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In vivo imaging of drug delivery systems in the gastrointestinal tract

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ABSTRACT

An essential basis for the understanding of the complex interplay between oral drug delivery systems and gastrointestinal physiology is the ability to relate deposition of the dosage form to the plasma concentration time profile. The pharmaceutical scientist requires an array of methods that provide information on formulation disposition without influencing the physiological process, commonly termed "non-invasive" imaging modalities. In this paper, a short historical view on the suitability of different imaging modalities for the investigation of the fate of drug delivery systems in the GI tract is given. The focus of the review is the presentation of currently mostly used methodologies scintigraphy, magnetic tracking techniques like magnetic marker monitoring (MMM), magnetic moment imaging (MMI), AC biosusceptometry (ACB) and magnetic resonance imaging and the discussion of their strengths and weaknesses.

1. Introduction

Drug substances have to reach the desired therapeutic target and maintain the appropriate concentration for a defined time span in order to be effective. In addition, the specificity of this physicochemical association determines the safety profile for the drug. This prerequisite holds true for every kind of delivery system and every route of administration. Among the different possibilities of introduction, the oral route is the most familiar mode for the administration for pharmacologically active substances. On a first, and superficial view, this seems logical as the gastrointestinal tract is the natural route for the uptake of all essential substances with exception of oxygen; however, unlike macronutrients potential drug substances are absorbed from the gastrointestinal tract to a variable extent since appropriate biochemical triggers are not stimulated. In the past, we tended to think of the gut as a simple muscular tube that responded strongly to acetylcholine; but we are now aware of many short and longer range afferent/efferent loops innervated by a staggeringly large range of neurotransmitters, some of which are possibly generated by digestion. Over the last two decades, we have appreciated that the gastrointestinal processing of food is a very complex process that is in part managed by the so-called "gut brain axis" which consists of about 30% of all nerve cells (Romijn et al., 2008).

Not every component of a meal is useful and some are harmful. With precise and ultra-sensitive analytical methodology, we are aware of naturally occurring "impurities" in meat and vegetables including platicisers from packaging, sexual hormones in meat or fish and of course, alkaloids in plant seeds which are toxic. Some of these enemies are new, some have been around for millennia. The human gut responded by selection of a defense line consisting of metabolic enzymes and efflux transport systems which can be traced through evolution and differs in species. In addition, the gut is host to symbiotic microbes that also have the capability to degrade xenobiotics (Sousa et al., 2008). As a consequence, the delivery of drug substances via the oral route is more challenging than digestion of burgers and salad. In therapy, the problem is solved by using less convenient routes of administration as for example the direct delivery into the body via injection or infusion. The complexity of oral drug absorption is challenging and despite numerous attempts, a completely robust prediction of the rate and extent of the absorption of drug substances from the human gastrointestinal tract is neither provided by in silico methods nor by recourse to animal models.

Our knowledge of drug absorption and application of these principles to drug design has moved beyond the simpler applications of the pH-partition hypothesis, for example through application of Lipinski rules. The key issue is that the new drug candidates get bigger, with lower solubility and more chirality which generates problems in delivery. In practice, for many promising candidates, the lack of an appropriate mode of delivery is becoming a limiting factor.

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The successful development of a medicine and even the choice of an appropriate drug delivery technology requires a profound knowledge of the interplay of the drug substance with the body from the cellular to the organ level. At the ligand level, the enterocyte based micro-scale mechanisms of cellular uptake (apical transporters), intracellular transport, cellular escape (basolateral transporters), apical efflux transporters and enzymatic first-pass metabolism (International Transporter Consortium et al., 2010) come into play. At the dose level, additional issues such as the interaction of the drug delivery system with the physiology of the gastrointestinal tract become important determinants of rate and extent of absorption. Thus we can contrast the interplay on the cellular level as substance (or substance class) specific, the interplay with the physiology of gastrointestinal transport, fluid balance and media composition is delivery system related.

1.1. The need for Images

An essential basis for the understanding of the complex interplay between oral drug delivery systems and gastrointestinal physiology is the ability to relate deposition of the dosage form to the plasma concentration time profile. The pharmaceutical scientist requires an array of methods that provide information on formulation disposition without influencing the physiological process, commonly termed "non-invasive" imaging modalities. Ideally, such methods should cover the complete fate of the drug molecules contained in the delivery system from ingestion until their appearance in the circulation. This would include the transit of the delivery system through the gastrointestinal organs, the release pattern of the drug molecules contained in the formulation, the fate of the active pharmaceutical ingredient in the gastrointestinal milieu with respect to chemical stability and physical state and, finally, also the route through the gut into the blood or the lymphatic system. Unfortunately, there is at the moment no single technique available that has the capabilities to meet all of these requirements and many methods provide approximations of the probable behavior.

In medical imaging five imaging modalities are at the moment predominant: (1) techniques based on the application of X-rays like radiography, mammography, computed tomography (CT), fluoroscopy and angiography, (2) ultrasound based techniques including B-mode imaging and colour doppler, (3) magnetic resonance tomography (MRT), (4) radionuclide based imaging techniques including scintigraphy, single photon emission computed tomography (SPECT) and positron emission tomography (PET), and (5) endoscopy including endoscopic *in situ* microscopy (Singh et al., 2010) and wireless swallowable camera systems (Sidhu et al., 2006). Other imaging modalities such as impedance tomography (Bayford, 2006) and near infrared imaging (NIR) (Klohs et al., 2008) are evolving. In addition to technologies that provide images in a more or less "classical" sense, there are data measurement and recording techniques which provide cruder maps – for example methods based on the recording of electric activity of organs:electrocardiography (EKG), electroencephalography (EEG) and electrogastrography; and the magnetic activity of organs: magnetocardiography (MCG) and magnetoencephalography (MEG) and finally measurements of mechanical forces inside organs such as gastrointestinal manometry. Other examples of such indirect imaging techniques are swallowable radiotransmitting sensors comparable to the capsule endoscope (Singh et al. 2006) that are capable to record either only pH (Noeller, 1960) and in addition to pH, further parameters including pressure and temperature (Kuo et al., 2008).

Many of these direct or indirect medical imaging modalities have already been applied for the investigation of the fate and behavior of drug delivery systems within the gastrointestinal tract. We include in this paper, a short historical view on the suitability of the different imaging modalities for the investigation of the fate of drug delivery systems in the GI tract but the focus of the review is the presentation of currently mostly used methodologies scintigraphy, magnetic tracking techniques and magnetic resonance imaging and the discussion of their strengths and weaknesses.

1.2. The historical perspective

Gastric and duodenal ulceration were commonly encountered conditions in general surgery and required immediate medical intervention if serious. Measurement of gastrointestinal transit, especially gastric emptying, was therefore a key task in medical physics and radiopharmaceutical investigation clinics (for a review of this subject, see Wilson, 2010). Planar radiography in combination with barium sulfate as a contrast agents was applied as early as 1935 in the determination of gastric emptying times in humans (Van Liere and Sleeth, 1935) since the gut is translucent in X-ray examination. At this very early stage, radiographic imaging was also utilised for the determination of the in vivo disintegration behavior of enteric coated tablets (Bukey and Rhodes, 1935). Since then radiographic studies have been widely used for the investigation of the performance of oral dosage forms, a practice that continued to the beginning of the 1980s (Galeone et al., 1981, 1982). Although radiography provides excellent spatial resolution, its application in pharmaceutical research is severely hampered by the health risks associated with the use of high doses of ionizing radiation (0.16–1.71 mSv, Ogundare et al., 2004). This problem is amplified in gastrointestinal transit studies as typically, a series of images are required. Another disadvantage of the use of contrast agents is the very density of barium sulfate which may alter the characteristics of the dosage forms. As alternatives became available, radiography generally diminished as a choice for pharmaceutical applications.

A further possibility for the in vivo imaging of dosage forms is their direct visualization in the stomach or colon via endoscopy. A first attempt to use endoscopy for the visualization of tablets in the stomach was reported by Steinberg et al. (1965). A successful endoscopic study has been performed by Ehrhardt et al. (1972). They determined the behavior of different pancreatin tablets in the stomach. Although this method provides direct visualization of the dosage form and the surrounding anatomy it has to be regarded as highly invasive. However, interesting new applications might in future be found in the application of the wireless capsule endoscopy technique for biopharmaceutical studies.

First attempts to visualize dosage forms in the gastrointestinal tract using diagnostic ultrasound failed as early as 1965 (Steinberg et al., 1965). Successful localizations of tablets in the stomach using ultrasound were later reported (Maublant et al., 1988; Amitai et al., 1992). The use of ultrasound for the detection of dosage forms in the GI tract is hampered by many difficulties. First, the gastrointestinal tract contains plenty amounts of gas; and gas serves as an efficient reflector for ultrasound waves. Therefore, ultrasound investigations of the colon or the small intestine are very difficult. Secondly, it is impossible to measure proximal and distal gastric regions simultaneously. For these reasons ultrasound is at the current stage of technical development not employed for the determination of the in vivo fate of oral drug delivery systems.

Swallowable radiotransmitting capsules that are capable to measure the luminal pH have also been used for the last 50 years for the determination of gastric emptying of solids (Noeller, 1960; Gröning and Heun, 1984). However, such systems can only serve as a model for non-disintegrating dosage forms.

The breakthrough towards an comprehensive understanding of the fate and behavior of drug delivery systems in the gastroin-

testinal tract based on imaging was achieved when the application of gamma scintigraphy was introduced for these purposes (Casey et al., 1976; Hardy and Wilson, 1981).

1.3. Scintigraphy

In physiological measurement of soft tissues where X-ray techniques had issues of contrast, the development of nuclear medicine technology greatly increased the potential scope of investigations. This was based on two emerging sciences: the development of radiolabelled ligands which could be used to identify and measure the physiological or metabolic activity of tissues and instrumentation which could non-invasively monitor the temporal changes in organ activity to calculate uptake and emptying. It was soon apparent that radionuclide imaging had great potential as a tool in pharmacological and physiological research studies in animals as well as in the clinic (Hardy and Wilson, 1981). In particular, our group and others began to utilize the technique to study the fate of formulations in the gut, lungs and eye as well as formulation influences on parenteral deposition. Early limitations of the technique were due to the range of radiopharmaceuticals available generally based on technetium, iodine and indium chemistry and the liability of the label (see Hardy and Wilson, 1981). Nevertheless, the technology was clearly invaluable in the study of formulation deposition. The scintillation detector used in early studies gave rise to a system based on a photomultiplier array optically coupled to a thallium-doped crystal of sodium iodide, The whole structure was enclosed in lead with removable lead collimators to facilitate focusing gamma rays emission onto the crystal. The optimal isotope in clinical imaging remains the gamma-emitting isotope technetium-99 m (gamma energy = 140 keV) due to the low dosimetry. In addition, for pharmaceutical imaging (formulations), the dose can be greatly reduced compared to that used for a clinical investigation.

Radiopharmaceuticals based on [^{99m}Tc-] technetium chemistry are short-lived ($t_{1/2}$ = 6.03 h) and formulations are generally prepared within 12 h of administration. [^{111}In-] indium is a longer-lived isotope ($t_{1/2}$ = 2.8d, gamma energies 173, 247 keV), facilitating imaging or preparation of the dosage form over several days. The radiation dose from [^{111}In-] indium is higher than that of technetium-99 m but acceptable for oral studies. Iodine radiopharmaceuticals are occasionally used in oral formulations – for example Malagelada et al. (1984) used for covalently labeling cellulose, but due to concern about uptake in the thyroid of labile isotope, the use is uncommon.

1.4. Dual isotope studies

A significant advantage of gamma scintigraphy is that the energies of the two isotopes can be gated in separate energy windows, and dual-channel acquisition enables multiple phases labeled separately with [^{111}In] and [^{99m}Tc] to be followed simultaneously. Overlap of the [^{111}In] energy causes cross-talk (about 20%) into the lower-energy [^{99m}Tc] channel and must be accounted for. In theory, the collimators could also be switched with the use of a higher energy collimator to filter [^{99m}Tc] channel activity but this is impractical for most studies and rarely used. The decay-out approach has been used in our laboratories to measure lung deposition in which the patient breathes a radioactive gas with an extremely short half-life (for example [^{81m}Kr, $t_{1/2}$ = 13 s] while standing in front of the gamma camera (Ashworth et al., 1991; Harnor et al., 1993). Such a technique might also be of use in following swallowed water in the measurement of oesophageal clearance where the tablet is labeled with [^{111}In] or [^{99m}Tc].

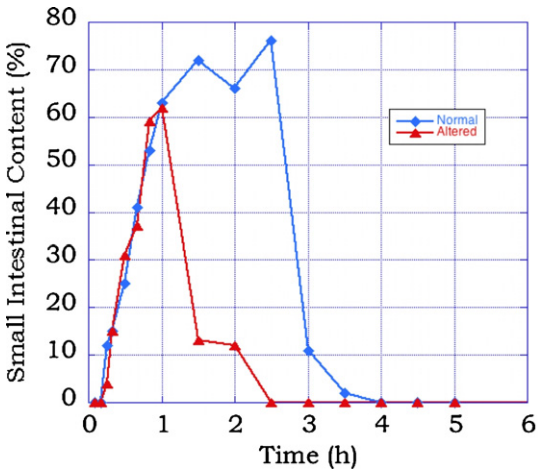

Fig. 1.

1.5. Gastrointestinal transit studies using gamma scintigraphy

Scintigraphic measurements of the gastrointestinal transit of meals become a standardized methodology in the clinic. It proved more relevant than use of radio-opaque markers, which as an 'off-line' measurement was less sensitive (Wilson, 2010). Moreover, the regional measurement of movement of the labeled meal showed previously unrecognized phenomena, for example how conditions such as diarrhoea involved earlier segments of the intestine (Read et al., 1986). Read's group noted that at the end of the small intestinal transit of the meal, the caecum appeared to fill in a linear manner, with approximately 16% of the labeled meal residues entering the colon every hour. The shape of the filling curve mirrored that of gastric emptying curve, and from that a symmetrical bell shaped curve describing small intestinal exposure (SITT) was easily derived. Fig. 1 illustrates a typical example of how the small intestinal transit time may be calculated. McConnell et al. (2008) comment that although the small intestine transit time of dosage forms is almost invariably quoted at 3–4 h, individual transit times vary greatly. Dr. Basit, in the same paper, has commented that serial measurements, of his own gastrointestinal transit have varied over the years, and not in an age-related manner.

For drugs whose absorption is neither limited by solubility or permeability i.e., Case I in the biopharmaceutics classification proposed by Amidon and others, the rate of gastric emptying is the primary variable influencing drug absorption (Amidon et al., 1995). In the pursuit of more effective control of pain, it is a requirement to have as fast an onset of action as is possible; however, it is undesirable to take so many early plasma samples that the haemodynamics of the body may be disturbed. In the interests of the safety of the patient for volunteer, we must be prudent in the number of samples we take. This generally confounds the ability to discriminate a ideal pharmacokinetic sampling regime, as a variable lag time in gastric emptying, and usually prevents accurate prediction of the 'ideal' sampling scheme. It is however possible to take an almost continuous sequence of imaging and from this, to be able to discern small differences in the rate of gastric emptying. Thus if a formulation has a faster gastric dissolution rate, or encompasses a mechanism to aid early exposure to the intestinal tissue, it can be detected by gamma scintigraphy reasonably well.

We previously described the general the performance of a novel formulation of paracetamol which was shown to yield faster gastric emptying rates in both fasted and fed conditions (Kelly et al., 2003). In this study paracetamol (1 g) was administered as either Panadol Actifast® or as a conventional Panadol® formulation in fasted and fed conditions in a four way, within-subject, crossover study. The

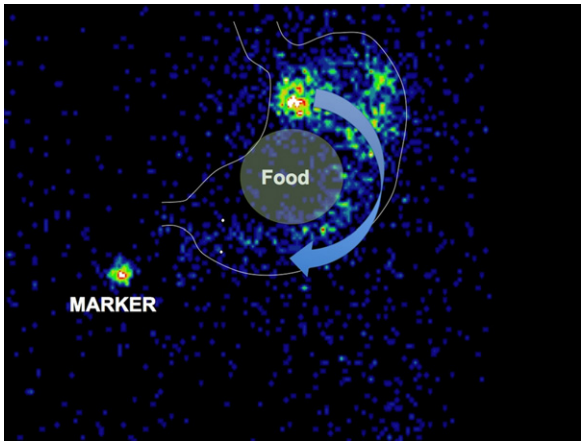

Fig. 2.

tablets were each radiolabelled with 2 MBq technetium DTPA at the time of dosing. 11 of the 12 healthy volunteers completed the study. However, two subjects showed dramatically retarded gastric emptying of the new tablets in the fasted state (T_{50} = 70.3 and 104.6 min) which against an overall mean of 22.4 min could be regarded as atypical. The rate of paracetamol absorption, as expected, reflected the gastric emptying profiles but it was a surprise that the formulation also showed a faster onset in the fed state. It was expected that the key ingredient sodium bicarbonate would be diluted by the gastric contents. An explanation was eventually found from the scintiscans which revealed that dissolution was occurring at the top of the stomach, with the dissolved material moving around the bulk of the food along the Magenstrasse, an interfacial zone created by secretion of fluid around the bulk of the semi-solid food mass (Fig. 2).

In later studies, the same techniques have been used to refine variants of the concept, gamma scintigraphy being shown to be extremely useful as a method of exploring the relationship between in vitro and in vivo performance (Palmer et al., in press).

Scientists at AstraZeneca noted that in the clinical development of gefitinib, a subset of around 18% of the healthy subjects routinely recruited into pharmacokinetic studies showed a different pharmacokinetic profile for the drug compared to the majority of the dosed cohort. The 'abnormal' profile was characterized by a faster elimination and a lower C_{max} resulting in lower systemic exposure and was consistent over long time periods. A study that combined scintigraphy with pharmacokinetic analysis was conducted to examine whether gastrointestinal transit was an important variable (Wilson et al., 2009). Five subjects were selected from the fast excretor group and balanced against seven normal volunteers. The two cohorts were dosed with a 250 mg gefitinib tablet labeled with [^{111}In]-DTPA. Blood samples were taken and it was found that the rapid excreters had faster gastric emptying and faster colon filling approximately halving the small intestinal exposure. These data showed the clear effects of afternoon mass movements in the colon, facilitating earlier emptying of the distal small intestine.

1.6. Tracking of magnets

As an alternative to the application of radioisotopes in human volunteer studies methods that are based on the detection of magnetic material have been developed (Weitschies et al. 2004; Corá et al. in press; Weitschies et al., 2010). The basic idea is to label dosage forms with magnetic material instead of radioisotopes and to use a magnetic sensor system instead of a scintillation camera for the tracking of the magnetically labeled delivery system inside the gastrointestinal tract.

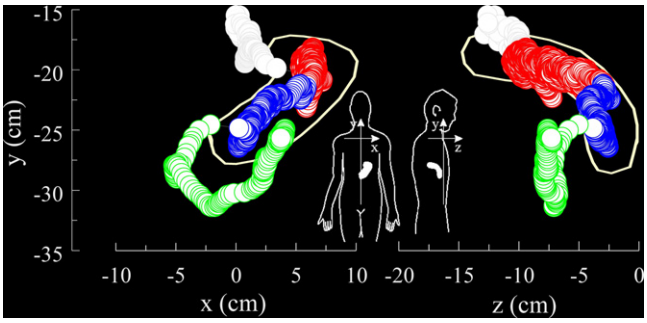

Fig. 3.

In a first approach biomagnetic measurement equipment has been used as detection system (Weitschies et al., 1994) as it is used for the recording of magnetic signals derived from currents generated within the body, mainly magnetoencephalography and magnetocardiography (Schittenhelm, 1990). The basic concept of this magnetic tracking method is to label the dosage from as a permanent magnetic dipole. The dipole field is measured by appropriate magnetic sensor systems. From the recorded data the three-dimensional localization and orientation as well as the strength of the magnetic dipole are reconstructed. This methodology is known as Magnetic Marker Monitoring (MMM) (Weitschies et al., 1994; Corá et al., in press) or GI magnetomarkergraphy (GIMG) (Hu et al., 2000). An example for a localization result is given in Fig. 3.

There are two principle strategies that can be followed. The first strategy is to use only trace amounts of magnetic labeling material in order to preserve the original properties of the dosage form. However, the obtained magnetic dipolar moments are very low. This can be illustrated that after labeling of a tablet with about 5–10 mg of magnetite (black iron oxide, Fe_3O_4) a dipolar moment of about 50 μAm^2 is obtained. Such a magnetically labeled tablet generates in a distance of 10 cm below to abdominal wall a magnetic flux density at the surface of the abdominal wall of less than 10^{-12} T (Weitschies et al., 2005a,b). This is more than 6 orders of magnitude less than the earth's magnetic field, which is about 5×10^{-5} T. In order to detect such a weak signal extremely sensitive magnetic sensor systems have to be used. Furthermore, the earth's magnetic field as well as magnetic noise as it is generated by electrical currents or elevators has to be reduced.

The tracking of dosage forms that are labeled as a magnetic dipole by the incorporation of less than 50 mg of ferromagnetic iron oxides and subsequent magnetization requires the use of biomagnetic measurement systems. Biomagnetic instrumentation is based on Superconducting Quantum Interference Devices (SQUIDs) as the most sensitive magnetic sensors available, which provide a noise level of only a few fT/Sqrt (Hz). SQUIDs are usually operated in Dewar flasks filled with liquid Helium. Modern biomagnetic measurement devices are equipped with up to several hundred SQUIDs in various arrangements, which simultaneously record the development of magnetic field components at multiple locations with a temporal resolution of up to 20 kHz (Drung, 1995). In order to reduce environmental magnetic disturbance and the influence of the earth's magnetic field, biomagnetic measurement devices usually are operated in so-called magnetically shielded rooms, where magnetic perturbations are damped by a factor of typically 30–100,000 depending on frequency and the quality of the shielding (Bork et al., 2001).

During the in vivo examination the magnetic dipolar field of the ingested magnetically labeled delivery system is continuously measured at different, fixed positions above thorax or abdomen. The recorded signal can directly be used for the localization proce-

dure, a correction for attenuation by tissues in not required, as the magnetic dipolar field generated by the delivery system penetrates human tissue without distortions. In order to reconstruct location, orientation, and strength of the dipole the field of a magnetic dipole is fitted to the measured magnetic field components as described in detail elsewhere (Weitschies et al., 2005a,b). The overall accuracy of the localization procedure depends on several parameters like the sensitivity, arrangement and number of sensors, the strength of the magnetic dipolar moment and the level of magnetic noise. For a region of interest within 15 cm below a planar arrangement of 56 SQUID channels covering an area of 21 cm diameter, the localization accuracy in all three dimensions was found to be better than 1 mm (Weitschies et al., 2001a,b, 2010).

Magnetic labeling of solid dosage forms for MMM is achieved by the incorporation of small amounts of the black ferrimagnetic iron oxide magnetite (Fe_3O_4) as it is used as a colorant for food and pharmaceutical products (E172, 21CFR73.1200, 21CFR73.200). Alternatively, the red iron oxide maghemite (γ-Fe_2O_3) can also be used. Both ferrimagnetic iron oxides are not soluble in gastrointestinal fluids and are not absorbed from the gastrointestinal tract.

In order to generate a dipolar magnetic moment the magnetic orientations of the individual magnetic particles in the dosage form have to be aligned by magnetization using strong bar magnets or electro magnets prior to administration. Any magnetic particle loss or magnetic particle reorientation results in a decrease of the net magnetic moment. This can be used for the determination of dosage from disintegration or drug release patterns as long as the loss of magnetization is correlated with the release process. The correlation function can be investigated in dissolution experiments using modified dissolution test appa-

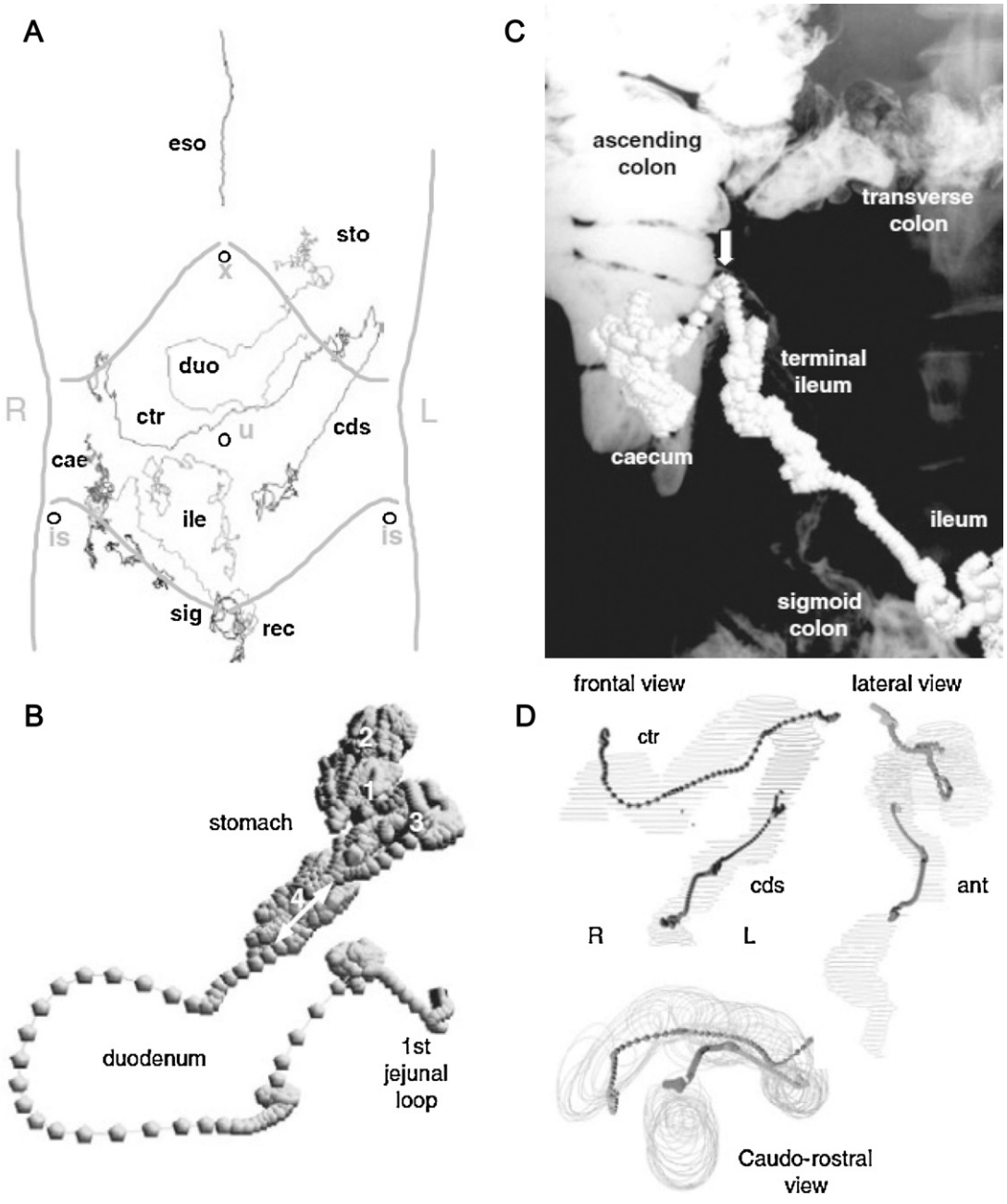

Fig. 4.

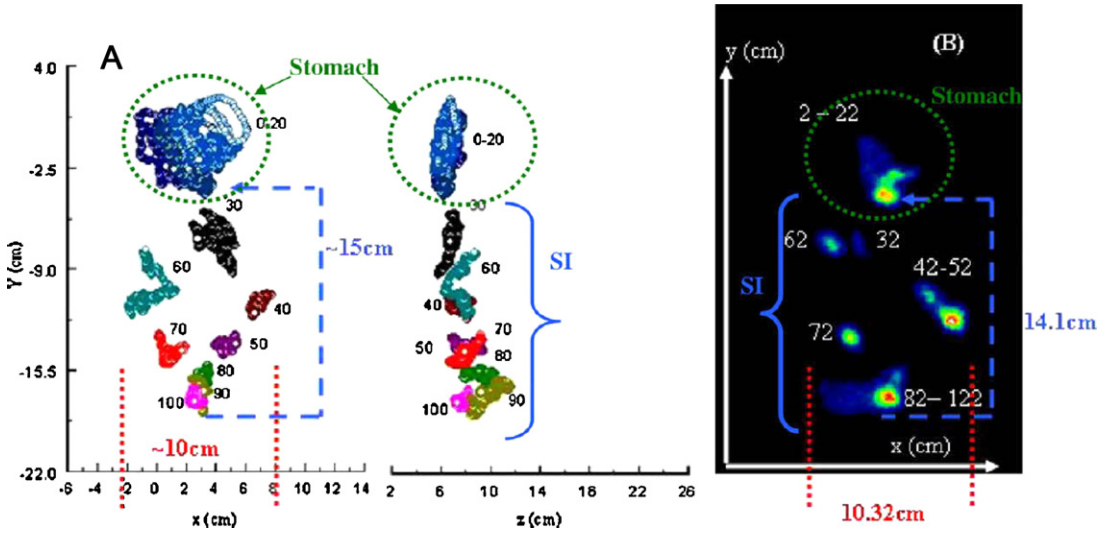

Fig. 5.

ratuses with integrated magnetic field sensors (Weitschies et al., 2001a,b).

The quantity of iron oxide required for labeling depends on the sensitivity of the measurement device and the aims of the study. Successful transit studies of single alginate particles with a size of 1–2 mm have been performed with very small amounts of about 0.1–0.2 mg of magnetite (Anschütz et al., 2009). For transit studies of tablets or capsules amounts of 1–5 mg iron oxide have been typically applied. In case a high magnetic contamination caused by other instruments is likely during the investigation, e.g., when catheters with pressure sensors are additionally applied for simultaneous manometry amounts of up to 10 mg might be favourable (Osmanoglou et al., 2004). The incorporation of the iron oxide can be achieved in different ways depending on the product and the accessibility of the production process. Tablets can be labeled by adding the iron oxide to the powder mixture or the granulate that is used for tabletting. Alternatively, tablets can also be labeled by filling of a suitable amount of iron oxide into a bore hole. 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 by magnesium stearate (Weitschies et al., 2010).

The second strategy that can be followed is the use of a strong magnet as detectable marker. Typically rare earth magnets are used due to their very high magnetic moments. These magnets are covered with insoluble material (mostly plastics) in order to avoid dissolution inside the gastrointestinal tract. The use of strong magnets as marker has the advantage that the magnetic dipolar field is several orders of magnitude higher than in case of using only trace amounts of iron oxides. Such strong dipolar fields can be detected with magnetic sensors like fluxgate sensors or magneto resistive sensors that are much cheaper and much easier to operate than SQUIDs. Furthermore, such systems do not require shielding from external magnetic fields, they can be operated in regular unshielded environment. Several different not SQUID-based measurement devices for the detection of the field of ingested magnets have been reported during the last ten years (Andrä et al., 2000; Stathopoulos et al., 2005; Hocke et al., 2009; Goodman et al., 2010). An example for results obtained with these modalities is given in Fig. 4. Goodman and co-workers performed even a comparison between scintigraphy and magnetic tracking (Fig. 5). In order to be able t o detect the in vivo disintegration behavior of solid dosage forms they used high amounts (about 1 g) of black iron oxide for labeling.

1.7. Alternating current biosuscceptometry (ACB)

As an alternative to the detection of the field generated by a solid dosage form that is labeled as a magnetic dipole the presence of magnetic material in the gastrointestinal tract can also be detected using a setup of detection and excitation coils. This was first demonstrated by Benmair and co-workers. They added magnesium ferrite to a test meal and investigated the rate of gastric emptying using such a coil system (Benmair et al. 1977). Baffa et al. (1995) reported the development of an alternating current biosusceptometer for the investigation of transit times of ferrimagnetic tracers throughout the gastrointestinal tract. Since that time the method was developed also for the investigation of the behavior of different dosage forms like fast disintegrating tablets (Corá et al., 2003) and enteric-coated tablets (Corá et al., 2006) as well as multiparticulate systems like pellet formulations (Miranda et al., 2010). The data obtained by ACB can also be transformed into images as it is illustrated in Fig. 6 (Corá et al., 2005).

ACB is based on the use of ferrites with high magnetic susceptibility like $MgFe_2O_3$ as signal generators. The material does not need to be premagnetized, as it is continuously magnetized by an alternating field with a frequency of 10 kHz and a magnetic field of 20 G generated by the excitation coils. The flux variation generated between excitation and detection coils is measured. The magnetic signals detected by the ACB sensors depend on the surface area of the detection coil, number of turns, rate of change of the magnetic flux (i.e., applied field), amount of ferromagnetic material and distance among the sensors. Typically, at least 1 g of ferromagnetic material is required (Corá et al., in press).

1.8. Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) is a noninvasive imaging technique that is based on the principle of nuclear magnetic resonance (NMR). In clinical practice, MRI is used to distinguish pathologic tissue from normal tissue. MRI provides very high spatial resolution in combination with very good contrast resolution, which is achieved by a complex library of available pulse sequences.

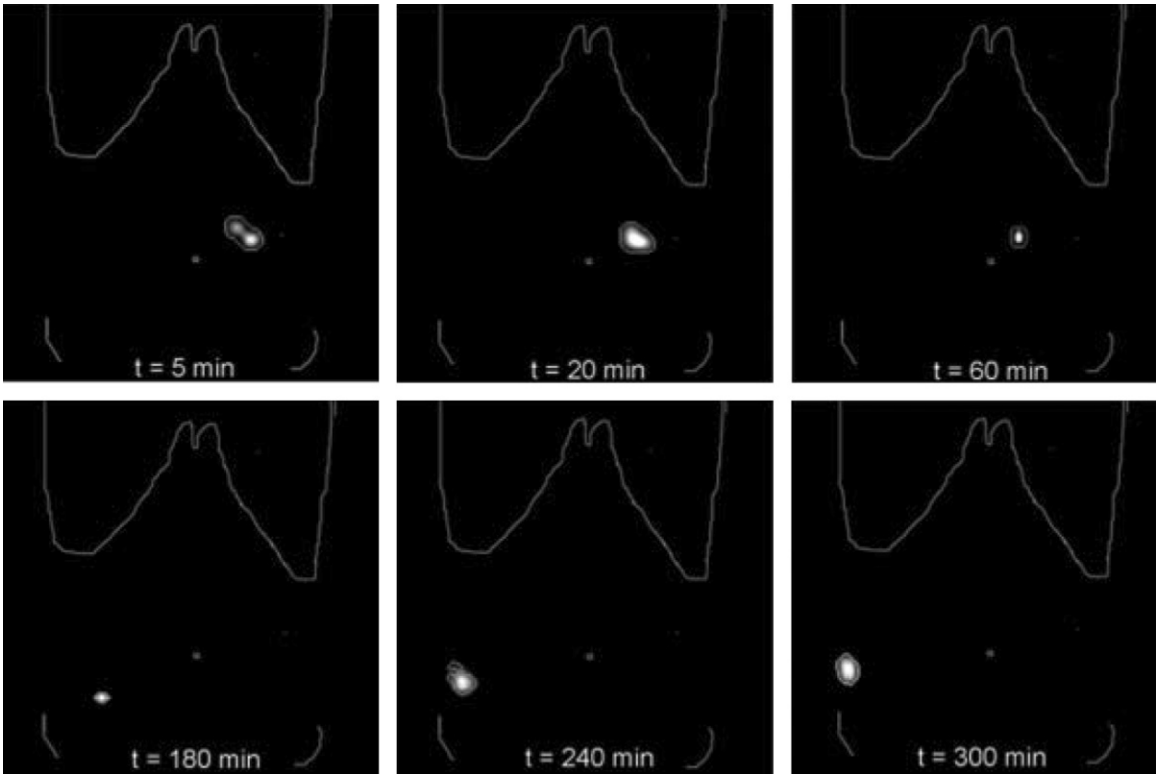

Fig. 6.

Since the first report on the application of MRI for the monitoring of a the distribution of an oil based formulation in the human gastrointestinal tract (Wilson et al., 1997) a number of studies on the transit behavior and distribution of drug delivery systems using MRI have been published (Faas et al., 2001, 2002; Steingoetter et al., 2003a,b, 2005; Kagan et al., 2006; Knörgen et al., 2010).

Although MRI has many advantages like the avoidance of ionization radiation, excellent anatomical imaging and high scan volumes its application for pharmaceutical research in the gastrointestinal tract is also hampered by several problems. Main issues are the acquisition time and the signal to noise ratio. A typical fast scan requires roughly one second. This results for a typical slice thickness of 5–7 mm even for the visualization of the stomach in an acquisition time of at least 20 s (i.e., 20 slices). During that time motions have to be avoided. This is usually achieved by breath holding. Motility derived motions can only be suppressed using anticholinergic drugs, however this influences gastrointestinal transport heavily and has to be regarded as being invasive. Therefore, motion derived artifacts are a serious problem limiting at most the imaging of the small bowel as the most flexible gastrointestinal organ with the highest motility. Furthermore, due to required acquisition times of about 20–90 s per abdominal scan the detection of gastrointestinal transport events in real time is impossible.

Fast imaging sequences provide a low signal to noise ratio. Thereby it becomes very demanding to clearly distinguish in MRI images dosage forms from other material like food particles or even air bubbles. In order to solve this problem different strategies can be followed. Very common is the use of either paramagnetic or ferrimagnetic contrast agents for the labeling of the delivery system (Faas et al., 2001, 2002; Steingoetter et al., 2003a,b; Kagan et al., 2006; Knörgen et al., 2010). In particular the ferromagnetic iron oxides may be helpful as they provide a strong disturbance (artifact) in the signal that can be identified. Using this strategy several small pellets that were labeled with 1% black iron oxide (magnetite) could recently for the first time be quantitatively identified in the stomach (Knörgen et al., 2010). For larger objects a significant combination of materials with very different contrast properties can also be used (Schiller et al., 2005).

In Fig. 7 the use of MRI for the determination of the distribution pattern of a liposomal encapsulated paramagnetic contrast agent as a model for a drug delivery system is shown.

1.9. Strengths and weaknesses

A comparison of characteristic parameters of the different imaging modalities used for the monitoring of dosage forms in the gastrointestinal tract is given in Table 1. Scintigraphy and methods based on magnetic tracking techniques require intrinsically the inclusion of detectable labels into the dosage form. The detected signal is always the label, never the drug substance contained. Imaging of the behavior of labeled drug substances without changing their properties is only possible using detectable radioisotopes with sufficiently high emitted energy. In principle suitable radioisotopes are the positron emitting radioisotopes carbon-11 (half-life about 20 min), nitrogen-13 (half-life about 10 min), oxygen-15 (half-life about 2 min), and fluorine-18 (half-life about 110 min). However, the short half-lives of these positron-emitting radioisotopes are prohibitive with respect to the required chemical synthesis of the radio labeled drug substance, the manufacturing of the dosage form and the transit times within the GI tract.

In case of magnetic dipole tracking methods like MMM that are based on the incorporation of ferromagnetic particles the detected signal is a cooperative function of an ensemble of particles with aligned magnetization. Any loss of alignment of particles e.g., by disintegration of the dosage form, erosion (i.e., release of magnetic

Table 1
Characteristics of methods used for the imaging of delivery systems in the gastrointestinal tract.

Factor	Scintigraphy	MMM		ACB	MRI
		High sensitivity	Low sensitivity		
Temporal resolution	>1 s[a]	Real time	Real time	Real time	>1 min[b]
Spatial resolution	mm	mm	mm	cm	mm[b]
Dimensions	2D	3D	3D	2D	3D (cross sections)
Availability	High	Very low	Low	Extremely low	Very high
Ease of performance	Specialized	Very specialized	Easy	Specialized	Easy
Number of objects to be imaged	No restriction	One	One	No restriction	No restriction
Number of objects than can be identified	Two (dual labeling)	One	One	One	–[c]
Size of objects	No restriction	Limitation only by required magnetic moment	Limitation only by required magnetic moment	Limitation only by required magnetic moment	–[c]
Types of dosage forms that can be monitored	No restriction	Only solids	Only solids	Solids and suspensions	No restriction
Capability for quantification of dosage form disintegration	Good	Very good	Limited to model dosage forms	Limited to model dosage forms	Poor
Capability for determination of in vivo drug release profiles (extended release)	Difficult but possible	Very good for erosion based systems	No	No	?[d]
Kind and required amount of labeling material	99m-Tc, 111-In: trace amounts	Black iron oxide: ≥0.1 mg	Black iron oxide: ≥500 mg; high permeability magnets: ≥50 mg	Ferric oxides: ≥1000 mg	Labeling material not intrinsically required;Black iron oxide: μg
Availability of labeling material in pharmaceutical quality (IMPD)	Yes: 99 m-Tc, 111-In; No: Sm	Yes	Yes	No	Yes
Complexity of labeling procedure for delivery systems	Very high (unstable isotopes, dedicated equipment required)	Low (stable material, no dedicated equipment necessary)	Not applicable	Not applicable	Low if required at all (stable material, no dedicated equipment necessary)
Radiation exposure	Yes	No	No	No	No
Expense	High	High	Low	Low	Low

[a] Depends on several parameters like radiation dose and emitted energy.
[b] Depends on several parameters like scanned volume and imaging sequences.
[c] Depends on several parameters like size of objects, kind of label, organ to be imaged.
[d] Not demonstrated yet.

particles) or even swelling results in a decrease of the measured signal. Released particles are not "visible". The spreading of released material over the GI tract as it can be seen in scintigraphy using non-absorbable radiolabels cannot be seen in MMM. This is also the reason why only solid or at least semi-solid dosage forms with sufficiently high viscosity can be monitored by MMM. Otherwise the net magnetization is due to rotational diffusion of the magnetized particles not stable enough for the time of the magnetic measurements. On the other hand, as released magnetic particles do not disturb the measured signal MMM is very strong in the detection of disintegration, erosion or even swelling what can be used for the determination of in vivo release profiles as shown in Fig. 8.

In contrast to radio-emitting isotopes magnetic labeling materials like iron oxides or gadolinium chelates are very stable. Magnetic labeling of dosage form can be performed in advance of the imaging study without any time pressure. Furthermore, for magnetic labeling regular production equipment can be used, while radio-labeling requires dedicated environment.

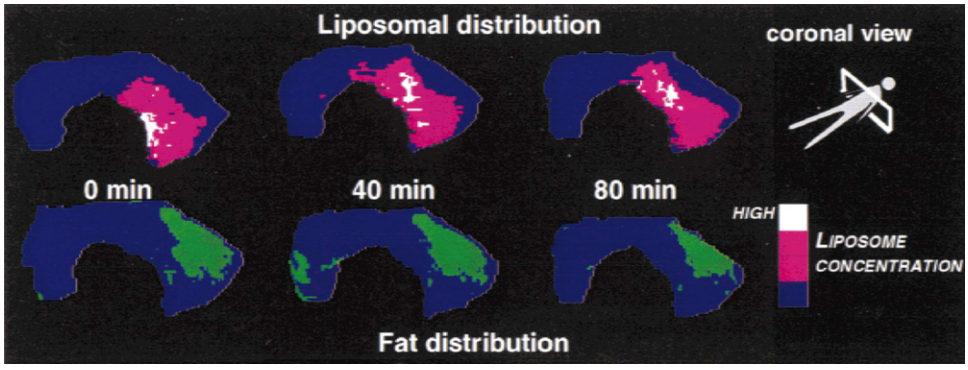

Fig. 7.

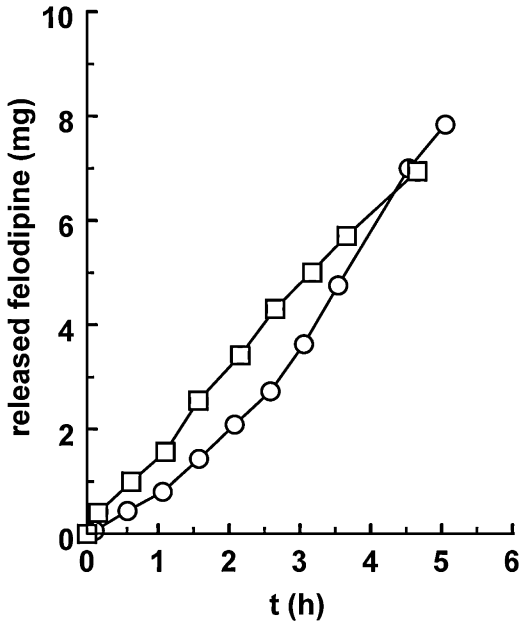

Fig. 8.

Methods with low sensitivity like AC biosusceptometry and magnetic dipole tracking without using biomagnetic sensors require such high amounts of physiologically acceptable labeling material like iron oxides, that these methods cannot be applied for the labeling of commercial drug delivery systems. Accordingly these methods are restricted to the investigation of the transit behavior of the magnetic dipole that can either be a model for a drug delivery system (Corá et al., 2003; Goodman et al., 2010; Laulicht et al., 2010) or serve as a medical device to study the physiology of intestinal transport (Andrä et al., 2005; Hocke et al., 2009; Hiroz et al., 2009). These systems can also be applied for pharmacokinetic studies with regard to the investigation of absorption sites of drug substances or release characteristics of formulation principles like for example enteric coatings (Corá et al., 2006). A very promising combination might be seen in magnetically labeled drug delivery systems with programmable or remote switchable drug release. Such systems might be used as tools for the investigation of drug absorption sites and a fast verification of the suitability of modified release profiles. Ideally, such systems might combine magnetic tracking, remote drug delivery and recording of parameters like pH and pressure.

Magnetic tracking methods that do not require magnetic shielding can be operated in regular clinical environment. Therefore, they seem ideally suitable for the investigation of the transit behavior of formulation principles in different populations (for example the elderly) and patients (for example diabetic patients). The easy accessibility in combination with the very low health risks due to the avoidance of radiation or external fields makes such magnetic tracking methods also suitable as a tool for medical imaging in children (Stathopoulos et al., 2005).

A further strength of MMM and related methods is the very high temporal and spatial resolution that allows the determination of gastrointestinal transport in real time in all three dimensions. Thereby, velocity profiles can be calculated (Weitschies et al., 2005a,b) and fast transport events like duodenal passage can be monitored (Weitschies et al., 1999). Furthermore, the analysis of perpendicular movements of the dipole proved very helpful for the determination of motility patterns (Hocke et al., 2009).

A major disadvantage of the imaging methods based on the measurement of dipolar magnetic fields is their limitation to the detection of one single dipole. All attempts to develop methodologies that achieve a reliable detection of two or more dipoles simultaneously failed so long. Thereby, at the moment MMM and related methods cannot be used to investigate an ensemble of particles like it is useful for multiple unit dosage forms. In case of MMM the very high costs of biomagnetic measurement equipment and the low number of available devices hampers the spreading of the methodology.

ACB systems have the advantage that they are robust, easy to construct, do not need to operate in magnetically shielded rooms, and allow for simplification of electronic instrumentation. Due to the high data acquisition frequency of 10 kHz the system allows real time measurements and accordingly the determination of frequency patterns of gastrointestinal motility. Furthermore, ACB can be applied for single unit and multiple unit dosage forms. The method allows for the detection of the disintegration of dosage forms as well as for the correlation of magnetic disintegration data with pharmacokinetic parameters derived from simultaneous blood sampling (pharmacomagnetography) (Corá et al., in press). A major disadvantage is the requirement of high amounts (at least 500 mg) of ferrimagnetic material like magnesium ferrite that is currently not available in pharmaceutical quality.

MRI provides excellent anatomical imaging. It offers the unique possibility to determine the water distribution quantitatively within gastrointestinal organs without the need for contrast agents (Schiller et al. 2010; Hoad et al., 2005; Marciani et al., 2010). At the current stage of development it is very suitable for the detection of large single delivery systems in the stomach and the colon when they are labeled in a way that they can be clearly identified (see for example Kagan et al., 2006). Recent work shows that a reliable detection of delivery systems in the stomach can also be achieved for a number of small objects that are labeled with ferrimagnetic iron oxide (Knörgen et al., 2010). However, dynamic imaging of the progression of delivery systems through the gastrointestinal tract remains an unsolved problem in MRI.

Scintigraphy is probably regarded as the gold standard with regard to the non-invasive imaging of dosage forms in the clinic. It has the advantage of being able to follow the dispersion of a formulation when applied to the eye, administered into the lungs and formulated into an oral dose in almost any physical form. The low dosimetry associated with [^{99m}Tc-] technetium and [^{111}In-] indium typically permits up to a 4 way crossover in a pharmacokinetic study. The use of dual isotopes allows the simultaneous study of multiple phases; for example, a dosage form and a meal (Washington et al., 1990), or two formulations swallowed together (Davis et al., 1984), or different parts of the same labeled formulation (Watts et al., 1992). In addition, nuclear medical departments are generally based on gamma scintigraphy for physiological measurements and therefore the instrumentation is widely available.

The negative issues associated with scintigraphy include radiation exposure which is unacceptable for children and mothers-to-be, high atomic weights associated with the radionuclide and thus unlikely to be a component of drug molecule, and the short half life is associated with gamma emitting isotopes of carbon, nitrogen and oxygen. This necessitates the production of the radiopharmaceuticals for positron emission tomography close to the point of administration. Complex formulations which require significant handling might expose formulators to high levels of radioactivity and in this situation, and 'cold' precursors such as the oxides of samarium or erbium are used. These are irradiated in a nuclear reactor to generate the gamma-emitting radiopharmaceutical *in situ*, e.g., [^{152}Sm] + $n \Rightarrow$ [^{153}Sm] and [^{170}Er] + $n \Rightarrow$ [^{171}Er](Digenis et al., 1991; Watts et al., 1994). The studies are generally restricted to incorporation of the powdered oxide in the formulation. The oxides are not available in pharmaceutical quality. The number of available sites for this kind of work in

the UK has decreased sharply in recent years; however, there has been a great increase in the interest in radiolabelled ligands that are suitable for PET. This innovation has however had little impact on conventional pharmacoscintigraphic studies.

The comparison shows that the choice of a suitable method for the imaging of drug delivery systems in the gastrointestinal tract depends on several factors. There is not one ideal method that fits for all tasks and systems.

References

Amidon, G.L., Lennernäs, H., Shah, V., Crison, J.R., 1995. A Theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. 12, 413–420.

Amitai, Y., Silver, B., Leikin, J.B., Frischer, H., 1992. Visualization of ingested medications in the stomach by ultrasound. Am. J. Emerg. Med. 10, 18–23.

Andrä, W., Danan, H., Eitner, K., Hocke, M., Kramer, H.H., Parusel, H., Saupe, P., Werner, C., Bellemann, M.E., 2005. A novel magnetic method for examination of bowel motility. Med. Phys. 32, 2942–2944.

Andrä, W., Danan, H., Kirmsse, W., Kramer, H.H., Saupe, P., Schmieg, R., Bellemann, M.E., 2000. A novel method for real-time magnetic marker monitoring in the gastrointestinal tract. Phys. Med. Biol. 45, 3081–3093.

Anschütz, M., Garbacz, G., Kosch, O., Donath, F., Wiedmann, J., Hoeckh, W., Trahms, L., Schug, B., Weitschies, W., Blume, H., 2009. Characterization of the behavior of alginate-based microcapsules in vitro and in vivo. Int. J. Clin. Pharmacol. Ther. 47, 556–563.

Ashworth, H.L., Wilson, C.G., Sims, E.E., Wotton, P., Hardy, J.G., 1991. Delivery of propellant soluble drug from a metered dose inhaler. Thorax 46, 245–247.

Baffa, O., Oliveira, R.B., Miranda, J.R.A., Troncon, L.E.A., 1995. Analysis and development of an AC Biosusceptometer for orocaecal transit time measurements. Med. Biol. Eng. Comput. 33, 353–357.

Bayford, R.H., 2006. Bioimpedance tomography (electrical impedance tomography). Annu. Rev. Biomed. Eng. 8, 63–91.

Bork, J., Hahlbohm, H.D., Klein, R., Schnabel, A., 2001. The 8-layered magnetically shielded room of the PTB: Design and construction. In: Nenonen, J., Ilmoniemi, R.J., Katila, T. (Eds.), In Biomag 2000, Proc. 12th Int. Conf. on Biomagnetism. Helsinki Univ. of Technology, Espoo, Finland, pp. 970–973.

Bukey, F.S., Rhodes, P., 1935. A comparative study of enteric coatings. J. Pharm. Sci. 24, 567–570.

Casey, D.L., Beihn, R.M., Digenis, G.A., Shabhu, M.B., 1976. Method for monitoring hard gelatin capsule disintegration times in humans using external scintigraphy. J. Pharm. Sci. 65, 1412–1413.

Corá, L.A., Américo, M.F., Oliveira, R.B., Baffa, O., Moraes, R., Romeiro, F.G., Miranda, J.R., 2003. Disintegration of magnetic tablets in human stomach evaluated by alternate current biosusceptometry. Eur. J. Pharm. Biopharm. 56, 413–420.

Corá, L.A., Américo, M.F., Oliveira, R.B., Serra, C.H., Baffa, O., Evangelista, R.C., Oliveira, G.F., Miranda, J.R. Biomagnetic methods: technologies applied to pharmaceutical research. Pharm. Res., in press.

Corá, L.A., Andreis, U., Romeiro, F.G., Américo, M.F., Oliveira, R.B., Baffa, O., Miranda, J.R., 2005. Magnetic images of the disintegration process of tablets in the human stomach by ac biosusceptometry. Phys. Med. Biol. 50, 5523–5534.

Corá, L.A., Romeiro, F.G., Paixão, F.C., Américo, M.F., Oliveira, R.B., Baffa, O., Miranda, J.R., 2006. Enteric coated magnetic HPMC capsules evaluated in human gastrointestinal tract by AC biosusceptometry. Pharm. Res. 23, 1809–1816.

Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R., Wilson, C.G., 1984. A comparative study of gastrointestinal transit of a pellet and tablet formulation. Int. J. Pharm. 21, 117–167.

Digenis, G.A., Sandefer, E., Beihn, R.M., Parr, A.F., 1991. Dual-isotope imaging of neutron-activated Erbium-171 and Samarium-153 and the in vivo evaluation of a dual-labeled bilayer tablet by gamma scintigraphy. Pharm. Res. 8, 1335–1340.

Drung, D., 1995. The PTB 83-SQUID System for biomagnetic applications in a clinic. IEEE Trans. Appl. Supercond. 5, 2112–2117.

Ehrhardt, L., Hartmann, V., Patt, L., 1972. Vergleichende Untersuchung der Enzymaktivität einiger Pankreatinpräparate. Dtsch. Apoth. Ztg. 112, 2005–2009.

Faas, H., Schwizer, W., Feinle, C., Lengsfeld, H., de Smidt, C., Boesiger, P., Fried, M., Rades, T., 2001. Monitoring the intragastric distribution of a colloidal drug carrier model by magnetic resonance imaging. Pharm. Res. 18, 460–466.

Faas, H., Steingoetter, A., Feinle, C., Rades, T., Lengsfeld, H., Boesiger, P., Fried, M., Schwizer, W., 2002. Effects of meal consistency and ingested fluid volume on the intragastric distribution of a drug model in humans—a magnetic resonance imaging study. Aliment. Pharmacol. Ther. 16, 217–224.

Galeone, M., Nizzola, L., Cacioli, D., Moise, G., 1981. In-vivo demonstration of delivery mechanisms from sustained release pellets. Curr. Ther. Res. 29, 217–234.

Galeone, M., Nizzola, L., Cacioli, D., Moise, G., 1982. In-vivo demonstration of delivery mechanisms from diversified controlled-release preparations. Curr. Ther. Res. 31, 456–466.

Goodman, K., Hodges, L.A., Stevens, H.N.E., Weitschies, W., Wilson, C.G., 2010. Assessing gastrointestinal motility and disintegration profiles of magnetic tablets by a novel magnetic imaging device and gamma scintigraphy. Eur. J. Pharm. Biopharm. 74, 84–92.

Gröning, R., Heun, G., 1984. Oral dosage forms with controlled gastrointestinal transit. Drug Dev. Ind. Pharm. 10, 527–539.

Hardy, J.G., Wilson, C.G., 1981. Radionuclide imaging in pharmaceutical, physiological and pharmacological research. Clin. Phys. Physiol. Meas. 2, 71–121.

Harnor, K.J., Perkins, A.C., Wastie, M.L., Wilson, C.G., Sims, E.E., Feely, L.C., Farr, S.J., 1993. Effect of vapour pressure on the deposition pattern from solution phase metered dose inhalers. Int. J. Pharm. 95, 111–116.

Hiroz, P., Schlageter, V., Givel, J.C., Kucera, P., 2009. Colonic movements in healthy subjects as monitored by a magnet tracking system. Neurogastroenterol. Motil. 21, 838–857.

Hoad, C.L., Marciani, L., Foley, S., Totman, J.J., Wright, J., Bush, D., Cox, E.F., Campbell, E., Spiller, R.C., Gowland, P.A., 2005. Non-invasive quantification of small bowel water content by MRI: a validation study. Phys. Med. Biol. 52, 6909–6922.

Hocke, M., Schöne, U., Richert, H., Görnert, P., Keller, J., Layer, P., Stallmach, A., 2009. Every slow wave impulse is associated with motor activity of the human stomach. Am. J. Physiol. Gastrointest. Liver Physiol. 296, G709–G716.

Hu, Z., Mawatari, S., Shibata, N., Takada, K., Yoshikawa, H., Arakawa, A., Yosida, Y., 2000. Application of a biomagnetic measurement system (BMS) to the evaluation of gastrointestinal transit of intestinal pressure-controlled colon delivery capsules (PCDCs) in human subjects. Pharm. Res. 17, 160–167.

International Transporter Consortium, Giacomini, K.M., Huang, S.M., Tweedie, D.J., Benet, L.Z., Brouwer, K.L., Chu, X., Dahlin, A., Evers, R., Fischer, V., Hillgren, K.M., Hoffmaster, K.A., Ishikawa, T., Keppler, D., Kim, R.B., Lee, C.A., Niemi, M., Polli, J.W., Sugiyama, Y., Swaan, P.W., Ware, J.A., Wright, S.H., Yee, S.W., Zamek-Gliszczynski, M.J., Zhang, L., 2010. Membrane transporters in drug development. Nat. Rev. Drug Discov. 9, 215–236.

Kagan, L., Lapidot, N., Afargan, M., Kirmayer, D., Moor, E., Mardor, Y., Friedman, M., Hoffman, A., 2006. Gastroretentive accordion pill: enhancement of riboflavin bioavailability in humans. J. Control. Release 113, 208–215.

Kelly, K., O'Mahony, B., Lindsay, B., Jones, T., Grattan, T.J., Rostami-Hodjegan, A., Stevens, H.N.E., Wilson, C.G., 2003. Comparison of the rates of disintegration, gastric emptying and drug absorption, following administration of a new and a conventional paracetamol formulation, using gamma scintigraphy. Pharm. Res. 20, 1668–1673.

Klohs, J., Wunder, A., Licha, K., 2008. Near-infrared fluorescent probes for imaging vascular pathophysiology. Basic Res. Cardiol. 103, 144–151.

Knörgen, M., Spielmann, R.P., Abdalla, A., Metz, H., Mäder, K., 2010. Non-invasive MRI detection of individual pellets in the human stomach. Eur. J. Pharm. Biopharm. 74, 120–125.

Kuo, B., McCallum, R.W., Koch, K.L., Sitrin, M.D., Wo, J.M., Chey, W.D., Hasler, W.L., Lackner, J.M., Katz, L.A., Semler, J.R., Wilding, G.E., Parkman, H.P., 2008. Comparison of gastric emptying of a nondigestible capsule to a radio-labelled meal in healthy and gastroparetic subjects. Aliment. Pharmacol. Ther. 27, 186–196.

Laulicht, B., Tripathi, A., Schlageter, V., Kucera, P., Mathiowitz, E., 2010. Understanding gastric forces calculated from high-resolution pill tracking. Proc. Natl. Acad. Sci. U.S.A. 107, 8201–8206.

Malagelada, J.R., Robertson, J.S., Brown, M.L., Remington, M., Duenes, J.A., Thomforde, G.M., Carryer, P.W., 1984. Intestinal transit of solid and liquid components of a meal in health. Gastroenterology 87, 1255–1263.

Marciani, L., Cox, E.F., Hoad, C.L., Pritchard, S., Totman, J.J., Foley, S., Mistry, A., Evans, S., Gowland, P.A., Spiller, R.C., 2010. Postprandial changes in small bowel water content in healthy subjects and patients with irritable bowel syndrome. Gastroenterology 138, 469–477.

Maublant, J.C., Hassine, H., Sournac, M., Dapogny, M., Veyre, A., Aiache, J.M., Goutay, E., 1988. Ultrasonic visualization of tablets in the gastrointestinal tract. J. Nucl. Med. 29, 129.

McConnell, E., Fadda, H.M., Basit, A.W., 2008. Gut instincts: explorations in intestinal physiology and drug delivery. Int. J. Pharm. 364, 213–226.

Miranda, J.R., Corá, L.A., Américo, M.F., Romeiro, F.G., 2010. AC biosusceptometry technique to evaluate the gastrointestinal transit of pellets under influence of prandial state. J. Pharm. Sci. 99, 317–324.

Noeller, H.G., 1960. The endoradio sound for electrical pH measurement in the stomach and its clinical significance. Dtsch. Med. Wochenschr. 85, 1707–1713.

Ogundare, F.O., Uche, C.Z., Balogun, F.A., 2004. Radiological parameters and radiation doses of patients undergoing abdomen, pelvis and lumbar spine X-ray examinations in three Nigerian hospitals. Br. J. Radiol. 77, 934–940.

Osmanoglou, E., van der Voort, I.R., Fach, K., Kosch, O., Bach, D., Hartmann, V., Strenzke, A., Weitschies, W., Wiedenmann, B., Trahms, L., Mönnikes, H., 2004. Oesophageal transport of solid dosage forms depends on body position, swallowing volume, and pharyngeal propulsion velocity. Neurogastroenterol. Motil. 16, 547–556.

Palmer H., Wilson C.G., Clarke C P., Starkey Y L., Clarke G D. Comparison of a novel fast dissolving acetaminophen tablet formulation (FD-APAP) and standard acetaminophen tablets using gamma scintigraphy and pharmacokinetic studies. Drug Dev. Ind. Pharm., in press.

Read, N.W., Al-Janabi, M.N., Holgate, A.M., Barber, D.C., Edwards, C.A., 1986. Simultaneous measurement of gastric emptying Small bowel residence and colonic filling of a solid meal by the use of the gamma camera. Gut 27, 300–308.

Romijn, J.A., Corssmit, E.P., Havekes, L.M., Pijl, H., 2008. Gut–brain axis. Curr. Opin. Clin. Nutr. Metab. Care 11, 518–521.

Schiller, C., Fröhlich, C.P., Giessmann, T., Siegmund, W., Mönnikes, H., Hosten, N., Weitschies, W., 2005. Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging. Aliment. Pharmacol. Ther. 22, 971–979.

Schittenhelm, R., 1990. Biomagnetic imaging. Digitale Bilddiagn. 10, 76–85.

Sidhu, R., Danders, D.S., McAlindon, M.E., 2006. Gastrointestinal capsule endoscopy: from tertiary centres to primary care. BMJ 332, 528–531.

Singh, R., Chen, Yi Mei, S.L., Tam, W., Raju, D., Ruszkiewicz, A., 2010. Real-time histology with the endocytoscope. World J. Gastroenterol. 16, 5016–5019.
Sousa, T., Paterson, R., Moore, V., Carlsson, A., Abrahamsson, B., Basit, A.W., 2008. The gastrointestinal microbiota as a site for the biotransformation of drugs. Int. J. Pharm. 363, 1–25.
Stathopoulos, E., Schlageter, V., Meyrat, B., Ribaupierre, Y., Kucera, P., 2005. Magnetic pill tracking: a novel non-invasive tool for investigation of human digestive motility. Neurogastroenterol. Motil. 17, 148–154.
Steinberg, W.H., Grey, G.H., Masci, J.M., Hutchins, H.H., 1965. Method for determining in vivo tablet disintegration. J. Pharm. Sci. 54, 747–752.
Steingoetter, A., Kunz, P., Weishaupt, D., Mäder, K., Lengsfeld, H., Thumshirn, M., Boesiger, P., Fried, M., Schwizer, W., 2003a. Analysis of the meal-dependent intragastric performance of a gastric-retentive tablet assessed by magnetic resonance imaging. Aliment. Pharmacol. Ther. 18, 713–720.
Steingoetter, A., Weishaupt, D., Kunz, P., Mäder, K., Lengsfeld, H., Thumshirn, M., Boesiger, P., Fried, M., Schwizer, W., 2003b. Magnetic resonance imaging for the in vivo evaluation of gastric-retentive tablets 20, 2001–2007.
Van Liere, E.J., Sleeth, C.K., 1935. Some normal variations in gastric emptying-time of the human stomach (using a carbohydrate meal). Am. J. Dig. Dis. 2, 671–672.
Washington, N., Greaves, J.L., Wilson, C.G., 1990. Effect of time of dosing relative to a meal on the raft formation of an anti-reflux agent. J. Pharm. Pharmacol. 42, 50–53.
Watts, P.J., Barrow, L., Steed, K.P., Wilson, C.G., Spiller, R.C., Melia, C.D., Davies, M.C., 1992. The transit rate of different-sized model dosage forms through the human colon and the effects of a lactulose-induced catharsis. Int. J. Pharm. 87, 215–221.
Watts, P.J., Wilson, C.G., Davies, M.C., Melia, C.D., 1994. Radiolabelling of polymer microspheres for scintigraphic investigations by neutron activation 4. The biopharmaceutical performance of colon-targeted Eudragit RS: sulphapyridine microspheres in human volunteers. Int. J. Pharm. 102, 101–108.
Weitschies, W., Blume, H., Mönnikes, H., 2010. Magnetic marker monitoring: high resolution real-time tracking of oral solid dosage forms in the gastrointestinal tract. Eur. J. Pharm. Biopharm. 74, 93–101.
Weitschies, W., Cordini, D., Karaus, M., Trahms, L., Semmler, W., 1999. Magnetic marker monitoring of esophageal, gastric, and duodenal transit of non-disintegrating capsules. Pharmazie 54, 426–430.
Weitschies, W., Grützmann, R., Hartmann, V., Breitkreutz, J., 2001a. Investigation of the disintegration behavior of magnetically marked tablets. Eur. J. Pharm. Biopharm. 52, 221–226.
Weitschies, W., Karaus, M., Cordini, D., Trahms, L., Breitkreutz, J., Semmler, W., 2001b. Magnetic marker monitoring of disintegrating capsules. Eur. J. Pharm. Sci. 13, 411–416.
Weitschies, W., Kosch, O., Mönnikes, H., Trahms, L., 2005a. Magnetic marker monitoring: an application of biomagnetic measurement instrumentation and principles for the determination of the gastrointestinal behavior of magnetically marked solid dosage forms. Adv. Drug Deliv. Rev. 57, 1210–1222.
Weitschies, W., Wedemeyer, J., Stehr, R., Trahms, L., 1994. Magnetic markers as a noninvasive tool to monitor gastrointestinal transit. IEEE Trans. Biomed. Eng. 41, 192–195.
Weitschies, W., Wedemeyer, R.S., Kosch, O., Fach, K., Nagel, S., Söderlind, E., Abrahamsson, B., Trahms, L., Mönnikes, H., 2005b. Impact of the intragastric location of extended release tablets on food interactions. J. Control. Release 108, 375–385.
Wilson, C.G., 2010. The transit of dosage forms through the colon. Int. J. Pharm. 395, 17–25.
Wilson, C.G., McJury, M., O'Mahony, B., Frier, M., Perkins, A.C., 1997. Imaging oily formulations in the gastrointestinal tract. Adv. Drug Deliv. Rev. 25, 91–101.
Wilson, C.G., O'Mahony, B., Connolly, S.M., Cantarini, M.V., Farmer, M.R., Dickinson, P.A., Smith, R.P., Swaisland, H.C., 2009. Do gastrointestinal transit parameters influence the pharmacokinetics of gefitinib? Int. J. Pharm. 376, 7–12.