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EXPERT REVIEW

Biomagnetic Methods: Technologies Applied to Pharmaceutical Research

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ABSTRACT Biomagnetic methods have been designed for a wide range of applications. Recently, such methods have been proposed as alternatives to scintigraphy for evaluating of a number of pharmaceutical processes *in vitro* as well as under the influence of gastrointestinal physiological parameters. In this review, physical characterization as well as the most recent applications of Superconducting Quantum Interference Device (SQUID), Anisotropic Magnetoresistive (AMR) and AC Biosusceptometry (ACB) in the pharmaceutical research will be explored. Moreover, their current status and how these technologies can be employed to improve the knowledge about the impact of gastrointestinal physiology on drug delivery in association with pharmacokinetic outcomes, termed *pharmacomagnetography*, will be presented.

KEY WORDS drug delivery · gastrointestinal physiology · imaging · pharmacokinetic · solid dosage forms

INTRODUCTION

The successful development of solid pharmaceutical dosage forms is often dependent on the knowledge of physiological parameters that influence their *in vivo* performance. Although *in vitro* dissolution tests are employed to obtain meaningful *in vitro/in vivo* correlations, such methods are not always predictive of all aspects of physiological conditions in the gastrointestinal (GI) tract (1,2).

For many years, gamma scintigraphy was the standard method for the noninvasive monitoring of solid dosage forms in human GI tract (3–5). Scintigraphic studies are conducted after incorporating a radioactive marker into the formulation or by the use of neutron activation, i.e., a nonradioactive isotope is added and is converted to a radioactive isotope by exposure to a neutron flux (4,6). The modality known as *pharmacoscintigraphy*, which combines scintigraphic outcome

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with pharmacokinetic assessment, has been applied to provide information about the transit of a variety of solid dosage forms and subsequent drug release and absorption (3–7).

Although gamma scintigraphy has indubitable potential for evaluating dosage forms in human GI tract, the costs associated with equipment and materials, radiation exposure, licensing for handling radioactive materials and approval by appropriate institutional committee as well as limited temporal and spatial resolution are some of the drawbacks of this technique (6).

In order to overcome such technical limitations, alternative methods based on biomagnetic field detection have been developed (8–10). The measurement of magnetic field produced within the human body is referred as biomagnetism. This concept involves the use of a class of sensitive magnetic sensors applied for monitoring solid dosage forms, and they have been recognized as valuable tools for pharmaceutical research (11,12). Superconducting Quantum Interference Device (SQUID), Anisotropic Magnetoresistive (AMR) and AC Biosusceptometry (ACB) are the noninvasive and radiation-free sensors currently available for pharmaceutical purposes. Such techniques provide effective monitoring of a number of pharmaceutical processes *in vitro* as well as under the influence of physiological parameters (13–20). The key aspects regarding the biomagnetic methods from theory to practice will be exploited in this review. Basically, their current status and how these technologies may be utilized to improve our fundamental understanding about the complexity of GI physiology and its impact on drug delivery will be presented.

GASTROINTESTINAL PHYSIOLOGY: IMPACT ON DRUG DELIVERY

Oral is the main route for drug administration due to the advantages related to convenience, patient compliance and practicality. Moreover, most drugs marketed worldwide are available as oral dosage forms. The efficacy and safety of these drugs is dependent on the bioavailability, a biological property which refers to the extent and rate of absorption. Absorption from oral dosage form is related to processes of drug delivery (dissolution/solubility) from its pharmaceutical form into body fluids and drug absorption (permeability) through biological membranes. Therefore, drug solubility and permeability will be fundamental to the absorption processes and consequently to bioavailability (21–23).

Drug absorption is mainly assessed by bioavailability/bioequivalence assays (24–26). However, such studies are subject to a number of sources of variation, for example, the individual variability (intra-individual and inter-individual); have a high cost; and involve healthy individuals, promoting discussion of comprehensive ethical issues of these tests (27,28). Thus, the Biopharmaceutical Classification System (BCS) has been developed to provide a scientific approach to classify drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from immediate-release solid oral dosage forms: dissolution, solubility and intestinal permeability (23,29).

Several formulation strategies have been developed to improve the solubility and bioavailability of poorly water-soluble and poorly permeable drugs. Numerous approaches, such as the use of absorption enhancers, innovative dosage forms and polymers that increase solubility and permeability, have been explored in order to attain peroral delivery of drugs (30,31).

Drug absorption in GI tract is complex and can be influenced by several factors, which impact drug solubility and permeability. Physicochemical properties of the drug, dosage forms characteristics, pharmaceutical excipients, technology for obtaining the pharmaceutical product and anatomical as well as physiological characteristics of the administration site have fundamental importance in drug absorption (32–34). Among these factors, in this review, we will emphasize those related to the GI physiology.

Several physiological factors may influence the GI absorption of drugs, especially the surface absorption, mechanism of transport across cell membranes, GI motility and transit, pH, food, bile salts, enzymes, volume of liquid and pre-systemic metabolism (34).

Surface Absorption

The GI tract is highly specialized in functions that involve the processes of secretion, digestion and absorption. It presents four main segments—esophagus, stomach, small intestine (duodenum, jejunum and ileum) and colon—that differ with regard to properties and constitution of the membranes and motility patterns, promoting variations in drug absorption (35,36).

The stomach is where the release of a drug from an immediate release dosage form initiates. The surface of the gastric mucosa is formed by a layer of columnar cells and secretory cells specialized to secrete approximately 2,000 mL of gastric fluid per day. The stomach has a capacity of approximately 1,500 mL but, in the fasting state, contains approximately 50 mL of fluid. Gastric secretions are comprised of acid, gastrin, pepsin and mucus (22).

The small intestine represents 60% of the GI tract, and it is divided into duodenum, jejunum and ileum, comprising 5%, 50% and 45% of the total length, respectively. The

luminal side of the small intestine has villi and folds of Kerckring. On the surface of the villi, there are the epithelial cells, mostly constituted by enterocytes, which represent 90% of all cells constituting villi (37). The apical zone of enterocytes is characterized by the presence of a brushed structure which forms microvilli. These structures are covered by a 0.1 mm thick glycoproteic layer (glycocalix). The folds, villi and microvilli multiply 600 times the absorbing surface of the small intestine. Due to these characteristics, approximately 90% of all absorptive processes occur in the small intestine (38,39).

Enterocytes are highly polarized cells, *i.e.*, they have an apical side (mucosal or intestinal lumen), which faces the lumen of the intestine, and a basolateral side (serosal). Apical and basolateral membrane sides differ in relation to morphology, biochemical composition, drug-transporter protein and function. The basolateral membrane side has a lower content of cholesterol and glycolipids in relation to the apical membrane side, making it more fluid and permeable. The microvilli forming the brush border layer are on the enterocyte apical side. The enterocytes are connected by intercellular complex, called tight junctions. The lipidic characteristic of enterocyte membrane and tight junctions are the main physical barrier to the drugs permeability (35,40–42).

The colon, the terminal segment of the GI tract, presents lower absorption capacity in relation to the small intestine. The cells in the mucosa, colonocytes, have no microvilli and also differ with regard to carriers of drugs (35,40,42). Moreover, these epithelial cells are coated with a 100–500 nm thick layer layer consisting of water and mucus. This layer can hinder or delay the absorption of drugs. The colon has a high number and variety of bacteria involved in several metabolic reactions, such as hydrolysis of fatty acids and reduction of drug in its inactive conjugated form to the active form (43,44).

Mechanism of Transport across Cell Membranes of Gastrointestinal Tract

Drug transport across the intestinal membrane is a dynamic and complex process and may occur through one or more mechanisms either transcellular or paracellular. Transcellular uptake processes can be passive, facilitated or active. Most of the drugs are absorbed through passive diffusion (45–47).

Transcellular active transport is a mechanism that may occur against a concentration gradient and involves carriers, consumes energy, and is a saturable process. There are influx (uptake) carriers and efflux carriers, which mediate drug transport in the opposite direction, *i.e.* from the basolateral membrane side to the apical side (the intestinal lumen), resulting in the secretion of the drug. These carriers may be present both at the apical membrane and basolateral side. The P-glycoprotein is a major representative of drug efflux. Its activity tends to increase progressively from the stomach to the colon, which is a factor to be considered in the development of extended release dosage forms (33,47–50). The low bioavailability of some drugs has been attributed to this type of transport, also designated as efflux. Moreover, some pharmaceutical excipients, such as polyethylene glycol 300, polyethylene glycol 400 and polysorbate 80, have been indicated to inhibit the action of P-glycoprotein (1).

Paracellular process involves the passage of drugs by intercellular spaces (tight junctions) and is more expressive in the upper portions of the small intestine. It is a passive transport, *i.e.* not requiring external energy. Due to the great barrier that the tight junctions offer, this transport route is only possible for hydrophilic drugs and for those of small or moderate molecular size. Several studies have reported increase of drug permeability by co-administration of an absorption enhancer, including surfactants, calcium chelating agents, cyclodextrins, and chitosans. These substances improve the permeability of poorly permeable drugs mainly by opening the tight junctions (41,45,51–53).

Endocytosis is a transport mechanism whereby the substances are actively absorbed through the formation of vesicles from the plasma membrane. This transport is especially important for the permeation of macromolecules. There are three main forms of endocytosis: phagocytosis, pinocytosis and receptor-mediated endocytosis (45,46).

Gastrointestinal Motility and Transit

Drug absorption is dependent on GI motility and transit, with absorption kinetics varying remarkably in different segments of the GI tract (54,55). Furthermore, the influence of feeding and temporal patterns on GI transit has been considered of great relevance in attempting to optimize drug absorption (56).

The movement of ingested material, including pharmaceutical dosage forms, through the GI tract begins with the oral ingestion. The esophagus propels material from the pharynx to the stomach, and this propulsion is accomplished by coordinated contractions of the muscular layers. The barrier functions of the esophagus are performed by the presence of sphincters that act in a coordinated manner during the process of swallowing (57).

The motility of the stomach and upper small intestine is organized to accomplish the orderly emptying of contents into the duodenum taking into account the variable quantity and composition of ingested material. Contractile activity at any level in the GI tract is based on fundamental electrophysiologic properties. A consistent feature of GI myoelectric activity is an omnipresent electrical pattern

called the slow wave that does not lead to contractions; contractions are related to the occurrence of action potentials (spikes) on the crest of slow waves. In the stomach, the frequency of contractions is three cycles per minute. Similarly, the maximal duodenal frequency of contractions is between 11 and 12 cycles per minute and these frequencies decline along the intestine, reaching 9 cycles per minute in the distal ileum (58). The colon presents a motility pattern complex and variable characterized by very slow frequency of contractions arranged according to the segment function (59).

Patterns of motor activity during fasting and after meal differ fundamentally. In the fasted state, motor activity of the upper gastrointestinal tract is highly organized into a distinct and cyclically recurring sequence of events known as the migrating motor complex (MMC). The MMC consists of three distinct phases of motor activity that occur in sequence and migrate aborally. Each sequence takes place at nearly 90 min and begins with a period of motor quiescence (phase I), which is followed by a period of apparently irregular contractions (phase II), and culminates in a burst of powerful contractions (phase III) (58). When food is ingested, the MMC is abolished and replaced by a group of random contractions called the fed pattern, lasting 1 h for each 200 kcal ingested, at which time the fasted pattern resumes, assuming that no more food has been ingested (60).

Concerning these physiological conditions, it has been supposed that GI motility has significant implications on drug delivery, and, notwithstanding, *in vivo* behavior of solid dosage forms cannot simply be predicted from commonly used *in vitro* testing methods. This is particularly important for the pharmacokinetics of a drug, which are influenced by the interplay of parameters such as gastrointestinal physiology, drug solubility, dissolution, permeability, distribution and elimination (61,62). Even before drug absorption, the release mechanisms should be considered since it reflects the dynamics of rate and extent of drug absorption.

Gastrointestinal Transit

For pharmaceutical purposes, the transit of a dosage form through the GI tract determines how long a drug molecule remains in contact with its absorptive site. Additionally, the bioavailability of a drug may be affected by factors that change gastrointestinal transit.

Gastric emptying, also called gastric residence time or gastric emptying rate, is the time taken by a dosage form to pass through the stomach and can be the rate-limiting step in absorption of drugs. It is influenced by a number of factors, including volume of ingested fluids, food type, fluid viscosity, drug action, physical characteristics of the solid dosage form, and biological factors such as age, posture, body mass index, physical activity, and certain diseases (36,63,64). A number of studies have stated that gastric emptying plays an important role in determining the retention time of dosage forms, even though it is highly variable (65–67). Under usual conditions, the gastric emptying time ranges from 5 min to 2 h. In general, the presence of food, especially fatty, reduces the gastric emptying time. Delayed gastric emptying might be exploited as an interesting approach to enhance the absorption of drugs presenting an absorption window in the upper GI tract (17,68–70).

On the other hand, the small intestinal transit time seems to be less variable, despite some recent studies demonstrating that intra-individual data can vary significantly (65,71). The small intestine transit time is determined by two main kinds of intestinal movement classified as aboral propulsion and mixing. The intestinal transit determines how long the drug or dosage form remains in contact with absorptive sites in small intestine. Considering that the small intestine is the main site for absorption, the transit time between the stomach and the colon is an important factor for drug bioavailability (64).

In healthy subjects, the transit time of a drug along the small intestine ranges from 3.5 to 4.5 h. However, some pharmaceutical excipients, such as mannitol, reduce this transit time, compromising the drug absorption (34,36). Such a parameter is especially important for slow-release dosage forms (controlled extended-release forms), enteric coated dosage forms, drugs that dissolve slowly in the intestinal fluids and drugs that are absorbed by carrier-mediated transport (72).

Colonic drug delivery has gained increased importance for treatment of local diseases as well as for systemic release of proteins and therapeutic peptides (73,74). Movements through the colon are markedly slow, and the transit time in this region is generally considered to be longer than in the small intestine. The transit of drugs in the colon may last from 2 up to 48 h, depending on several conditions, including the dosage forms, prandial state and certain diseases (74).

GI Fluids and Ph

The pH of the GI tract varies across its length, ranging from acidic in the stomach to alkaline in the large intestine. Intestinal pH values are considerably higher than those of gastric fluid, due to the neutralization of acid by pancreatic secretion. Intestinal fluids from the small intestine present pH from 5.0 to 8.0; in the large intestine, these values are around 8.0. pH values may be modified according to diseases, food intake and age (33,72,75). It is important to consider that chemical stability of a drug and its dissolution or absorption may be affected by pH (72,76). In addition, the different pH values along GI tract can be exploited to achieve GI targeting for drugs.

According to the principle of partition of pH, polar and ionized molecules are more soluble in water but more slowly absorbed than the non-ionized. Considering approximately 95% of the molecules of the drugs are weak acids or weak bases and that pH varies according to GI segment, the drug solubility also depends on the drug pKa and pH of GI fluid (61,72). Notwithstanding, in practice, other factors must be taken into account. For example, the absorbing surface, which is considerably larger in small intestine, may compensate the high degree of ionization of weakly acidic drugs in the intestinal pH rates. Moreover, the longer staying time in the small intestine is considered a favorable element for absorption of weak acids at that site (22).

The volume of GI fluids can be decisive for the dissolution of drugs, especially of those poorly soluble. Besides the volumes of secretions and of water flowing across the intestinal surface, the amount of co-administered liquid will be also counted in the total volume available for drug dissolution (2,22,33).

The presence of food in the GI tract has a great influence on the rate of absorption and drug bioavailability, since it is responsible for alterations in motility patterns, transit rates, secretions, physical-chemical interactions, fluid viscosity, and volume and changes in blood flow. Such alterations are dependent not only on the amount ingested but also on individual components of the meal. Moreover, the nature and quantity of food intake may influence the processes of disintegration and dissolution of drugs, changing, consequently, the drug absorption (77,78).

For instance, grapefruit juice may considerably increase peroral bioavailability of many drugs, since components of grapefruit juice have higher affinity for P-glycoprotein than most drugs, so drug efflux may be inhibited, and bioavailability increases such as found for cyclosporine, digoxin, fexofenadine (45).

Bile salts secreted by the gallbladder have the function of providing the emulsification of fat droplets and also may change drug absorption. The bile salt concentrations in the proximal small intestine generally are in the range from 3 up to 5 mM in the fasting state, reaching values near 15 mM after meal. Because of its surfactant properties, bile salts may help in the dissolution of drugs of hydrophobic nature, increasing, consequently, their bioavailability (2,72,78).

Pepsin and pancreatic proteases may interfere with the stability and release of peptide drugs. On the other hand, lipases affect drug release from dosage forms containing fatty components. In addition, bacteria, which are located especially in the ileum and colon, also secrete several enzymes able to break specific chemical bonds. This capability has been used to develop programmed drug release dosage forms targeting the colon (1,2,74).

Presystemic Metabolism

The presystemic metabolism corresponds to the biotransformation of drugs before they reach the systemic circulation. Presystemic metabolism involves the cytochrome P450 (CYP subfamily) belonging to a class of drug metabolizing enzymes and may occur in the liver and in the intestinal wall. Therefore, drugs which are substrates for these enzymes may have a significant reduction of bioavailability (47,50,79,80).

The bioavailability of a drug may be influenced by the interaction of physiological parameters and by those related to dosage form and physicochemical properties of a drug. Nevertheless, there are still gaps in our knowledge on GI physiology to move forward effectively in developing more reliable therapeutic systems (1,81). Non-invasive techniques are responding to the demands to improve our fundamental understanding for providing information on drug delivery and its relationships at specific organs.

BIOMAGNETIC TECHNIQUES: FROM THEORY TO PRACTICE

Biomagnetism refers to the study of magnetic fields generated in biological systems from several sources including electrical currents associated with the movement of ions, magnetic moments in magnetic contaminants, and magnetic moments of magnetic materials when subject to an applied magnetic field (82). The range of the possibilities covered by biomagnetism continues to expand with improvements in instrumental sensitivity and ease of use as well as the growing interest from diverse areas of study.

Regarding the magnitude of biomagnetic fields from biological or external sources, there is specific instrumentation that has been proven to be appropriate for biomagnetic measurements. At present, the most commonly used biomagnetic sensors are the superconducting quantum interference device (SQUID), Anisotropic Magnetoresistive Sensors (AMR) and Induction Coils, that are the principle of AC Biosusceptometry (ACB) (83–85).

Because of the progress already achieved in this field as well as recent technical developments which allowed the use of such methods in a number of applications, this review will highlight the potential use of biomagnetic methods for pharmaceutical research purposes. It begins with a brief review of the physical principles of the sensors, and then the pharmaceutical applications will be discussed.

SQUID Systems

Superconducting Quantum Interference Device (SQUID) is the most sensitive magnetic field detector used nowadays,

and it consists of a superconducting loop interrupted by one or two insulating barriers which must be maintained at low temperature by immersion in liquid helium or liquid nitrogen contained in a dewar (Fig. 1). These sensors are able to detect magnetic fields from 5 fT to 1,000 nT.

These magnetic sensors combine two physical phenomena explained by quantum mechanics: magnetic flux quantization and quantum tunneling though the Josephson junction (82,83,86,87). Magnetic flux quantization means that the magnetic flux through a superconducting loop is always an integer multiple of the magnetic flux. Josephson junction consists of two superconductors separated by a thin insulating barrier that allows tunneling of a pair of electrons (Cooper pair) through the barrier to maintain phase coherence (86,88). Cooper pair tunneling through the barrier introduces a phase shift in the supercurrent that translates in an intensity given by $I=I_0\sin\delta$, where I_0 is the critical current and δ is the phase difference as the current tunnels the two insulating barriers in the superconductors. The relationships between the dynamics of the phase difference and flux quantization when a constant voltage (V) is applied to the junction are described as Eq. 1:

$$\frac{d}{dt}(\theta_2-\theta_1)=\frac{d}{dt}\delta=\frac{2eV}{h}=\frac{2\pi V}{\theta_0} \tag{1}$$

where $\phi_0=h/2e$ is the flux quantum.

By integrating Eq. 1, it is found that the phase differences change over time according to $\delta(t)=\delta_0+2\pi\frac{2e}{h}Vt$, producing a time varying current $I=I_0\sin(\delta_0+2\pi Vt)$.

Because SQUIDs are very small, they are not adequate to directly detect biomagnetic fields. Therefore, SQUID systems employ primarily detection coils in a first- or second-order gradiometric configuration. This can be made by a single or few turns of superconducting wire spaced, when just one coil arrangement is used the system is called a magnetometer. Depending on the application, the detection coils are projected in different geometry and physical dimensions (86).

The first-order magnetometer is obtained by arranging two magnetometers in opposite sense by a baseline distance, and they are displaced as axial or planar magnetometer. The coil nearest to the biomagnetic field source is called the detection coil, and the other positioned far from the biomagnetic source is called the input coil, which is directly coupled on the SQUID (Fig. 2). Detection and input coils constitute a superconducting loop named flux transformer.

The external magnetic field generated by a source induces a current (I_{in}) in the superconducting loop which is proportional to the field applied (B_n) as well as to the detection coil area (A_p), which produces a magnetic flux (ϕ_p), as described by Eq. 2:

$$I_{in}=\frac{\phi_p}{L_p+L_{in}}=\frac{B_nA_p}{L_p+L_{in}} \tag{2}$$

L_p and L_{in} are the inductances of the detection and input coils, respectively.

Hence, the signal detected by a first-order gradiometer is the difference of the magnetic flux (ϕ) sensed between detection coil and the flux sensed by the input coil, according to Eq. 3:

$$\phi=C\left(\frac{1}{r^2}-\frac{1}{(r+d)^2}\right)=\frac{C}{r^2}\left(1-\frac{1}{(1+d/r)^2}\right) \tag{3}$$

where r is the distance of the source, and d is the baseline of the gradiometer.

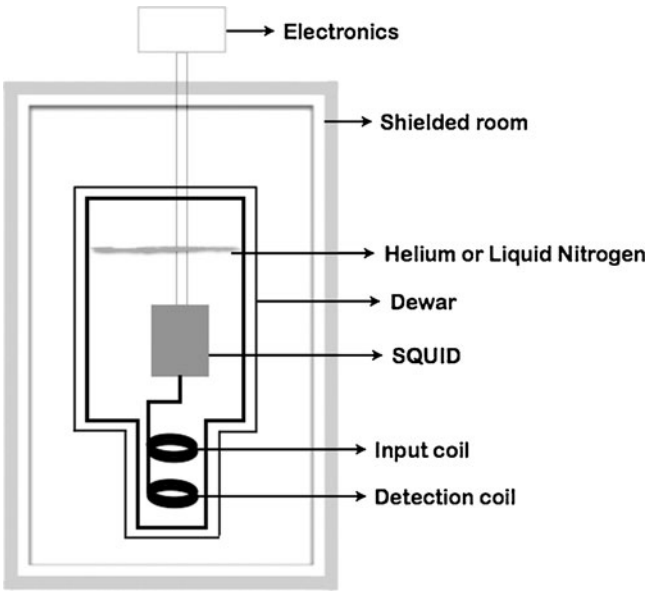

Fig. 1 Schematic representation for a single channel SQUID system. Detection and input coils are superconducting loops coupled to SQUID maintained in low temperature in a magnetically shielded room (86).

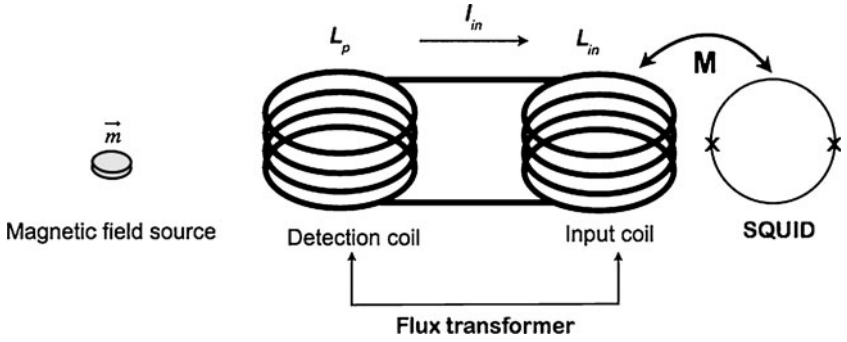

Fig. 2 Representative diagram for a magnetic field source coupled to a SQUID through the flux transformer. The magnetic field generated by the source induces a current in the flux transformer towards generating a magnetic flux on the SQUID through the inductance *M* (86).

As this system is designed for measuring weak magnetic signals, it is susceptible to environmental magnetic disturbance as well as the influence of Earth's magnetic field. For these reasons, to attain the highest sensitivity, SQUID systems must be operated in magnetically shielded rooms made by multiple walls of shielding material.

For pharmaceutical applications, SQUID systems are composed by multichannel sensors in various arrangements, and they are used for monitoring magnetic fields generated by magnetically marked dosage previously magnetized (8, 12). The measured magnetic fields are generated by the magnetic dipole moments of the magnetized tablets. The magnetic moment of a dipole is determined by the amount of magnetic material incorporated, the remanent magnetization of this material and the magnetization process itself. Once marked, the magnetic dipole moment (m) of the dosage form is given as Eq. 4:

$$\vec{B}(\vec{m},\vec{r}) = \frac{\mu_0}{4\pi|\vec{r}|^5}\left[3(\vec{r}\times\vec{m})\times\vec{r} - |\vec{r}|^2\vec{m}\right] \quad (4)$$

where B is the magnetic field measured, and r is the distance of the magnetic dipole to the coil

If the dosage form does not disintegrate, the magnetic moment is constant, and the magnetic field generated can be continuously monitored at different positions. However, when the disintegration of the dosage form occurs, this magnetic moment is reduced due to decreased alignment of the magnetic particles (Fig. 3). The location, orientation and strength of the magnetic dipole are determined through the inverse problem, and it is solved from the measured field components applying the Levenberg-Marquardt algorithm and other signal conditioning techniques. The accuracy of the localization procedures depends on the sensitivity, arrangement and number of sensors, the amount of magnetic material as well as the strength of the magnetic dipole.

AMR Sensors

Magnetoresistive sensors based on the anisotropic magnetoresistance effect (AMR) are available for a wide range of applications (84, 89). Most AMR sensors are made of Permalloy (NiFe) thin film deposited onto a silicon substrate in various Wheatstone resistor bridge configurations to provide highly predictable outputs when subjected to magnetic fields (84). In order to introduce the anisotropy, the deposition of the permalloy film is carried out in the presence of magnetic field. Their principle of operation is based on the electrical resistance of the film, which can be modulated by the application of a magnetic field to change the direction of its inherent magnetization (89). AMR sensors detect magnetic field varying between 100 pT to 100 mT.

AMR sensors consist of a hard axis with a high requirement of magnetization energy in one direction in the plane of the film and orthogonal to the hard axis, which indicates the magnetic preference direction. As the magnetization (m) has preferential direction of the magnetic field applied, the resistance (R) of the thin film varies according to the magnetization, and, consequently, it is highest when the magnetization is parallel to the current (I) and lowest when it is perpendicular (Fig. 4).

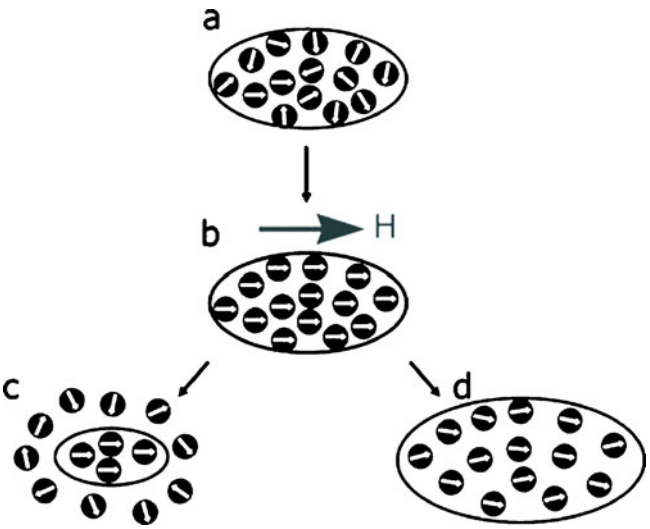

Fig. 3 Magnetic labelling of dosage forms. **a** individual magnetic particles before magnetization. **b** alignment of particles at strong magnetic field applied. **c** release of magnetic particles after disintegration. **d** swelling of dosage form resulting in a loss of alignment of magnetic particles (12).

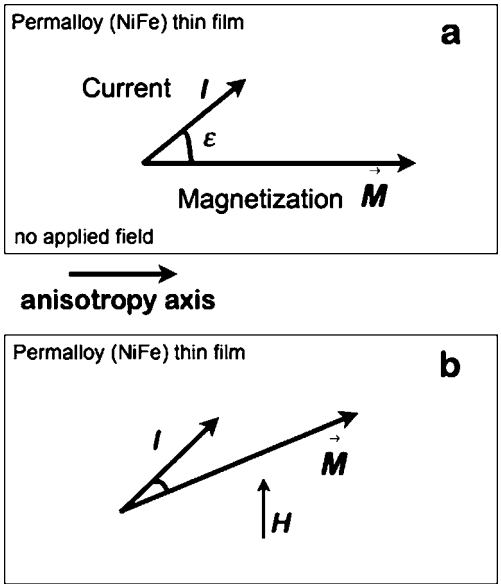

Fig. 4 **a** Magnetization and current in direction to the anisotropy axis when no magnetic field is applied. **b** Application of external magnetic field changes the magnetization and consequently the resistivity.

Changing the magnetization from an initial state consistent with anisotropy axis, through the application of an external field H_x in the film plane, causes the maximal resistivity change. The resistance change ΔR_x making an angle ε with the anisotropy axis can be described as Eq. 5:

$$\Delta R_x \approx \Delta R_m (h_x^2 \cos 2\varepsilon + h_x \sqrt{1 - h_x^2 \sin 2\varepsilon - \frac{1}{2}\cos 2\varepsilon}) \quad (5)$$

where h_x is the relative value of magnetic field perpendicular to anisotropy axis and ΔR_m is the maximum change of resistance.

Basically, AMR sensors detect the field H_x in the film plane as a result of the difference of the resistance. In the case of measured field making an angle y with the sensor axis, the output signal should be proportional to the component of this field $H_x cosy$.

The main properties of AMR sensors are their sensitivity at weak magnetic fields and dimensions of the film, linearity and resolution. The sensitivity increases with diminishing film thickness, but due to practical limitations, manufacture of films thinner than 20 nm is not recommended (84). It can be assumed in practical design that for a fixed thickness t and width w, there is an optimum value t/w; thus, the sensitivity increases with decreasing t/w ratio. Regarding the linearity, anisotropy values vary markedly in the film due to the non-uniformity in the demagnetizing field and due to the magnetization direction that is variable into film with non-zero angle between the path and the anisotropy axis. For the resolution, it can be assumed that this parameter is limited for small output signal values by amplifier noise, and it can be improved by introduction of an AC supply (84,89).

In the area of pharmaceutical sciences, solid dosage forms can be monitored by employing AMR sensors. This can be performed by detection of a magnetic dipole derived from a permanent magnet which is repeatedly aligned by an oriented pulsed magnetic field. The permanent magnet consists of magnetic labelled dosage form which is magnetized in order to create a magnetic dipole moment. After ingestion, the magnetized dosage form can be localized at multiple positions in GI tract; then, the dipole is reconstructed from the magnetic field components (10,12).

Alternatively, the disintegration process of magnetically marked tablets in relation to the temporal development of the magnetic moments also can be investigated (90). In this case, the magnetic moments of the particles are aligned during magnetization into the direction of the magnetic field applied. The magnetically marked tablet is an ensemble of particles with a stable magnetic dipole moment. When the disintegration occurs, the particles are released from the tablet core; hence, this dipole moment is reduced due to the disarrangement in the alignment of the particles.

Like SQUID systems, AMR sensors have the same principle for localization of solid dosage forms and are also based on the detection of magnetic dipole (10,91). As these sensors are less sensitive, they can be operated in unshielded rooms; however, a higher amount of magnetic material for labelling the dosage forms is needed.

ACB System

ACB sensors are, nowadays, designed to suit a wide range of biological applications (9,11,92,93). These magnetic sensors are composed of pairs of induction coils separated by a fixed baseline; each pair consists of excitation (outer) and detection (inner) coils in a first-order gradiometric configuration that provides good signal-to-noise properties (Fig. 5).

The excitation coil operates with a low frequency of 10 kHz to avoid significant eddy current effects produced by the electrical conducting fluids present in the body, and a current of 15 mA to generate a magnetic field of 20 G for inducing equal magnetic flux in the detection coils. Hence, the output voltage (V_d) is given as the difference of inductance for the two pair of coils (ΔM) in relation to the currents supplied to the excitation coils (I_e) and amplifier (I) as well as the electrical resistance (R) in the detection coils, according to Eq. 6:

$$V_d = \Delta M \frac{dI_e}{dt} + RI \quad (6)$$

When a ferromagnetic sample is nearest to the sensor, an imbalance in the voltage (V_d) occurs due to the changes in

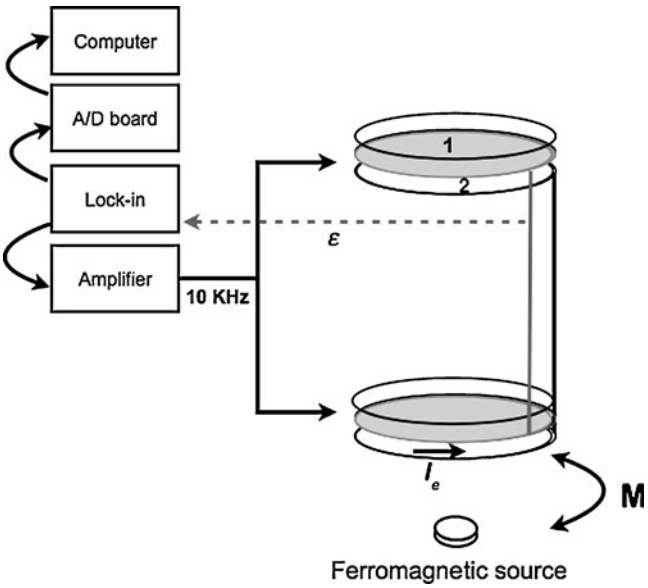

Fig. 5 Schematic diagram of ACB system. Detection (1) and excitation (2) coils are coaxially arranged. The current (I_e) in the excitation coils generates a magnetic field that is canceled by the gradiometric system. Only the signal from the ferromagnetic source coupled to the coil is detected as the difference of inductance (*M*).

the differential flux ($\Delta\phi$) between the detection coils. Then, ACB sensors can measure the magnetic flux variation (ε) generated between excitation and detection coils through lock-in amplifiers as described in Eq. 7:

$$\varepsilon = -\frac{d\Delta\phi}{dt} = M'\frac{dI_e}{dt} \tag{7}$$

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 and the ferromagnetic sample (9,11,85). ACB sensors are designed to detect magnetic field around 1 μT and have important advantages in comparison with other biomagnetic measurement devices, since they are robust, easy to construct, allow for easy assembly of axial and planar gradiometer, don't need to operate in magnetically shielded rooms, and allow for simplification of electronic instrumentation. Additionally, as the ferromagnetic particles are not previously magnetized, they allow for monitoring the marker location and subsequent processes that occur after the spreading of the particles.

In terms of drug delivery research, ACB sensors are feasible to monitor GI motility parameters in different segments as well as drug delivery process (11,13,15,17). Either magnetic markers or magnetic tracers can be detected; the difference is on the intensity and amplitude of the magnetic signal.

Besides magnetic signals, ACB sensors are also able to monitor pharmaceutical processes through magnetic images. Magnetic images are formed from the magnetic signals, which are generated as a response of ferromagnetic sources when subjected to a magnetic field (11). Once acquired, the magnetic signals represent time series matrices computed at regular time intervals. These matrices are derivative from magnetic field distribution which is mathematically interpolated and processed in order to obtain sequential degraded images. Afterwards, the images are submitted to the digital image processing tools. Details about this method to obtain images with ACB sensor were reported earlier (14).

MAGNETIC LABELING OF SOLID DOSAGE FORMS

In order to employ biomagnetic methods in pharmaceutical research, it is necessary to label a solid dosage form as magnetic marker by incorporating powdered ferromagnetic particles. Depending on the method used, the goal of magnetic labeling is to obtain a stable magnetic dipole after previous magnetization or simply to obtain a permanent magnet without need of such proceeding.

For SQUIDs or AMR systems, it is essential to label the dosage forms as magnetic dipole by incorporating magnetic materials with high remanent magnetization. To generate a magnetic dipole, it is necessary to align individually the magnetic particles in the direction of a strong applied magnetic field. Hence, this previous magnetization of the material is responsible for creating the alignment of the particles and, therefore, the magnetic dipole. Any process able to disturbed this alignment decreases the magnetization due to the loss of particle orientation can also be recorded (8). Among the materials used, black ferrimagnetic iron oxide magnetite (Fe_3O_4) and, alternatively, red iron oxide maghemite (γ-Fe_2O_3) can be applied. Both are ferrimagnetic materials which also are employed as colour pigments for food and drugs and are not absorbed by GI tract (12).

For ACB system, the most used materials are ferrites ($MeFe_2O_3$, where Me could be Ni, Co, Zn, Mg, Mn). Ferrites are made of ceramic and have high magnetic susceptibility, providing high response when a external magnetic field is continuously applied, and, consequently, previous magnetization of the material is not required in this case. Due to its nontoxic and insoluble nature, it can be used as magnetic labelling material (94,95).

The required amount of magnetic material depends predominantly on the sensitivity of the measurement system used. As SQUIDs are the most sensitive detector, amounts of material starting at about 0.1 mg provide acceptable precision. However, for accurate evaluation, amounts between 3 mg and 10 mg are usual (12,19). Regarding AMR sensors, the use amounts of magnetic material

around 1,000 mg are still required (96). At the current stage of development, ACB sensors are able to detect 300 mg of magnetic material incorporated into pellets or 500 mg for a magnetic tablet (10 mm diameter).

Real-time *in vitro* or *in vivo* measurements to locate the solid dosage form as well as to characterize pharmaceutical processes are generally related to the release of the magnetic material. Hence, particles that are concentrated can be taken as magnetic markers, with a magnetic signal that remains stable, with higher intensity and amplitude. For practical explanation, markers are dosage forms in a non-disintegrated status, such as tablets or hard capsules. On the other hand, particles that are spreading by disintegration will characterize magnetic tracers, and the magnetic signals will be distributed over a wider region with reduced intensity and amplitude. Besides disintegration, processes such as swelling of hydrophilic polymers either spreading of multiparticulate systems can be also monitored.

In principle, either conventional or modified release solid dosage forms may be labelled and, therefore, can be evaluated by biomagnetic sensors. Hard capsules can be labelled by addition of the magnetic material directly to the filling (15,97). Tablets can be labeled by addition of the magnetic material to the powder blend or by drilling a small hole to be filled with magnetic material (13,19). Further, magnetically marked tablets may be coated for improving appearance and stability, for taste masking, or for providing controlled drug release (13,98). As well as unit preparations, multiparticulate dosage forms can also be magnetically labeled (17,99). Pellets are spheres of varying diameter which may be manufactured by using classical extrusion-spheronization method or further techniques as spray-drying or layer building, in which the magnetic material can be added for labelling. Once labeled, magnetic dosage forms provide an excellent opportunity to investigate the complex interactions between pharmaceutical processes and gastrointestinal physiology.

EVALUATING DOSAGE FORMS: ROLE OF BIOMAGNETIC SENSORS

As aforementioned, biomagnetic sensors are versatile technologies that can be used for a wide range of applications. For pharmaceutical research, these methods offer a unique opportunity to monitor dosage forms as well as diverse processes related to drug delivery without the use of ionizing radiation. Moreover, their non-invasive nature provides an excellent approach for better and more reproducible monitoring of the performance of dosage forms in man highlighting the role of GI physiology on drug absorption. In this section, the role of these sensors in the pharmaceutical research will be presented.

Magnetic Marker Monitoring

The method known as Magnetic Marker Monitoring (MMM) or Magnetic Moment Imaging (MMI) has been applied for the evaluation of solid dosage forms *in vitro* as well as in human GI tract (8,12). SQUIDs and AMR are the sensors used in these approaches and are useful for monitoring components of the magnetic moment dipole enabling to reconstruct the location, orientation and strength of the dipole.

The disintegration process of tablets and capsules can be accurately determined *in vitro* (90,97). While the dosage form is characterized as a marker, the magnetic dipole moment remains stable; however, when the release of magnetic particles from the dosage forms occurs, those particles lose their orientation and do not generate a background signal; therefore, the time course of the magnetic moment is the direct measurement of disintegration (Fig. 6). Such property is useful for evaluating the influence of disintegrants, tableting conditions as well as *in vivo* behavior of tablets. Additionally, both swelling and erosion processes in modified release dosage forms might be investigated (18).

Concerning the complexity of GI physiological functions, it is expected that the transit parameters can lead to significant differences in the dosage form behavior as well as in the drug delivery process. MMM studies were able to evaluate the GI transit of solid dosage forms in different segments (8,18,19). The magnetic marked dosage form is located with very high precision (1 mm) in three dimensions (x, y, z) with respect to the body, and the data are transferred to a coordinate system referring to the anatomical references.

It was demonstrated that esophageal transit time of hard gelatin capsules is influenced by co-swallowed water volumes, body position and propulsion velocity (100). With respect to the gastric residence, small intestinal and colonic

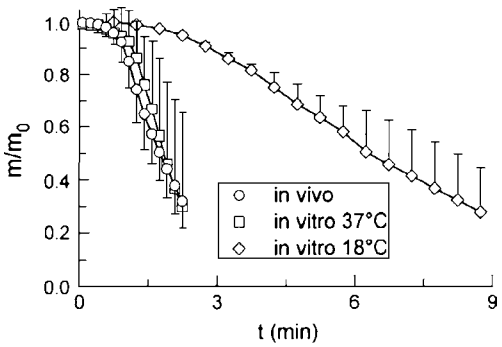

Fig. 6 Magnetic moments measured for capsules *in vitro* and *in vivo*. During the disintegration, the magnetic particles lose their orientation and do not produce a net magnetic moment (97).

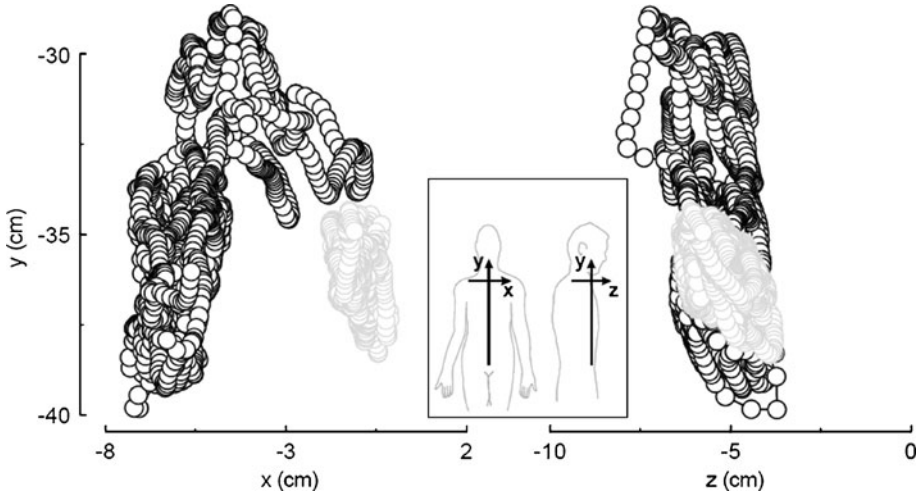

Fig. 7 Gastrointestinal transit of a magnetically labelled tablet. The measurements in different segments have been taken during 1 s (8).

transit times, non-disintegrating pellets, disintegrating and non-disintegrating hard capsules as well as enteric coated tablets can be evaluated. Intragastric and intestinal location of a non-disintegrating dosage form during its residence time has been monitored, showing that differences in the activity contraction are able to affect the disintegration rate (Fig. 7). Meanwhile, investigations regarding small intestinal transit have characterized periods of stasis intermitted by episodes of either slow or rapid transport. Similar to small intestine, colonic movements are not continuous and are extremely variable, depending on a number of factors. Colonic movements have been studied by employing MMM and showed to be influenced by mass transport.

MMM is a reliable tool for investigation of GI performance of solid dosage forms. The high spatial and temporal resolution towards monitoring dosage forms in real time is also suitable for quantitative determination of drug release processes as well as the relationships between GI physiology and drug absorption.

Biosusceptometric Analysis

ACB sensors are versatile tools for monitoring solid dosage forms *in vitro* and *in vivo* through magnetic signals as well as magnetic images (13–17,98). The major advantage of this method is the capability for recording GI motility in real time. Since the magnetic signal depends on the distance between the sensor positioned on the abdominal surface and the ingested magnetic material, the movements of the GI wall generated by smooth muscle contractions promote direct modulations in the signal representing either gastric or colonic motility (Fig. 8). Interactions between GI motility parameters and drug release processes can be exploited towards understanding the fundamental factors affecting dosage forms and, consequently, the drug bioavailability.

Recently, technological improvements of ACB sensors allowed evaluating GI motility and its interaction with pharmaceutical processes (11). Hence, the influence of different magnetic dosage forms (hard gelatine capsules

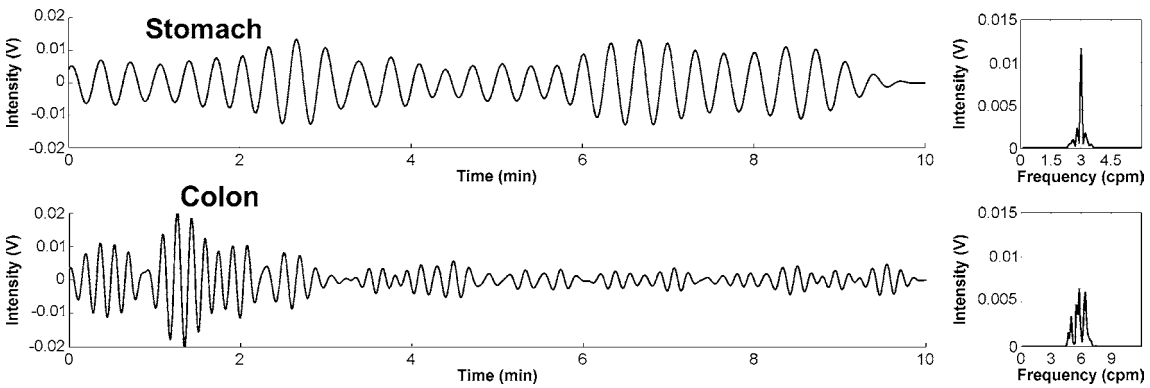

Fig. 8 Typical activity contraction from stomach and colon recorded by ACB sensors. Right panels: characteristics frequencies of contractions for both segments.

and tablets) on the oesophageal transit time and transport velocity has been evaluated. Gastric emptying and gastrointestinal transit of magnetic multiple-unit systems designed for colon-specific drug release were also evaluated under influence of both pre- and postprandial states (17).

Modified release dosage forms obtained from hydrophilic polymers are designed for achieving specific pharmacokinetic profiles, for maximizing the bioavailability and for improving the therapeutic effects (101). Notwithstanding, regional differences in GI physiology may exert critical influence on their performance. Regarding this, ACB sensors associated with standard methods can provide useful analysis of *in vitro* swelling as well as of drug release processes (Fig. 9). Moreover, data concerning GI transit and motility patterns can be useful for establishing appropriate *in vitro–in vivo* correlations.

ACB sensors have also been introduced as an alternative method to investigate the influence of compression forces on the disintegration process of tablets. In addition, this method can estimate the kinetics of disintegration process for uncoated and coated tablets (16). This approach can be useful for pharmaceutical development, since it can provide further investigation on the influence of different disintegrants in drug delivery processes.

ACB has gained acceptance for evaluating pharmaceutical processes *in vitro* and in the human GI tract. An important feature of this method is its ability to evaluate simultaneously pharmaceutical processes and its interactions with GI physiological parameters.

PHARMACOMAGNETOGRAPHY

Scintigraphy combined with pharmacokinetic studies has initiated the modality known as pharmacoscintigraphy (3).

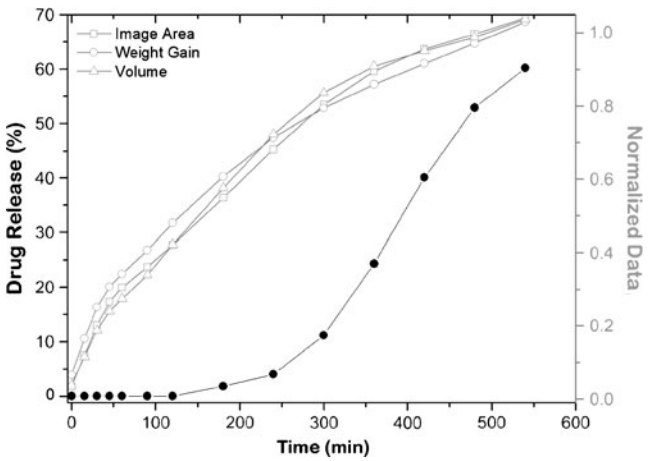

Fig. 9 *In vitro* characterization of swelling process of hydrofilic magnetic matrices in relation to the drug release profile. It was observed that the increases in the magnetic image area (*open circles*) correspond to the water uptake and subsequent drug release (*black squares*).

Until now, pharmacoscintigraphy had been an important approach for providing information about GI transit of radiolabelled dosage forms dealing with drug release and subsequent drug absorption (3–7).

Lately, successful attempts allowing the incorporation of magnetic particles instead of radioisotopes in dosage forms associated with the development of biomagnetic technologies have contributed to advances in pharmaceutical research, mainly due to the possibilities for monitoring the multiple factors affecting oral formulations. By combining biomagnetic monitoring with pharmacokinetic profiles, a new concept has been introduced (12). Hence, the pharmacomagnetography, in analogy to pharmacoscintigraphy, has the challenge of clarifying the complex interactions between GI physiology, drug release mechanisms and bioavailability.

How GI physiology influences the performance of dosage forms is notably relevant for the development of drug delivery systems designed to release drugs at specific sites. Hereafter, some data highlighting the interactions of GI parameters, drug release and pharmacokinetics will be exploited.

Extended-Release Tablets

Studies based on pharmacomagnetography, employing MMM, have demonstrated great predictability for the establishment of *in vitro-in vivo* correlations. Such applications intended to investigate the effect of food on plasma profiles of extended release formulations and for the development of dynamic pharmacokinetic models regarding drug absorption on different segments of GI tract (18–20).

Magnetic recordings and pharmacokinetics yielded comparisons between location of felodipine tablets and drug plasma concentrations under fasting and fed conditions (18). Plasma profiles were variable and highly influenced by intragastric location of magnetically marked tablets (Fig. 10).

In another study, the pharmacomagnetography was used to assess the food effect on the bioavailability of amoxicilin and clavulanic acid (19). The combined analyses allowed concluding that the reduced bioavailability of amoxicilin under fasting conditions is due to early gastric emptying, whereas the bioavailability of clavulanic acid decreases postprandially, due to the delayed gastric emptying (Fig. 11).

Accordingly, approaches like pharmacomagnetography are effective means to evaluate the real extension of complex interactions of oral drug delivery and GI tract, where a plethora of physiological factors interferes.

Enteric Coated Tablets

An essential prerequisite for colon-specific drug delivery systems is to prevent the drug release until the dosage form

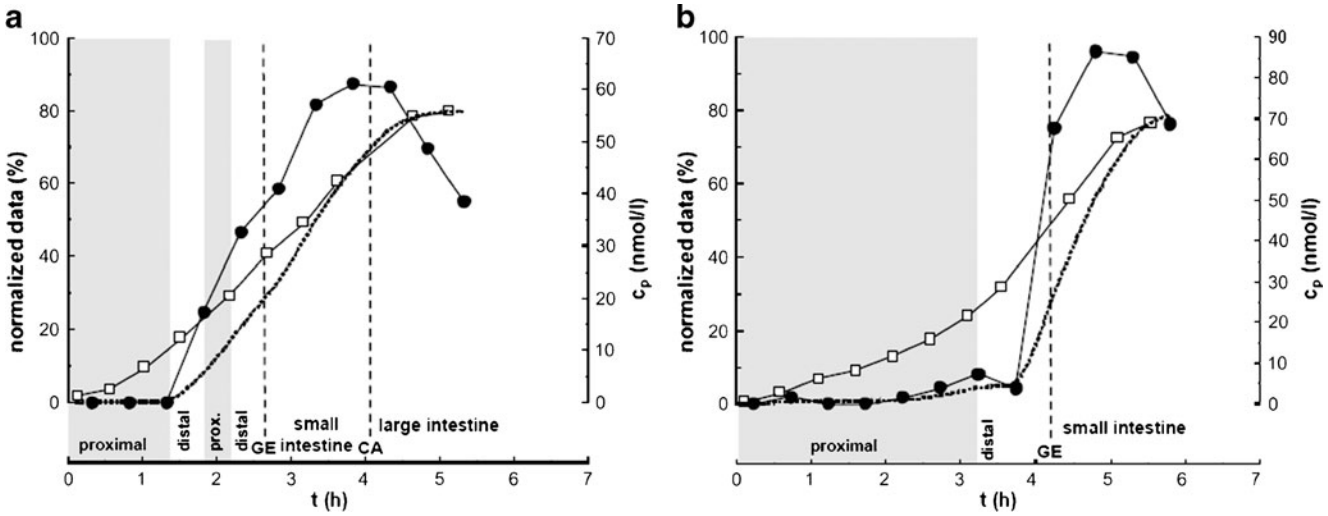

Fig. 10 Comparison of plasma concentrations (*black circles*), gastrointestinal transit (*grey areas*), drug release profiles (*open squares*) and bioavailability profiles (*dashed lines*) for fasting **a** and postprandial states **b** (18).

reaches the colon (73). A number of approaches such as prodrugs, pH-sensitive coatings as well as biodegradable polymers have been proposed to achieve colon-targeted release. Nonetheless, drug delivery to the colon based on pH-sensitive coatings involves critical considerations concerning highly variable pH in different segments and according to prandial state, gastric emptying and small intestine transit (74).

Realistic evaluation regarding the performance of enteric coated tablets with pH-sensitive polymers has been exploited by employing biosusceptometry and pharmacokinetic analysis. Typical pharmacomagnetography data obtained for a representative subject showed that no drug release had occurred until the dosage form reached the colonic region (Fig. 12).

ACB associated with pharmacokinetic data is a reliable approach for providing data concerning drug release processes from magnetic enteric coated tablets, since it is possible to evaluate simultaneously drug delivery processes and gastrointestinal transit parameters.

Modified-Release Dosage Forms

Modified-release systems either intended for delayed or sustained drug release can be formulated by using hydrophilic polymers, including cellulose derivatives (101). Drug release from these systems is dependent upon pharmaceutical and physicochemical factors highlighting diffusion as the dominant mechanism (102).

The variability in gastrointestinal transit has significant implications for the *in vivo* performance of modified-release

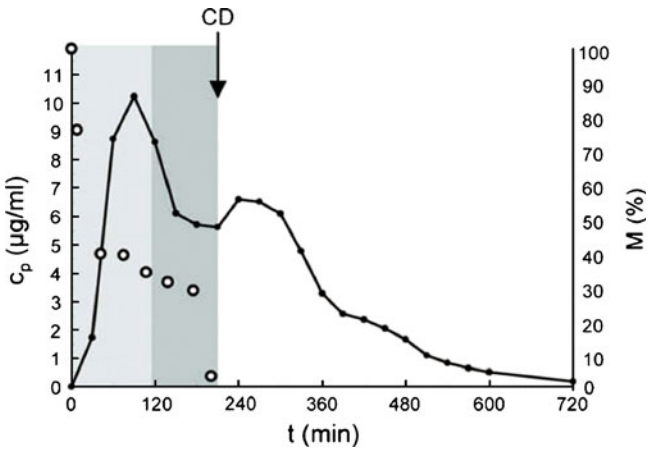

Fig. 11 Amoxicillin plasma concentrations (*black line*), relative magnetic moment (*open circles*), intragastric location (*grey areas*) and time point for complete disintegration (*CD*) (12).

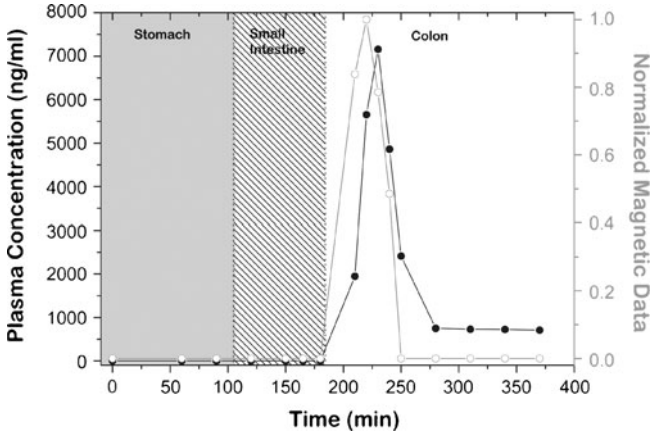

Fig. 12 Diclofenac plasma concentration (*black circles*) and magnetic image area (*open circles*) of magnetic enteric-coated tablet. Drug release had occurred after disintegration of the tablet in the colonic region.

systems, since the residence time in different segments must be suitable for allowing the complete drug release and absorption (81). Pharmacomagnetography relies on the investigation of gastrointestinal transit associated with bioavailabity outcomes. A typical analysis by employing ACB and pharmacokinetics demonstrated that a modified-release dosage form administered to a fasted subject has provided sustained drug release and absorption throughout GI tract (Fig. 13).

Multiparticulate Delivery System

Controlled drug delivery systems for oral administration can be basically divided into single and multiparticulate dosage forms, in which one dose is distributed into several subunits (103,104). Although similar drug release profiles can be obtained, multiparticulate dosage forms have great interest due the advantages for improved bioavailability and safety drug release (103–105). Other advantages are the more predictable gastric emptying and lower variability in absorption, since the GI transit of multiparticulate dosage forms is more predictable. Consequently, intra- and inter-individual variations in the drug absorption are less frequently observed (106).

A magnetic multiparticulate system for the colonic release of drugs, which showed efficient to target the triamcinolone as model drug, was developed and assessed by *in vitro* analyses (99). ACB associated with pharmacokinetic analysis was employed for providing a better characterization of the influence of food on the performance of the multiparticulate system. *In vivo* analyses proved the influence of the postprandial state on the multiparticulate system, i.e., the gastric retention time was altered in the postprandial condition, directly influencing the triamcinolone plasma concentration (Fig. 14).

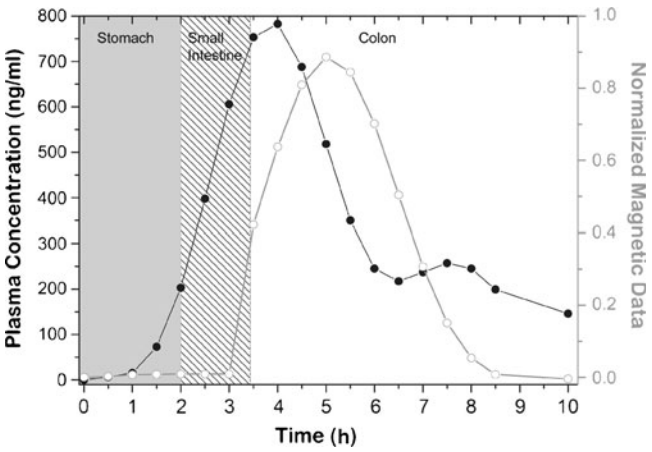

Fig. 13 Diclofenac plasma concentration (*black circles*) and magnetic image area variation (*open circles*) of swellable matrix. Sustained drug release and absorption throughout GI tract segments. Maximum concentration was observed in colonic region with subsequent maximum image area variation.

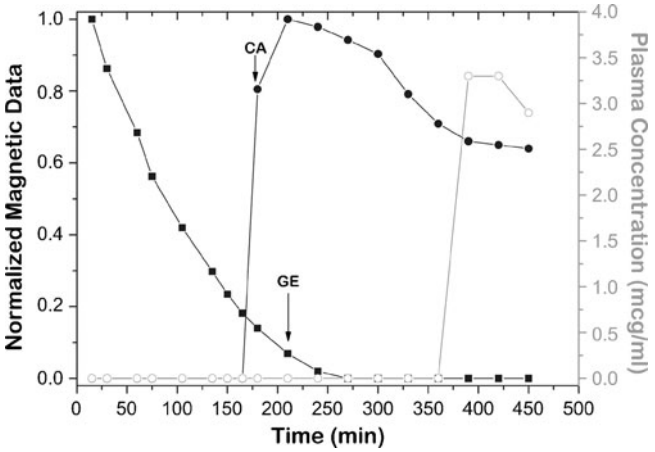

Fig. 14 Triamcinolone plasma concentration (*open circles*) and magnetic data (*black symbols*) representing the gastrointestinal transit of the multiparticulate delivery system. The arrows indicate the gastric emptying (*GE*) and colonic arrival (*CA*) of the magnetic pellets. Even before the complete gastric emptying, the pellets were detected on colonic region.

CHALLENGES AND FUTURE DIRECTIONS

The aforementioned biomagnetic methods are noninvasive and radiation-free techniques at our disposal. Such methods can now be utilized in combination with traditional pharmacokinetic analysis, referred as pharmacomagnetography, in order to improve our understanding of the role of GI physiology on drug release and absorption processes.

Successful development of more effective drug delivery systems relies on the full knowledge of the GI physiological parameters that influence the dosage forms and, therefore, drug bioavailability. In this sense, SQUIDs, AMR or ACB sensors can be useful for providing reliable analysis concerning site-specific drug delivery systems.

If *in vivo* performance of oral dosage forms is complex and not always completely elucidated, even less is understood about the gastrointestinal behavior of drug delivery systems in the disease state. Delayed gastric emptying influences the delivery and absorption of orally administered drugs in the small intestine, generally resulting in later or fluctuating maximal serum concentrations (107). This is particularly important when a rapid onset of drug action is required and has been documented with oral hypoglycemic drugs (108). Drugs with longer half-lives are less likely to be affected (109).

Since the small intestine is the gastrointestinal tract region where absorption takes place, it is likely that drug impairment occurs in patients with small intestine diseases (malabsorption syndromes). Abnormal absorption of rifam-

pin, an antimycobacterial drug employed for tuberculosis treatment, occurs in celiac disease (110), and malabsorption of antimycobacterial drugs was described in AIDS patients with small intestine involvement (111).

In addition to diseases, it is also possible to manipulate pharmacologically the gastrointestinal motility and transit. Concomitant administration of drugs such as prokinetics, laxatives, and opioids may result in a faster or delayed transit, consequently limiting the performance of drug delivery systems in human GI tract (112–114). Biomagnetic techniques are particularly interesting in order to evaluate the performance of dosage forms on such conditions, since they are suitable for evaluating pharmaceutical processes and gastrointestinal parameters simultaneously.

In this review, we highlight the recent applications of the most prominent biomagnetic methods on some aspects of gastrointestinal physiology and the interactions with pharmaceutical processes. The latest technical developments as well as the association with pharmacokinetics outcomes, termed pharmacomagnetography, have made these methods as prominent as scintigraphy to analyze drug release and consequent bioavailability. Technical improvements or the association with conventional analytical tools could extend their applicability to other areas comprising especially the pharmaceutical quality control.

There are still gaps in our knowledge regarding various aspects of GI physiology, diseases and drug delivery. Our expectation is that biomagnetic techniques can be extensively exploited to provide better understanding of such relationships for developing more reliable drug delivery systems.

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