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Research paper

Pharmaceutical applications of AC Biosusceptometry

Luciana A. Corá [a,c,*], Madileine F. Américo [a], Fernando G. Romeiro [b], Ricardo B. Oliveira [c], José Ricardo A. Miranda [a]

[a] Department of Physics and Biophysics, IBB, Sao Paulo State University, Botucatu, SP, Brazil
[b] Department of Clinical Medicine, FMB, Sao Paulo State University, Botucatu, SP, Brazil
[c] Department of Clinical Medicine, FMRP, Sao Paulo University, Ribeirão Preto, SP, Brazil

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ABSTRACT

AC Biosusceptometry offers an alternative to investigate noninvasively and without ionizing radiation the behavior of solid dosage forms *in vitro* and in the human gastrointestinal tract. This versatility allowed applying this technique in a wide field ranging from characterization of the disintegration process to elucidation of how the physiological parameters can interfere with pharmaceutical processes. It is increasingly important to understand how oral solid dosage forms behave in the human gastrointestinal tract. Once labelled, magnetic dosage forms provide an excellent opportunity to investigate complexes' interactions between dosage form and gastrointestinal physiology. In this paper, basic principles of this biomagnetic instrumentation and of the quantification based on magnetic images are reviewed. Also will be presented are some of the most recent applications of AC Biosusceptometry in the pharmaceutical research including oesophageal transit, gastric emptying and transit time of multiparticulate dosage forms, hydrophilic matrices and disintegration of tablets.

1. Introduction

The oral route is still preferred for drug administration, since over 80% of pharmaceutical products are given orally [1]. This extensive use of solid oral medication implies that the gastrointestinal tract is an appropriate site for drug absorption.

Drug absorption from the gastrointestinal tract can be regarded as a part of a serial process that includes the drug release from the disintegration of the dosage form, its dissolution on the gastrointestinal fluids, its solubility as well as the physicochemical properties and its effective permeability coefficient [2]. Product bioavailability can be markedly influenced by gastrointestinal environment, whose regional differences must be fully investigated to provide more reliable dosage form design, as well as more predictable *in vitro–in vivo* correlations [3].

Biomagnetic techniques are employed nowadays to investigate the performance of solid dosage forms in human gastrointestinal tract [4–6]. Such techniques have a number of advantages over classical methods towards elucidating how physiological variables can influence the drug release processes by employing sensitive magnetic sensors.

AC Biosusceptometry (ACB) embraces a class of magnetic sensors that employs induction coils to measure biomagnetic fields resulting from ferromagnetic sources in response to an applied magnetic field [7–9]. Currently, this method has been recognised as an alternative tool for pharmaceutical research due to its ability in evaluating conventional solid dosage forms and modified-release systems *in vitro* or under influence of gastrointestinal physiological parameters [10–14]. The aim of this review is to present the status of ACB technique and discuss its future application in pharmaceutical research.

2. How do ACB sensors work?

2.1. Instrumentation

AC Biosusceptometry (ACB) sensors are composed of pairs of induction coils separated by a fixed baseline (Fig. 1a and b). Each pair of coils consists of excitation (outer) and detection (inner) coils in a first-order gradiometric configuration that provides good signal-to-noise properties. Basically, the excitation coil works with a frequency of 10 kHz and a current of 15 mA that generates a magnetic field of 20 G and induces equal magnetic flux in the detection coils; hence, when the ferromagnetic sample is nearest to the sensor an imbalance in the voltage occurs, due to the changes in the differential flux between the detection coils. Therefore, the ACB sensor can measure the magnetic signals generated by the magnetic flux variation between these coils through lock-in amplifiers.

For measuring such magnetic signals, the instrumentation has been developed to improve spatial resolution and sensitivity for

* Corresponding author. Department of Physics and Biophysics, IBB, Sao Paulo State University, Botucatu, SP, Brazil. Tel.: +55 14 3811 6254.
E-mail address: lacora@ibb.unesp.br (L.A. Corá).

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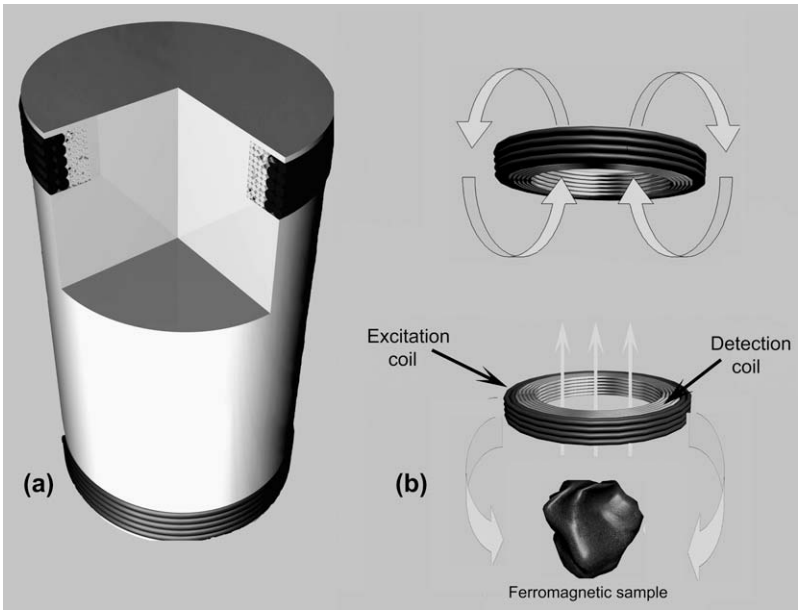

Fig. 1. Representation of an AC Biosusceptometry sensor. (a) Single-sensor magnetic device in coaxial arrangement, (b) diagram illustrating its work fundamentals.

pharmaceutical applications. The measurement device includes seven ACB sensors and a data acquisition system, recording the magnetic field distribution at multiple locations with high temporal resolution and reasonable spatial resolution (Fig. 2). The sampling frequency from 10 to 200 Hz may be employed and it depends on the aims of the study. A more detailed description of the physical principles of ACB sensors can be found in recent publications [9,15,16].

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), the amount of ferromagnetic material and the distance among the sensors and the ferromagnetic sample [7].

ACB sensors have an important advantage in comparison with other biomagnetic measurement devices, since it is needless to operate in magnetically shielded rooms. Additionally, as the ferromagnetic particles are not previously magnetised, they allow monitoring the marker location and subsequent processes that occur after the spreading of the particles in the gastrointestinal (GI) tract.

2.2. 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]. The signal intensity depends upon the amount of ferromagnetic material, and the distance between sensors and sample.

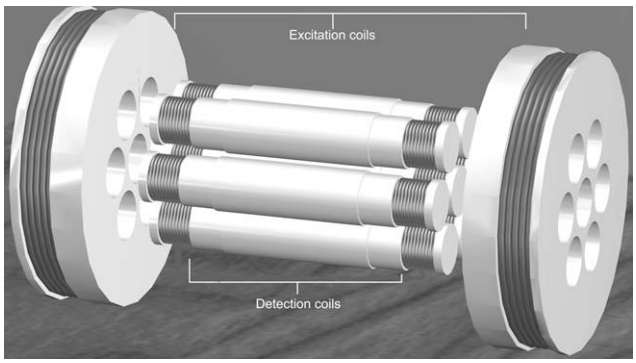

Fig. 2. AC Biosusceptometry multisensor system showing the individual arrangement of excitation coils and seven pairs of detection coils.

Once acquired, the magnetic signals represent time series matrices computed at regular time intervals. These matrices (7 points) are derivative from magnetic field distribution that are mathematically interpolated and processed in order to obtain sequential degraded images (256×256). Afterwards, the images are submitted to the digital image processing tools for background subtraction, brightness and contrast adjustments and to be segmented. The segmentation is the procedure useful to find edges in the magnetic images which allow calculating the area of all pixels in the delimited image by summing the areas of each pixel in the image. The overall accuracy of the imaging and quantification procedures has been determined by measurements on phantoms designed for magnetic markers that were moved by a mechanical device along transversal and longitudinal axis. Details about this method to obtain images with ACB sensor were reported earlier [11,14].

To obtain the location of the ferromagnetic source regarding to the body, data are transferred to a coordinate system according to the anatomical external references. Depending on the location, the intensity of the magnetic signals is influenced by variations in the position of the magnetic source. To avoid such variability, magnetic image area can be computed by associating the values of intensity measured at multiple locations that corresponds to each pixel in the greyscale images.

Imaging methods are becoming useful tools for monitoring pharmaceutical processes and offer opportunities to investigate the behavior of solid dosage forms both *in vitro* and *in vivo*. For this reason, magnetic images can also contribute to increase our knowledge of the gastrointestinal parameters variability on drug bioavailability.

3. Magnetic solid dosage forms

Solid dosage forms can be labelled as magnetic markers by incorporating powered ferromagnetic particles. Ferrites are permanent magnets made of ceramic with magnetic permeability (μ) around 3000. Due to its nontoxic and insoluble nature, it can be used as magnetic labelling material [17,18].

The required amount of ferrite depends predominantly on the sensitivity of the measurement system. Currently, the ACB sensors are able to detect 300 mg of magnetic material incorporated into pellets or 500 mg for a magnetic tablet (10 mm diameter). This amount of ferromagnetic material required is still too high in comparison with the amounts employed by others biomagnetic methods [5].

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 release of the ferromagnetic material. Hence, particles that are concentrated can be taken as markers, with a magnetic signal that remains stable, with higher intensity and amplitude. For practical explanation, markers are dosage forms in a nondisintegrated status, such as tablets, hard capsules and hydrophilic matrices. On the other hand, particles that are spreading by disintegration will characterize magnetic tracers, and the magnetic signals will be distributed over a longer region with reduced intensity and amplitude.

In principle, either conventional or modified-release solid dosage forms may be labelled and, therefore, they can be evaluated by ACB sensors. Briefly, hard gelatine as well as hydroxypropylmethylcellulose (HPMC) capsules are dosage forms in which a powder mixture can be filled directly into a capsule shell without granulation or compression processes [19]. Tablets are solid dosage forms containing therapeutic substances with or without added pharmaceutical ingredients, as diluents, disintegrants, colorants, binders, solubilizers, and coatings [20,21]. It can be manufactured on the industrial scale by compression, using punches and dies of various shapes and sizes enabling the preparation of a wide variety of products. Further, tablets may be coated for appearance, for stability, for taste masking or to provide controlled drug release.

Monolithic matrices are extensively utilized for the preparation of oral modified-release delivery systems [22]. Matrix systems generally consist of dissolved or dispersed drugs within a swelling or slowly eroding polymer matrix. Drug release from these systems is governed by water penetration into the matrix followed by the diffusion of drug into the surrounding medium, erosion of the matrix or combination of both [23–25].

Multiparticulate dosage forms offer a number of potential advantages over monolithic preparations in terms of their dispersion characteristics and performance when distal regions of gastrointestinal tract are desirable as a target of drugs [26]. Pellets are spheres of varying diameter that may be manufactured by using classical extrusion–spheronization method or further techniques as spray-drying or layer building [27].

It is increasingly important to understand how oral solid dosage forms behave in the human gastrointestinal tract. Once labelled, magnetic dosage forms provide an excellent opportunity to investigate complexes' interactions between dosage form and gastrointestinal physiology.

4. Dosage forms and gastrointestinal tract – how physiological parameters can influence it

Drug absorption can be highly dependent on gastrointestinal motility, with absorption kinetics varying hugely in different segments of the gastrointestinal tract [28–30]. Furthermore, the influence of feeding and temporal patterns on GI transit has been considered of great relevance in attempting to optimize drug absorption [31].

Gastrointestinal motility is controlled by motor patterns according to the prandial state. After cessation of the digestive processes, motility is governed by the migrating myoelectric complex (MMC), which is organized into alternating cycles of motor activity propagating distally from the stomach to the terminal ileum over 90–120 min [32,33]. Post-prandially, motility is characterized by contractions of variable amplitude and frequency according to the gastrointestinal segment and persists as long as the bulk of food remains in the stomach [34].

It is expected, therefore, that GI motility patterns have significant implications on drug delivery processes. A number of studies have stated that gastric emptying has an important role in determining the retention time of dosage forms besides to be highly variable [35–37]. On the other hand, the small intestinal transit time seems to be less variable, despite some recent studies demonstrate that intra-individual data can vary significantly [35,38]. Movements through the colon are markedly slow and are generally considered to have a longer transit time than the small intestine [39,40].

Concerning these physiological conditions, it may be supposed that *in vivo* behavior of solid dosage forms cannot simply be predicted from commonly used *in vitro* testing methods. This is particularly important for pharmacokinetics of a drug which is influenced by interplay of parameters such as gastrointestinal physiology, drug solubility, dissolution, permeability, distribution and elimination [41,42]. Even before drug absorption, the release mechanisms should be considered since it reflects the dynamics of rate and extent of drug absorption.

Besides gastrointestinal motility, there are still many aspects that are often considered well understood. However, gastrointestinal fluid volume, its composition, microflora and pH, which are still influenced by prandial state, gender, age and diseases, have been neglected in models for predicting oral drug absorption and bioavailability [3].

In terms of drug delivery research, there are still gaps in our knowledge of gastrointestinal physiology to move forward effectively in development of more reliable therapeutic systems [1,27,43,44]. Noninvasive techniques are responding to the demands to improve our fundamental understanding of gastrointestinal physiology towards providing information on drug delivery and its interplays at specific organs.

5. Evaluating pharmaceutical processes – role of ACB sensors

5.1. Oesophageal transit

Oesophageal transit of solid dosage forms is normally complete within few seconds. The volume of swallowed water, the body position, and the size, shape and surface properties of the dosage form have been described as important parameters to determine the oesophageal transit time [45–50]. Moreover, there are a number of reports about oesophageal damage related to pill-induced oesophagitis [51–53].

Since oral solid dosage forms are not identical in terms of size, shape and coating, studies should be conducted to establish the oesophageal transit for different formulations. Oesophageal transit scintigraphy has become the standard technique; however, the evaluation is limited by the low sample rate and the prolonged washout time for radioactivity from the gastrointestinal tract, despite minimal radiation exposure [54–56].

Biomagnetic techniques are valuable tools for oesophageal transit studies. It has been demonstrated the magnetic marker monitoring (MMM) as an alternative method with advantages over scintigraphy, mainly due to nonradiation exposure and high tempospatial resolution [57].

Likewise, ACB sensors could be employed to evaluate oesophageal transit of magnetic solid dosage forms noninvasively, with high tempospatial resolution and no magnetically shielded room is needed. In a recent study, the influence of different dosage forms (hard gelatine capsules and tablets) on the oesophageal transit

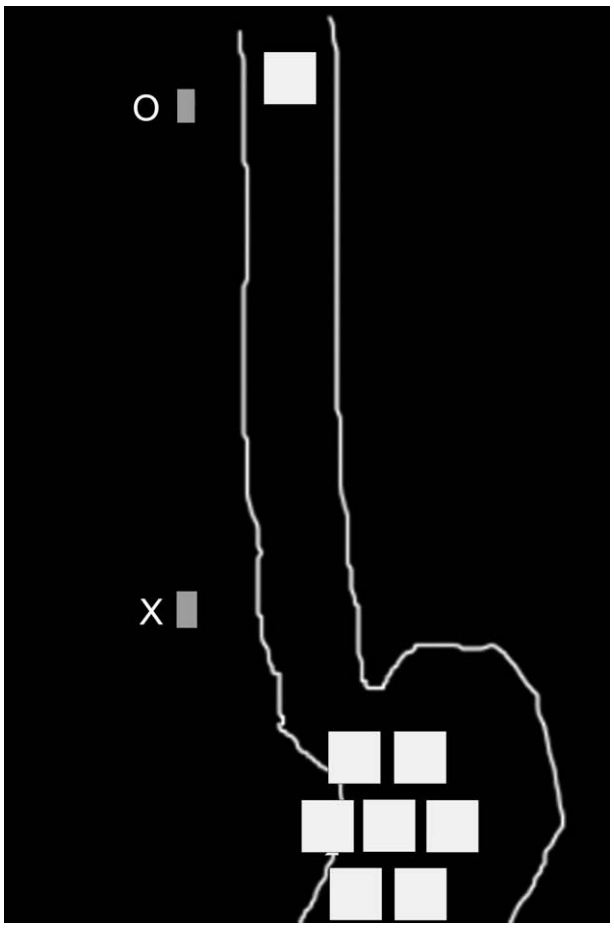

Fig. 3. Regions of interest (ROIs) drawn in the scintigraphic images based on oropharynx (O) and xiphoid (X) anatomical landmarks. This procedure was adopted to provide comparative analyses between scintigraphy and ACB.

time and transport velocity has been evaluated by ACB sensors and Scintigraphy (unpublished data). The investigations were performed in six healthy volunteers in upright position who swallowed hard capsules (size 0; 25 mm × 7.3 mm) and film-coated oblong tablets (16.2 mm × 8.1 mm) weighing 500 mg, 800 mg and 1000 mg with 50 ml of water. Each volunteer had oesophageal transit time evaluated twice on separate days. Oesophageal transit of tablets and capsules contained ferrite (Fe_2MnO_4; $\phi \leqslant 53$ μm) was evaluated by ACB sensors: one of them was placed on oropharynx and seven sensors over xiphoid and proximal stomach, with acquisition frequency of 200 Hz. For Scintigraphy studies, the formulations described above were radiolabeled by adding 37 MBq dose of technetium-99 m (^{99m}Tc) sodium pertechnetate. The dynamic-imaging protocol was composed of 10 frames per second for 60 s (total of 600 frames) in a 64 × 64 pixel matrix. Biomagnetic and scintigraphic data were converted to ASCII for further analysis and quantification.

Regions of interest (ROIs) with size and arrangement identical to ACB sensors (Fig. 3) were drawn on the scintigraphic images. ROIs were positioned based on anatomical landmarks to provide comparative analyses between both techniques.

Two parameters were determined for this study: the oesophageal transit time (s), defined as the time necessary for the dosage form to pass from the oropharynx until to reach the proximal stomach and the oesophageal transport velocity (cm/s) determined by measuring the distance and time from the oropharynx until the proximal stomach. Scintigraphic and magnetic data were expressed as mean ± SE. Influence of the weight of dosage forms in the oesophageal transit time was tested by one-way ANOVA design in the general linear model, followed by sequential contrasts with a Bonferroni correction of alpha values. Mean values were statistically significant for nonparametric *t*-test at least $p \leqslant 0.01$.

The results had shown no significant difference on the transit time evaluated for both techniques (Fig. 4a and b). Oesophageal transit time was not affected by dosage form administered either tablets or capsules. Mean transit times of both formulations had a significant difference for weights of 500 mg and 1000 mg ($p < 0.001$) (Table 1). This difference was not significant when formulations of 800 mg were swallowed. Oesophageal transport velocity was also investigated and the results showed no significant difference for both techniques, as well as for dosage form administered (Table 2). However, the oesophageal transport velocity of tablets or capsules with 1000 mg was significantly faster than of 500 mg formulations ($p < 0.02$). This difference was not significant in comparison with formulations of 800 mg.

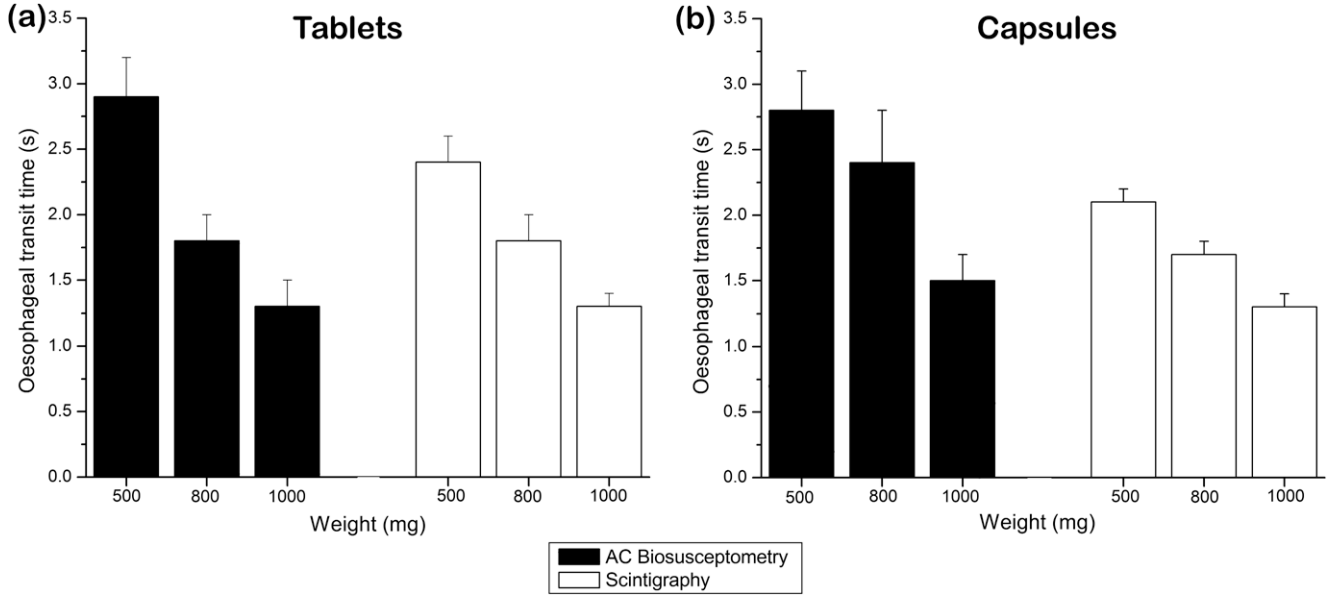

Fig. 4. Oesophageal transit times of tablets and capsules at different weights evaluated by AC Biosusceptometry and Scintigraphy.

Table 1
Oesophageal transit times of capsules and tablets at different weights obtained from biomagnetic and scintigraphic methods (mean ± SE).

Weight (mg)	Oesophageal transit time (s)			
	Biosusceptometry		Scintigraphy	
	Capsules	Tablets	Capsules	Tablets
500	2.40 ± 0.3	2.90 ± 0.3	2.10 ± 0.1	2.40 ± 0.2
800	2.80 ± 0.4	1.80 ± 0.2	1.70 ± 0.1	1.80 ± 0.2
1000	1.50 ± 0.2*	1.30 ± 0.2**	1.30 ± 0.1†	1.30 ± 0.1††

* $p < 0.009$.
** $p < 0.001$.
† $p < 0.002$.
†† $p < 0.003$ comparison between 500 mg vs. 1000 mg.

Table 2
Oesophageal transport velocities of capsules and tablets obtained from biomagnetic and scintigraphic methods (mean ± SE).

Weight (mg)	Transport velocity (cm/s)			
	Biosusceptometry		Scintigraphy	
	Capsules	Tablets	Capsules	Tablets
500	8.50 ± 1.70	7.80 ± 0.60	9.00 ± 0.90	9.80 ± 1.10
800	13.60 ± 3.80	16.40 ± 2.40	13.10 ± 1.70	13.10 ± 1.50
1000	16.10 ± 2.10*	18.30 ± 3.50*	16.40 ± 2.30†	18.50 ± 2.20††

* $p < 0.01$.
† $p < 0.01$.
†† $p < 0.007$ comparison between 500 mg vs. 1000 mg.

It has been demonstrated, for the first time, that ACB sensors may be employed to evaluate oesophageal transit time of solid oral dosage forms, towards providing new insights in analysis of oesophageal transport.

5.2. Gastric emptying and transit time of multiparticulate dosage forms

Colonic drug delivery has gained increasing importance for the delivery of drugs for treatment of local diseases, as well as for systemic delivery of proteins and therapeutic peptides [58]. Specific drug delivery systems to the colonic region should prevent drug release in the stomach and small intestine [59]. For this reason, development of multiparticulate delivery systems has demonstrated to be a reliable formulation and has advantages over single-unit dosage forms mainly due to its performance when distal regions of the GI tract are desirable as target of drugs [26,60].

In addition to prevent drug release before reaching the colonic region, gastric emptying and small intestinal transit must be considered. Gastric emptying is highly dependent on whether the dosage form is ingested in the fed or fasted state [61], and even though small intestinal transit times are fairly consistent, intra-individual variability should be investigated.

Recently, the ACB sensors have been proposed to evaluate a magnetic multiparticulate delivery system under influence of the prandial state on the gastric emptying and small intestinal transit time [62].

This study was performed in healthy volunteers after they have swallowed the multiparticulate dosage form, which consisted of 1000 mg of coated magnetic pellets filled into a size 00 uncoated hard HPMC capsules. Magnetic pellets were prepared by the powder layering method of binder solution and ferrite on nonpareils sugar beads (inert core; $\phi = 1.70$ mm) in a coating machine. The volunteers were evaluated on two circumstances, at least 1 week apart: on one occasion, the multiparticulate dosage form was administered after an overnight fasting (*Fasted phase*), and on another occasion following a standard breakfast with energy content of 502 Kcal (*Fed phase*). Measurements consisted of magnetic mon-

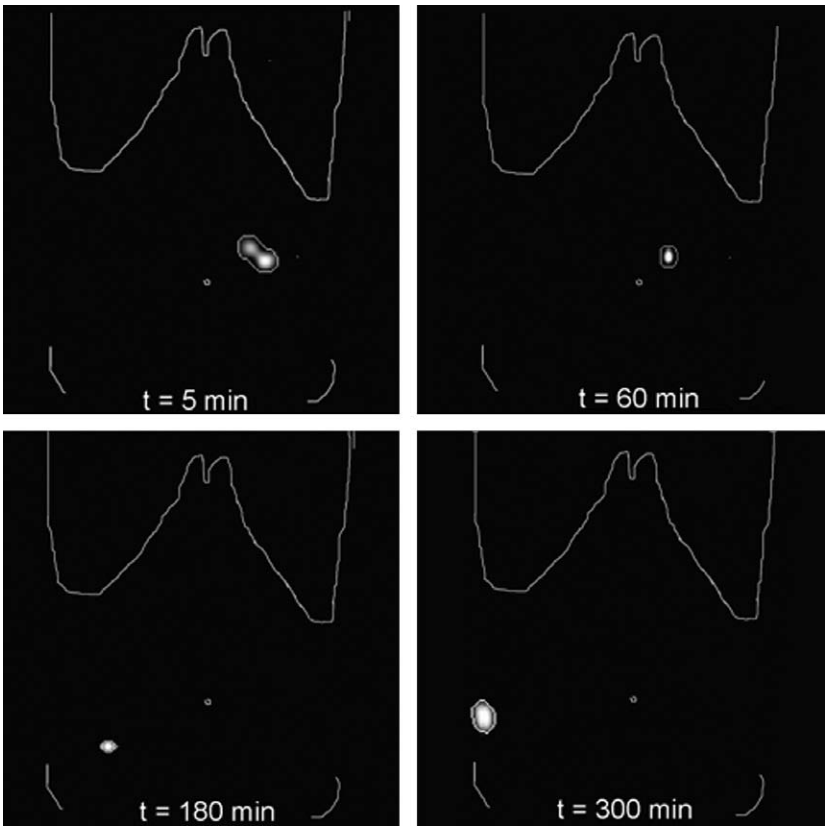

Fig. 5. Magnetic images of pellets at different time intervals towards illustrating the gastrointestinal transit time for a fasted subject.

Table 3
Gastric emptying, colon arrival and small intestinal transit time for multiparticulate formulation.

Subjects	Gastrointestinal transit		
	MGET (min)	MCAT (min)	MSITT (min)
Fasted			
1	28	218	190
2	37	244	207
3	22	133	111
4	34	201	167
5	34	195	161
6	42	176	134
7	30	160	130
8	16	127	111
9	66	269	203
Mean	34	191	157
SD	14	48	38
Fed			
1	172	336	164
2	92	369	277
3	90	296	206
4	120	346	226
5	210	412	202
6	150	354	204
7	131	335	204
8	62	321	259
9	98	337	239
Mean	125	345	220
SD	46	32	34

MGET is the mean gastric emptying time; MCAT is the mean colon arrival time; MSITT is the mean small intestinal transit time.

itoring of the abdominal surface in a square point matrix (5×5) drawn around the gastric and colonic regions. Each monitoring had 120 s duration and was recorded at 10 min intervals over 8 h. From the monitoring, field distribution was obtained magnetic to generate the magnetic images. Afterwards, digital image processing, magnetic images were segmented to calculate the area of all pixels in the image area. Gastric emptying time as well as the colonic arrival has been obtained by measuring the magnetic image area at different time intervals, and it was calculated by applying statistical moments.

Fig. 5 shows magnetic images of the multiparticulate system at different time intervals, towards illustrating key stages of the gastrointestinal transit for a fasted subject. The results showed that gastric emptying time was markedly different under fasted and fed conditions ($p < 0.01$). Delayed on emptying time of magnetic pellets is consistent with previously reported results that showed the gastric emptying time of solid dosage forms increases under fed conditions [63,64].

The small intestinal transit time of the magnetic multiparticulate system showed statistically significant differences between fed and fasted values ($p < 0.01$). Small intestinal transit of pharmaceutical dosage forms in humans presents periods of movements and stasis with considerable inter-subjects variability [38,65]. As expected, colonic arrival was notably influenced by the gastric emptying and transit time with significant difference for fasted and fed conditions ($p < 0.01$). Gastrointestinal transit time parameters for fasted and fed subjects are summarized in Table 3.

Regarding the importance of physiological parameters on the fate of dosage forms in humans, it is essential the development of noninvasive methods towards characterizing such delivery systems. Technologies such as ACB sensors have gained increased

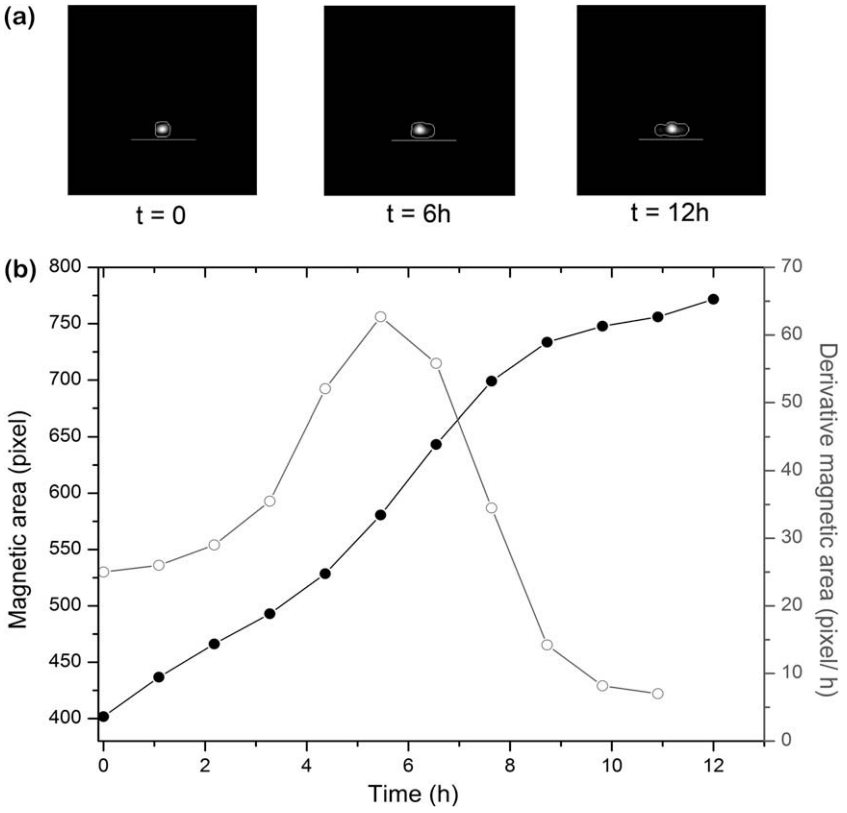

Fig. 6. Swelling profile of a matrix tablet *in vitro*. (a) Magnetic images of the tablet after immersion in the dissolution medium ($t = 0$), at 6 h and 12 h later, (b) kinetics of swelling represented by the first derivative of magnetic image area variation curves.

importance to evaluate pharmaceutical dosage forms under physiological conditions.

5.3. Hydrophilic matrices

Considerable attention has been focused on hydrophilic polymers in the design of oral modified-release systems [66]. HPMC is widely established as a release rate control polymer for hydrophilic extended release matrix tablets, due to its flexibility to obtain a desirable drug release profile, cost-effectiveness, variety of viscosity grade and regulatory acceptability [24].

Notwithstanding, all these innovations require methods able to characterize the behavior of modified-release dosage forms in humans, since the gastrointestinal physiology may exert a critical influence on its performance.

ACB sensors were employed in preliminary study (unpublished data) to investigate *in vitro* and in the human gastrointestinal tract the performance of a swellable matrix for controlled drug delivery. Circular hydrophilic matrix tablets (10 mm) consisted of 500 mg ferrite powder, 300 mg Methocel® K100LV, 190 mg microcrystalline cellulose, 5 mg Aerosil® and 5 mg magnesium stearate were compressed on the instrumented rotary tablet press. *In vitro* experiments were performed in 900 ml 0.05 M phosphate buffer (pH 6.8; 37 °C ± 0.5; rotation speed of 100 rpm). Matrices samples were placed in the dissolution medium and at regular intervals of 1 h for up to 12 h the ACB sensor was employed towards monitoring a square point matrix (5 × 5) drawn on the glass vessel. *In vivo* measurements were carried out in three healthy volunteers after ingestion of one tablet with 200 ml water. Magnetic monitoring was done on the abdominal surface at 20-min intervals up to 12 h post-dose. For both *in vitro* and *in vivo* monitoring magnetic field distribution to generate the magnetic images was obtained. In order to investigate the relationship between the magnetic area variation and the swelling process, time needed for the water absorbed to be able to promote the swelling and the variation in the magnetic area was calculated. For *in vivo* investigation gastrointestinal transit time and swelling rate were quantified.

This preliminary study was undertaken to evaluate whether the similarity observed in swelling profile *in vitro* was also reflected in *in vivo* measurements. Fig. 6 illustrates the swelling profile of a matrix tablet *in vitro* immediately after immersion in dissolution medium ($t = 0$), at 6 h and 12 h later. The overall kinetics of swelling tablet has been evaluated by the first derivative of magnetic image area variation curves. Results showed, in general, that liquid penetration occurred in a constant rate.

Fig. 7 shows the magnetic images of a matrix tablet in human colon 6 h post-dose, besides the kinetic of swelling process. It might be observed that swelling rate had a similar profile in comparison with the *in vitro* measurements. Gastric emptying time, small intestinal transit time and colon arrival time have been quantified in 3.5 ± 0.5 h; 2.5 ± 0.3 h and 6.5 ± 1.0 h (mean ± SD), respectively.

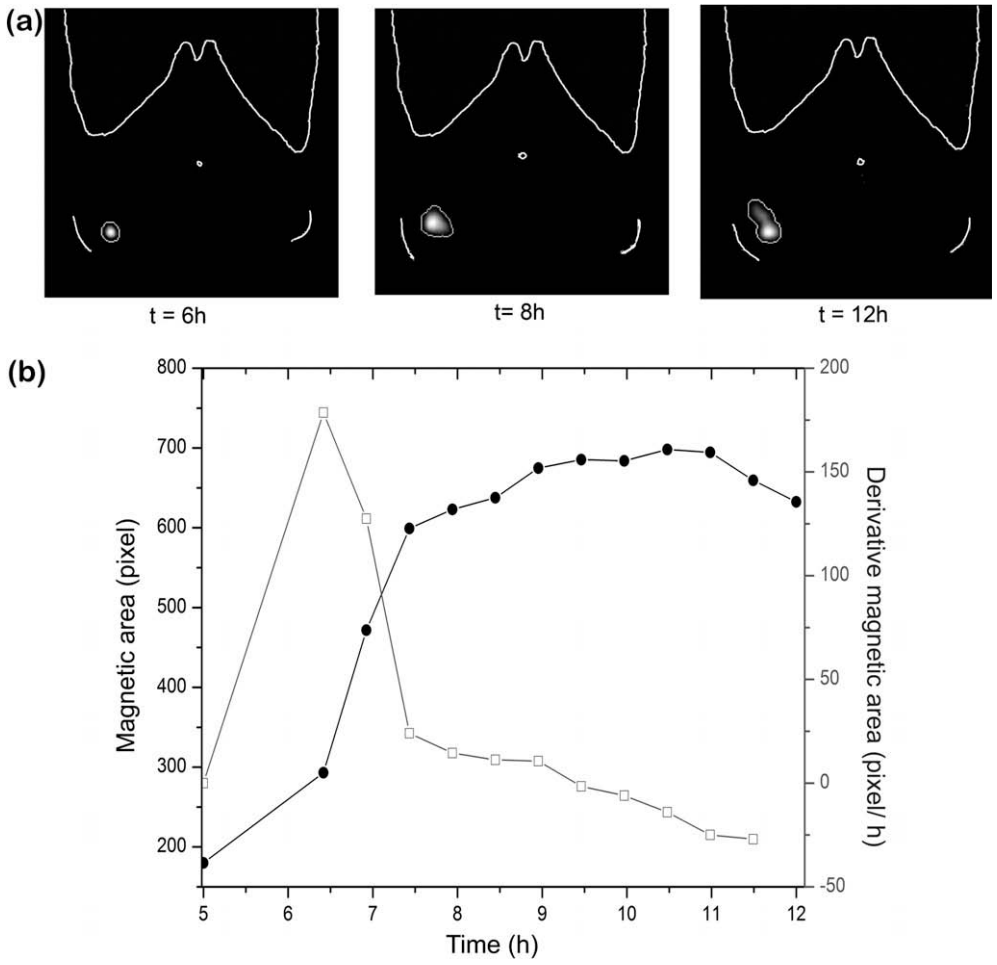

Fig. 7. Swelling profile of a matrix tablet in the human gastrointestinal tract. (a) Magnetic images taken post-colonic arrival ($t = 6$ h), at 8 h and 12 h later, (b) kinetics of swelling represented by the first derivative of magnetic image area variation curves.

Table 4
Parameters obtained for uncoated tablets according to Weibull fit (mean ± SD).

Compression Force (kN)	Parameters					
	Water Uptake (mg)		Disintegration Force (N)		Magnetic Area (pixel)	
	$t_{63.2}$ (min)	Q_{max} (mg)	$t_{63.2}$ (min)	F_{max} (N)	$t_{63.2}$ (min)	A_{max} (pixel)
10	0.55 ± 0.14	1.60 ± 0.05	0.17 ± 0.04	16.20 ± 0.6	0.06 ± 0.012	1150 ± 98
20	1.13 ± 0.13	1.57 ± 0.04	0.18 ± 0.03	13.30 ± 0.9	0.11 ± 0.014	1118 ± 108
30	1.39 ± 0.19	1.62 ± 0.06	0.26 ± 0.04	13.03 ± 1.1	0.16 ± 0.012	1011 ± 88
40	2.02 ± 0.26	1.61 ± 0.08	0.34 ± 0.08	11.82 ± 1.8	0.20 ± 0.024	975 ± 112
50	2.65 ± 0.35	1.65 ± 0.05	0.77 ± 0.07	11.50 ± 0.9	0.30 ± 0.022	885 ± 76

Based on this study, further bioavailability trials in humans will be conducted aiming to correlating the release properties of matrices tablets with drug absorption.

5.4. Disintegration of compressed tablets

Disintegration is the process that promotes the fast fragmentation of tablets under the action of disintegrants [67]. If this process is slow or incomplete the bioavailability of drugs might be impaired. For this reason, appropriate choice of the disintegrant and its consistency of performance have critical importance on the formulation development [21,68].

It is well established that the compression force has important influence on the tablet manufacturing process, since an increase in the compression force promotes a reduction of tablet porosity and, as a consequence, a linear increase in the disintegration time [69,70]. Based on disintegration force measurements, mathematical models have been developed towards quantifying and comparing the efficiency of disintegrants [71–73].

In terms of research, ACB sensors have been proposed towards evaluating the disintegration process of magnetic tablets *in vitro* and in the human gastrointestinal tract [10,11]. Recently, ACB sensors have introduced new opportunities to investigate the influence of compression force on disintegration time of tablets by associating the magnetic method with water uptake and disintegration force apparatus [14].

Magnetic tablets (11 mm) were directly compressed at five different force levels (10, 20, 30, 40 and 50 kN) and had the following composition: 71% ferrite, 21.5% microcrystalline cellulose, 7% effervescent mixture, 0.5% magnesium stearate. Sample tablets at each compression force were submitted to hardness and friability testing. The study also was performed on film-coated tablets.

A glass container filled with distilled water and covered by a quantitative filter paper was positioned on an electronic precision

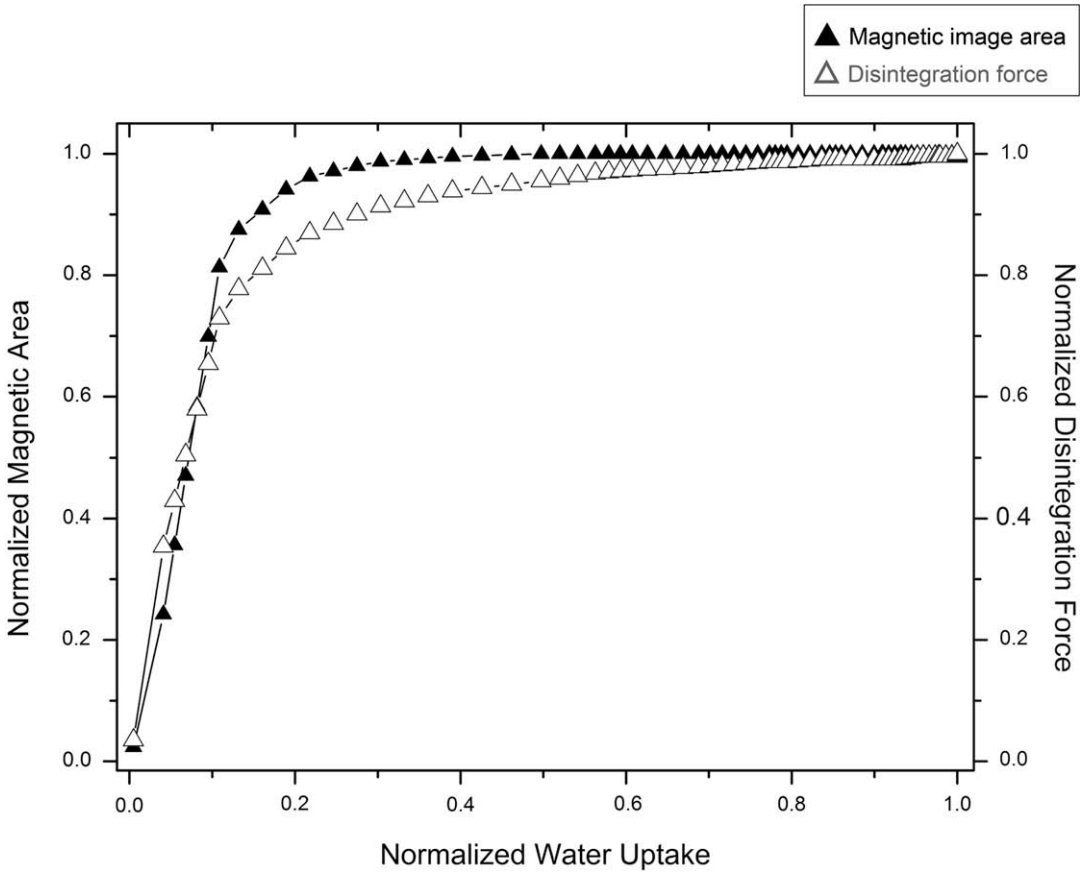

Fig. 8. Representation of magnetic area variation, water uptake and disintegration force. Contrasting with the amount of water absorbed, magnetic image area as well as disintegration force remained constant when reaching the maximum.

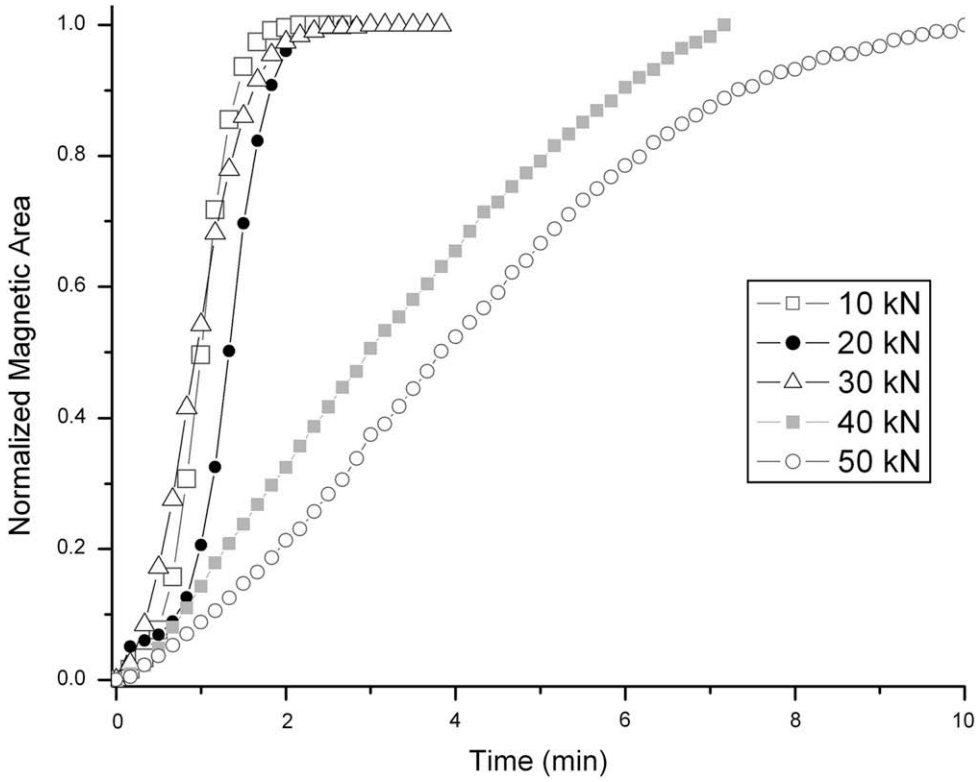

Fig. 9. Relationship between disintegration time and magnetic area variation evaluated for coated tablets compressed at different force levels.

balance with a force transducer connected to the upper side of a cylindrical frame towards passing through a slide guide locked by an arm. Samples of uncoated tablets at each compression force were then placed into the lower side of this slide guide towards measuring disintegration force during water uptake. Magnetic measurements of uncoated tablets were performed by using the apparatus described above, without the precision balance and the force transducer, which was positioned in the ACB sensors. For film-coated tablets, a glass vessel filled with 900 ml of fasted state simulated gastric fluid was placed in the ACB sensors and the tablets were added in the recipient test. Data were acquired at sample rate of 10 Hz for further analysis.

Magnetic data were analysed as magnetic image area variation, which was generated from magnetic signals. In order to investigate the relationship between the magnetic area variation and the disintegration process, data have been correlated with water uptake and disintegration force. Hence, water uptake *versus* time, disintegration force *versus* time and magnetic image area *versus* time profiles were fitted using classical exponential Weibull distribution.

As expected, all the parameters evaluated were classically compression force dependent (Table 4). Fig. 8 is an example of plots with magnetic area variation against water uptake and disintegration force. It was possible to observe that despite absorbing water continuously, the magnetic area as well as disintegration force remained constant when they reached the maximum value. Film-coated tablets were also evaluated in order to establish the relationship between compression force, disintegration time and magnetic image area variation (Fig. 9).

ACB sensors associated with standard methods allowed evaluating the relationship between compression forces and magnetic image area on the disintegration process of tablets. In addition, this method could estimate the disintegration properties as well as the kinetics of disintegration process for uncoated and coated tablets.

6. Concluding remarks – future directions

This review has covered some of the recent pharmaceutical applications of AC Biosusceptometry technique. As a noninvasive, low-coast and radiation-free technique, ACB has gained acceptance for evaluating pharmaceutical processes *in vitro* and in the human gastrointestinal tract. It is an important feature of this method, since ACB is facing the challenge of evaluating dosage forms and gastrointestinal parameters simultaneously.

How much we really know about the relationship among gastrointestinal physiological parameters and drug release processes? By providing valuable data *in vivo* focusing on different regions of the gastrointestinal tract, a wide range of dosage forms including enteric-coated formulations, gastroretentive and modified-release systems could be investigated, thereby, helping the drug development process.

Pharmaceutical development is a field that requires further research for providing new insights in the development of more reliable gastrointestinal drug delivery systems. Hence, better understanding of physiological parameters and their interactions with such delivery systems could provide valuable information on the bioavailability of the drugs administered. Considering the continuing improvements in instrumentation design, it is expected that magnetic methods will become a powerful tool for pharmaceutical processes monitoring.

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