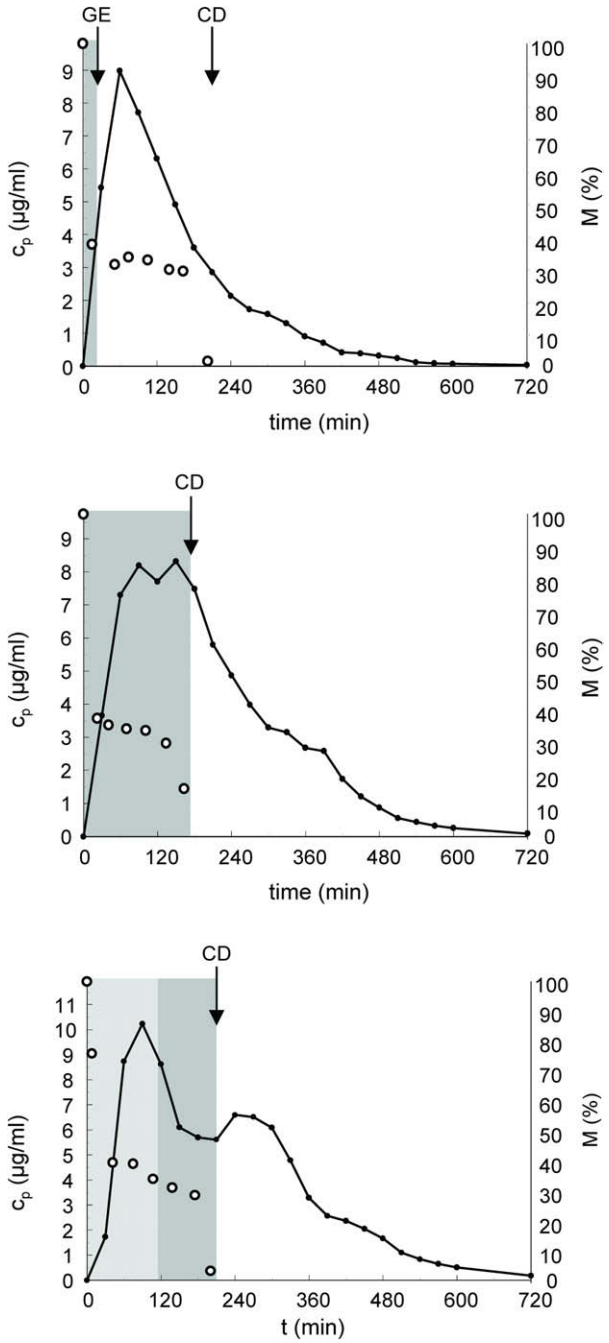

Fig. 9. Amoxicillin plasma concentrations (c_p), relative magnetic moment (M), intragastric location (bright grey: proximal stomach; dark grey: distal stomach), gastric emptying time (GE) and time point of complete disintegration (CD) observed after administration of a dually labelled Augmentin XR tablet in a healthy volunteer under fasting conditions (top), at the beginning of a meal (middle) and 30 min after a meal (bottom). Experimental details are given in [42].

The study performed with the dually labelled bilayer tablets can also serve as an example for the complexity of interactions between gastrointestinal physiology, intake conditions and dosage form behaviour. The understanding of the determining factors within such a complex interplay is often a key factor for successful development of modern dosage forms to our experience. This holds especially true for the development of controlled release systems for fixed dose combinations.

7. Conclusions

Magnetic Marker Monitoring (MMM) is a powerful tool for the investigation of the performance of solid dosage forms in the gastrointestinal tract. MMM provides very high temporal and spatial resolution; thereby, enabling real-time tracking of dosage forms in the gastrointestinal tract. Due to the basic principle that the dosage forms are labelled as magnetic dipoles MMM is also suitable for quantitative determination of dosage form disintegration [19,43], and in vivo drug release from appropriate extended release dosage forms like hydrogel-forming matrix tablets [27]. The combination of MMM with pharmacokinetic measurements (pharmacomagnetography) enables the determination of in vitro–in vivo correlations (IVIC) and the delineation of absorption sites in the gastrointestinal tract [27,42]. The results obtained with MMM can also serve as a data base for the development of improved pharmacokinetic models [37] and biorelevant dissolution test apparatuses and procedures [39].

In contrast to gamma scintigraphy, MMM avoids the exposure of the investigated subjects to radiation. This can be of essential benefit for studies in special populations as for example in children. Furthermore, MMM can be combined with further diagnostic procedures as for example gastrointestinal manometry [13]. The necessity to perform the measurements in a special magnetically shielded environment complicates the application of MMM. However, during the last years a number of new measurement devices for the detection of magnets in the gastrointestinal tract have been developed, which can be operated in magnetically unshielded environment and they have already been used for studies in children [21] or for investigations of gastrointestinal transit in combinations with further diagnostic tools [23].

With the increasing number of MMM studies that has been performed during the last years, we have learned that each study provides new and often unexpected insights into the interplay between gastrointestinal physiology, dosage form performance and drug absorption. However, one common lesson holds true in every study: in order to understand the in vivo performance of dosage forms in the gastrointestinal tract one has to look at the individuals. Mean values may be significantly misleading. We are, therefore, in full agreement with the concluding statement of McConnell et al. in their recent review on intestinal physiology and drug delivery: *There is no such thing as an average person* [40].

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