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Magnetic images of the disintegration process of tablets in the human stomach by ac biosusceptometry

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Abstract

Oral administration of solid dosage forms is usually preferred in drug therapy. Conventional imaging methods are essential tools to investigate the *in vivo* performance of these formulations. The non-invasive technique of ac biosusceptometry has been introduced as an alternative in studies focusing on gastrointestinal motility and, more recently, to evaluate the behaviour of magnetic tablets *in vivo*. The aim of this work was to employ a multisensor ac biosusceptometer system to obtain magnetic images of disintegration of tablets *in vitro* and in the human stomach. The results showed that the transition between the magnetic marker and the magnetic tracer characterized the onset of disintegration (t_{50}) and occurred in a short time interval (1.1 ± 0.4 min). The multisensor ac biosusceptometer was reliable to monitor and analyse the *in vivo* performance of magnetic tablets showing accuracy to quantify disintegration through the magnetic images and to characterize the profile of this process.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Medical imaging methods are essential to evaluate anatomically and functionally internal structures of the human body. Imaging techniques also play an important role in pharmaceutical research since they provide valuable information on the *in vivo* performance for any dosage forms (Wilson *et al* 1997, Singh and Waluch 2000, Newman *et al* 2003).

Oral administration is the most popular method for drug therapy and the active substances are conveniently administered in a solid form (Sastry *et al* 2000). Drug delivery occurs by the disintegration of the solid dosage form and promotes drug release to be absorbed in the gastrointestinal tract (Melia and Davis 1989). Physiological factors and the formulation design

have significant influences on the disintegration and drug absorption and therefore in the safety and efficacy of the drug product (Dressman *et al* 1993, Lipka and Amidon 1999).

For these reasons, imaging modalities introduced a new perspective for the *in vivo* investigation of drug delivery. γ-scintigraphy is the standard method widely used to assess complex interactions between the drug, the dosage form and the gastrointestinal physiology (Wilding *et al* 2001). The main drawbacks of this method are the exposure of patients to the ionizing radiation, precluding repetitive assays with a single subject and the complicated and expensive preparation of the radiopharmaceuticals.

The development of radiation-free techniques provides a non-invasive approach to acquire information about the *in vivo* performance of oral dosage forms within the gastrointestinal tract. Magnetic resonance imaging (MRI) was recently employed to monitor the intragastric course of a labelled and gastric-retentive tablet (Steingöetter *et al* 2003a, 2003b). Although there are favourable advantages for this purpose, including high temporal and spatial resolution, the use of MRI in studying oral delivery systems is restricted due to the cost of equipment and limitations in positioning of the patients, since up to now most MRI units do not operate with the subject in an orthostatic position.

Biomagnetic methods represent a feasible and promising alternative in clinical, physiological and pharmaceutical research. Magnetic fields associated with the flow of electrical activity or as a result of ingestion of a magnetically labelled dosage form are detectable by multichannel SQUID (superconducting quantum interference device) systems (Weitschies *et al* 1997, 2001, Hu *et al* 2000).

Whereas the SQUID has been developed to detect extremely weak magnetic fields, the need for a magnetically shielded environment and an expensive operational cost limit its use on a wide scale.

In the past few years, alternating current biosusceptometry (ACB) has been becoming an interesting and valuable tool in gastroenterology research. ACB uses induction coils for recording the magnetic flux variation obtained from the response of a magnetic material ingested (Miranda *et al* 1992). This material has a high magnetic susceptibility that produces a strong response when an alternating magnetic field is applied in a biological system containing small amounts of ferrite. ACB showed accuracy to evaluate, physiologically, gastric emptying (Baffa *et al* 1995, Oliveira *et al* 1996) and gastric motility in humans (Miranda *et al* 1997) and dogs (Moraes *et al* 2003) as well as colonic motility (Ferreira *et al* 2004). ACB was also employed to obtain magnetic imaging of ferromagnetic tracers *in vitro*, introducing a novel concept in imaging of biological systems (Moreira *et al* 2000).

Recently, a new instrumental arrangement comprising a multisensor system (multisensor ACB) was implemented and proposed for the first time to characterize the disintegration process of tablets *in vitro* and in the human stomach, through the acquisition of magnetic signals (Corá *et al* 2003). The results obtained were very satisfactory and emphasized the importance of studying how pharmaceutical forms behave in the human gastrointestinal tract (Corá *et al* 2005).

The aim of this investigation was to employ multisensor ACB to image the disintegration of tablets *in vitro* and in the human stomach.

2. Materials and methods

2.1. Fundamentals

The ac biosusceptometer consists of two pairs of coils separated by a fixed distance (baseline), where each pair of coils is composed of an excitation coil (outer) and a detection coil (inner), in a first-order gradiometric configuration (figure 1).

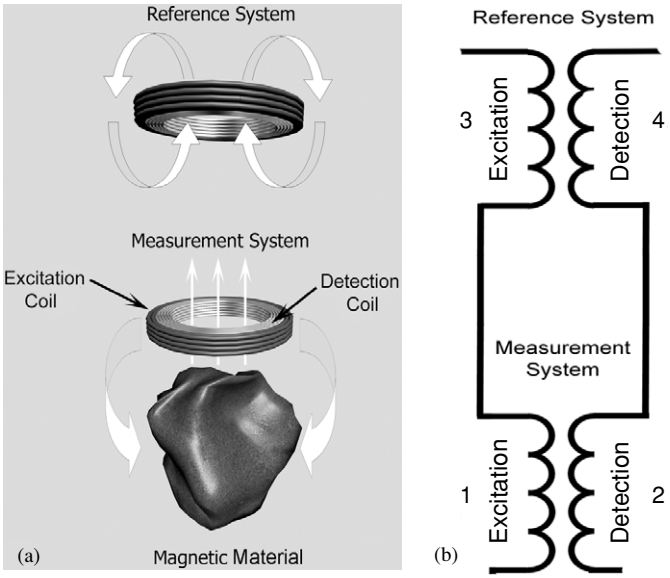


Figure 1. (a) Functional diagram of the single sensor ac biosusceptometer. The proximity of a magnetic material to the measurement system causes imbalance in the magnetic flux and the response is monitored. (b) Schematic diagram of the single sensor showing the pairs of excitation/detection coils in a coaxial arrangement.

This system is based on a couple of magnetic flux transformers with an air nucleus in which the pair (excitation/detection) located more distant from the magnetic material (ferrite) acts as a reference transformer (Miranda *et al* 1992, 1997, Baffa *et al* 1995, Oliveira *et al* 1996) and the pair closer to the sample as a measuring transformer.

Bastuscheck *et al* (1985), in accordance with the reciprocity theorem, evaluated the magnetic flux for the susceptometric magnetometer. From these findings, Baffa *et al* (1995) demonstrated that the output voltage (V_d) from the detection coils when an alternating current with frequency ω (10 kHz) is applied to the excitation coils can be written as equation (1):

$$V_d = (\Delta M)\frac{dI_e}{dt} + RI \tag{1}$$

where $\Delta M = M_{12} - M_{34}$ is the difference between the mutual inductance for the pair of excitation/detection coils, R is the electric resistance in the detection coil, I_e is the current supplied for the excitation coils and I is the current fed to the amplifier. The excitation coils induce equal magnetic flux in the detection coils which are arranged in a first-order gradiometric configuration, to minimize the output signal when there is no magnetic material near the detection system. With the proximity of a magnetic material an imbalance voltage in (V_d) occurs, due to the change in the differential flux between the detection coils. The gradiometric system detects the time variation of the magnetic flux between the detection coils as an electromotive force (emf) equal to ε, according to equation (2).

$$\varepsilon = -\frac{d\Delta\Phi}{dt} = M'\frac{dI_e}{dt} \tag{2}$$

where M' is the mutual inductance between the magnetic material and the detection coil and it is assumed that the magnetic material behaves as a magnetic dipole.

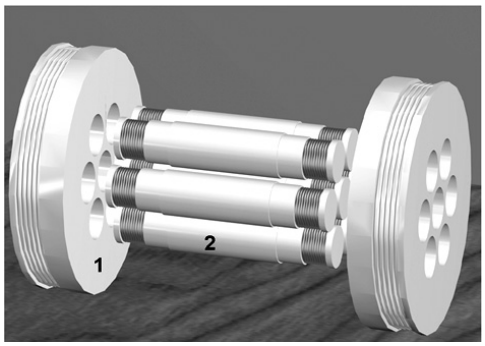


Figure 2. Multisensor ac biosusceptometer system. (1) A pair of excitation coils and (2) seven pairs of detection coils with hexagonal symmetry.

The multisensor ACB system employed in this study possesses only one pair of excitation coils ($\phi = 11$ cm) and seven pairs of detection coils ($\phi = 2$ cm) with 14 cm of baseline in a coaxial arrangement (figure 2). The first-order detection coils were arranged in a hexagonal configuration having a 4 cm separation between the centre of each gradiometer. This biomagnetic system is mounted in an adjustable vertical support that allows the acquisition of magnetic signals in distinct points distributed on the abdominal surface (Corá *et al* 2003).

2.2. Experimental protocol

2.2.1. Tablet preparation. In this study, magnetic tablets (10 mm diameter, 1.54 g weight) were prepared by direct compression from 1.00 g of ferrite ($MnFe_2O_3$), 0.50 g of microcrystalline cellulose (Merck, Germany), 0.01 g of magnesium stearate (Merck, Germany) and 0.10 g of an effervescent mixture (SmithKline, Brazil), coated by spray drying with a solution of a gastrosoluble polymer—Eudragit® E100 (Röhm, Germany). The ferrite is an inert material that is not absorbed by the GI tract, harmless to the organism and, therefore without biological side effects (Forsman 1998).

2.2.2. In vitro study. For the *in vitro* study, one coated magnetic tablet was used. A square glass vessel containing 1.5 l of acidic solution (pH = 1.2; 0.1 eq l^{-1} HCl; 37 °C) was positioned in front of the multisensor ACB system. A digital camera was used to obtain images of the tablets in the solution. The magnetic tablet was introduced in the solution, simulating the ingestion by the volunteer, and video and magnetic signals were acquired simultaneously.

2.2.3. In vivo study. The *in vivo* study was carried out in nine healthy volunteers, both genders and ages ranging from 21 to 41 years, that had no history of gastrointestinal symptoms or abdominal surgery. Written informed consent for the participation in the study was obtained. The *in vivo* investigation was approved by the Ethics Committee in Research of the Medical School, Universidade Estadual Paulista (UNESP). All volunteers fasted at least 12 h prior to the administration of magnetic tablets. Each volunteer, in an orthostatic position in the measurement system, swallowed a magnetic tablet with 200 ml of water. The multisensor ACB system was positioned on the abdominal surface (figure 3), and the magnetic signals were acquired concomitantly for 15 min. The magnetic signals were acquired continuously through lock-in amplifiers (Stanford Research Systems) and the lock-in output was sampled at 10 Hz in accordance with previous studies of gastrointestinal motility (Miranda *et al* 1997,

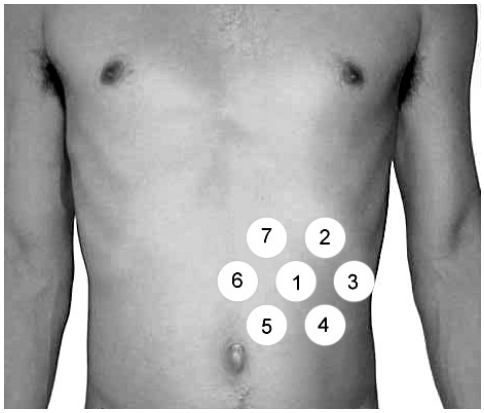


Figure 3. Positioning of the multisensor ac biosusceptometer in the gastric projection according to the external anatomic references.

Moraes *et al* 2003) and the disintegration of magnetic tablets (Corá *et al* 2003). This sampled frequency is enough to record the GI motility with frequencies below 20 contractions per minute (0.30 Hz) and allows enough time resolution to follow the disintegration process.

2.3. Magnetic images

As employed in our previous studies (Corá *et al* 2005), the lock-in amplifier and a magnetic phantom were used to calibrate and to adjust the intensity (mV) for each sensor, aiming to minimize the differences in the signal acquired, attributed to the geometric arrangement of the multisensor system.

The magnetic signals recorded by the multisensor ACB system are represented by a time series matrix. From these signals, stored in ASCII format, a seven-point matrix was calculated. Every data point in this initial matrix was obtained by computing an average in a 3 s time interval of the signal acquired, in order to obtain 30 matrices for each measurement (imaging sampled frequency at 0.33 Hz). The initial matrix corresponds to the configuration of the multisensor ACB system (figure 3).

To construct the imaging matrix the sensitivity profile of the multisensor ACB system was taken into account. Figure 4 shows the transversal sensitivity profile obtained for the central sensor for distinct distances between the sensor and a magnetic tablet. It can be observed that for distances greater than 25 mm, the variation rate of intensity (mV) in the magnetic signal is constant and practically null and, therefore, the points located laterally at 30 mm from the external detection coils were considered null, since $\frac{\partial \Phi}{\partial x} = \frac{\partial \Phi}{\partial y} = 0$. The other argument for using this condition is that the system is sensitive only to near sources, thus for a near field approximation the magnetic fields are essentially axial, supporting this condition.

Nevertheless, sensitivity contours for different susceptometers were obtained by Carneiro *et al* (2002), showing regions that contribute positively and negatively to the magnetic flux. For the first-order gradiometers, like this multisensor ACB system, the negative magnetic flux is detected only for distances smaller than 6 mm (figure 4).

According to these characteristics and establishing that the points located laterally to the external detection coils are zero, a square matrix (7×7) equivalent to the area of the detector system (16×16 cm) was calculated by fitting the data of each sensor to the sensitivity profile. The square matrices were then interpolated (256×256) by the spline method and appropriate

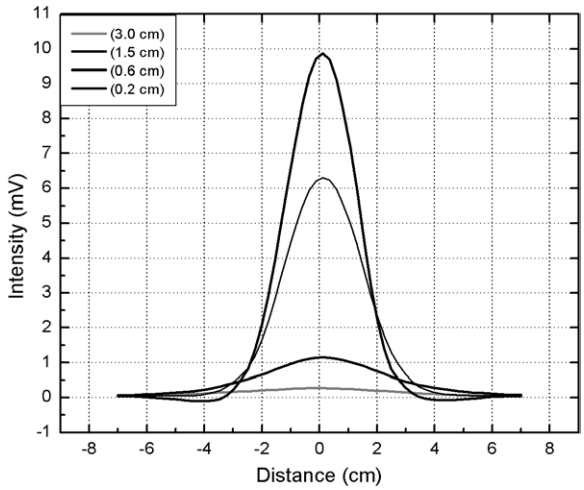


Figure 4. Transversal sensitivity profile of the multisensor ac biosusceptometer system. The variation rate of intensity (mV) in the magnetic signal was obtained for the central sensor for distinct distances between the sensor and a magnetic tablet.

routines to obtain the degraded images of the magnetic tablets *in vitro* and *in vivo* were applied. Further image processing for quantification included background subtraction, brightness and contrast adjustment and segmentation. The segmentation was used to quantify, in number of pixels, the imaging area. All the routines were implemented in MatLab® (Mathworks, Inc.).

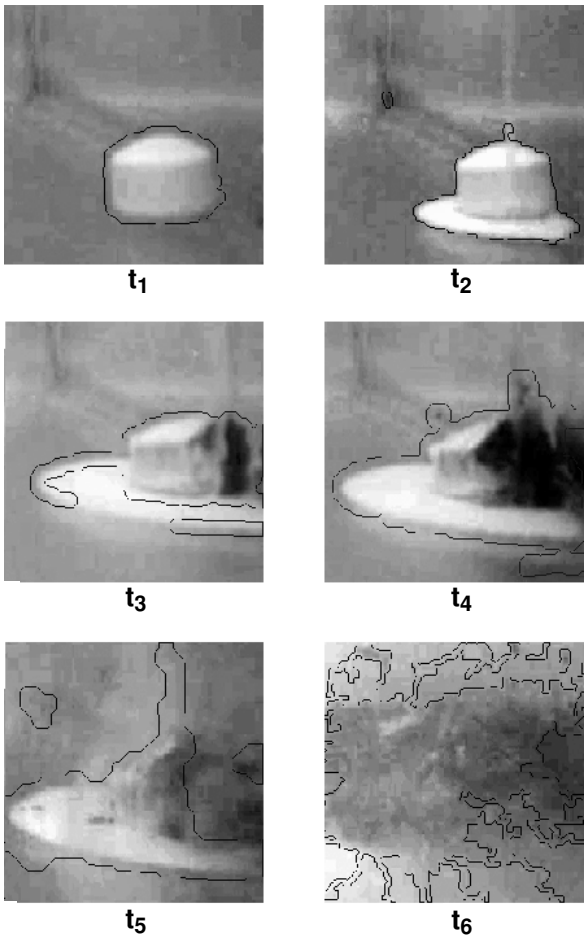
The disintegration process is characterized by the transition of a magnetic marker, MM (non-disintegrating tablet) to a magnetic tracer, MT (disintegrating tablet). In the magnetic images, the MM was clearly delineated and the MT showed the spreading of the magnetic material *in vitro* and in the stomach. Therefore, the onset of the disintegration process (t_{50}) was calculated from the 50% increase of pixels in the imaging area (Perkins *et al* 2001).

3. Results

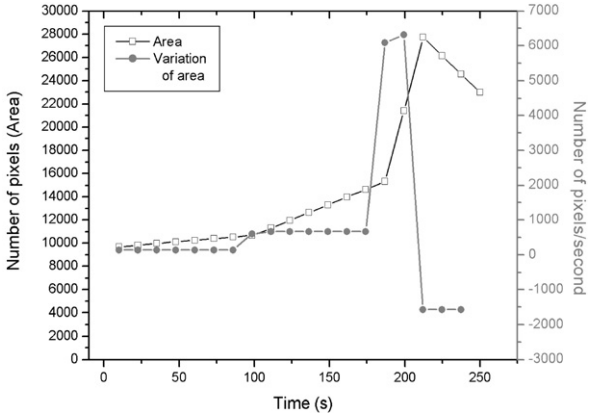
Figure 5(a) shows a series of photographs of a tablet in the acidic solution. In the instant t_1, the tablet arrived in the solution and the dissolution of the coating layer initiates (t_2). During this period, there is no occurrence of ferrite release, indicating a lag time until the onset of disintegration. When reducing the coating layer, the disintegration process (t_3) initiates and it is intensified from the instant t_4, due to the action of the excipients that promotes the spreading of the magnetic material in the glass vessel (t_5). The complete disintegration is shown in the instant t_6. The segmented area outlined in the photographs was used to calculate the spreading of the magnetic material from the number of pixels in that area (figure 5(b)).

For the same instants shown in the photographs, the magnetic images of the disintegration process of a tablet in the acidic solution (figure 6(a)) were obtained. In the image shown in t_1, the tablet can be observed as a MM. The onset of the disintegration process occurs from the instant t_3, with a gradual increase of the imaging area due to the spreading of the magnetic material. The instant t_6 represents the complete disintegration. Figure 6(b) shows the number of pixels contained inside a delineated area (spreading of the magnetic material) and its time variation ('velocity of disintegration').

The intragastric performance of the tablet for a volunteer is shown in the image sequence of figure 7(a). The expected stomach profile was delineated according to the external

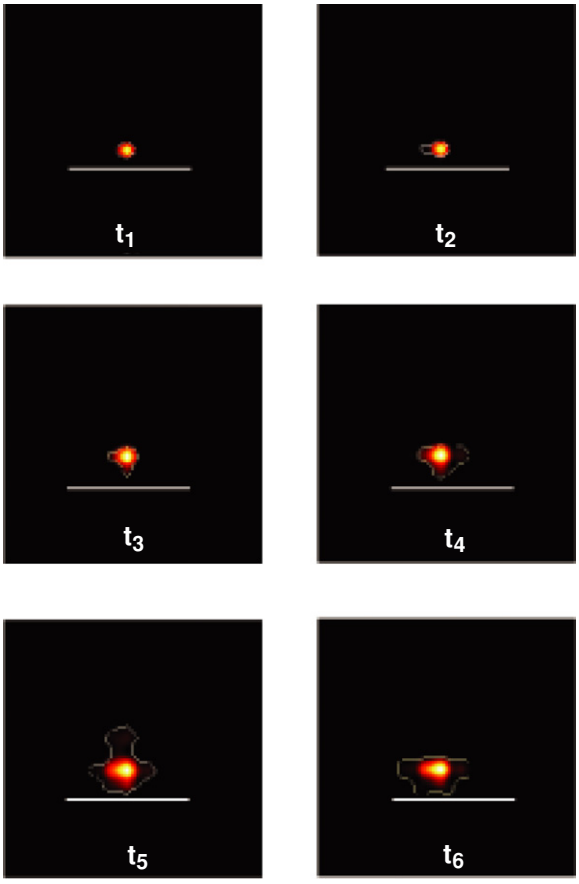


(a)

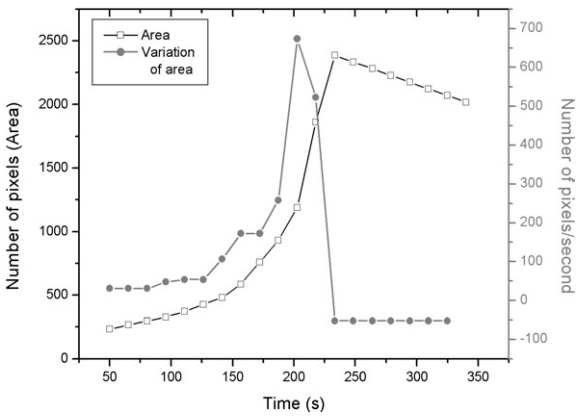


(b)

Figure 5. (a) Photographs of a tablet in the acidic solution to illustrate the disintegration process. The onset of disintegration (t_{50}) occurs in the instant t_3. (b) Spreading of the magnetic material and the time variation in the number of pixels in the segmented area of the photographs.

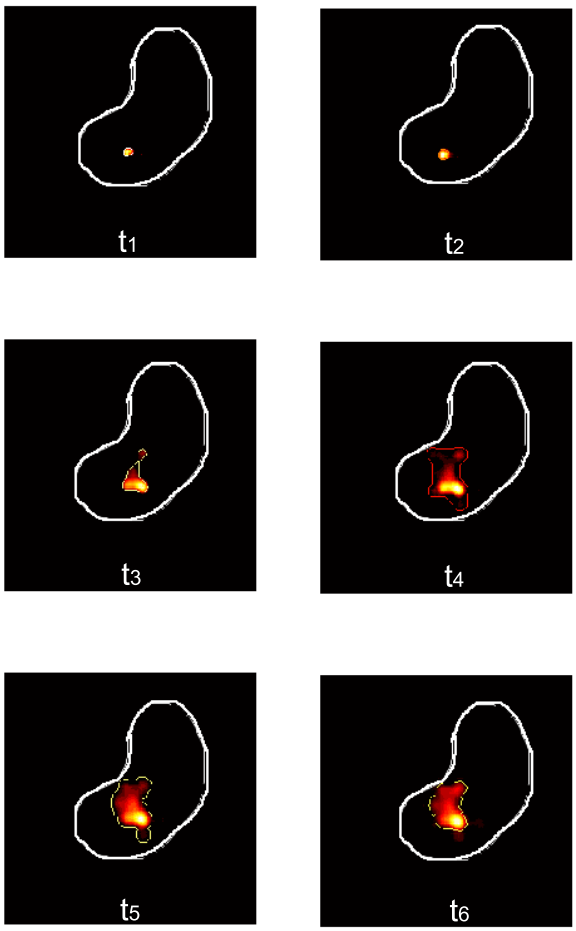


(a)

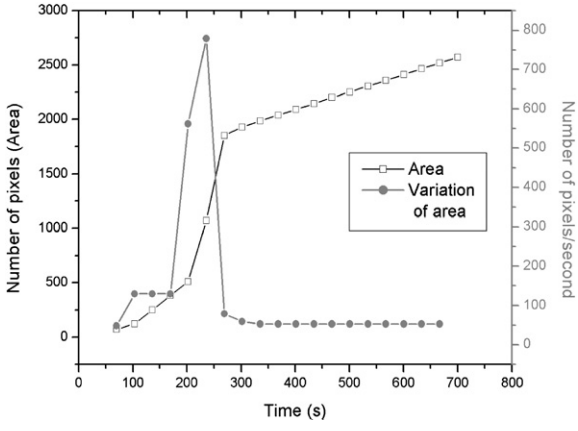


(b)

Figure 6. (a) Magnetic images of the disintegration process of a tablet *in vitro*. The onset of disintegration (t_{50}) occurs in the instant t_3. The gradual increase of the imaging area characterizes the spreading of the magnetic material. (b) *In vitro* spreading of the magnetic material and the time variation of the number of pixels contained inside a delineated area showing the 'velocity of disintegration'.



(a)



(b)

Figure 7. (a) Magnetic images of the disintegration process of a tablet in the human stomach at t_1–t_6. 50% disintegration (t_{50}) is located between t_i and t_{i+1}. (b) *In vivo* spreading of the magnetic material, as number of pixels, in the segmented area and its rate of change.

anatomic references and the positioning of the sensors in the abdominal surface (figure 3). In these images, the arrival of the tablet in the distal stomach can be observed (instant t_1). The onset of disintegration occurred in the instant t_2. After t_3, a gradual increase in the imaging area can be verified, characterizing the spreading of the magnetic material within the organ. The complete disintegration is represented in the instant t_6.

Figure 7(b) shows the number of pixels present inside a delineated area and its time variation ('velocity of disintegration'). The onset of disintegration (t_{50}) of the tablets in the stomach ranged from 0.5 to 2.1 min (mean 1.1 $\pm$ 0.4).

4. Discussion

Oral administration of solid pharmaceutical forms is a common practice in drug therapy and the imaging methods represent important tools to provide more reliable information about their performance in the human gastrointestinal tract.

In a recent study, single-sensor ACB was successfully used to generate images of ferromagnetic phantoms (Moreira *et al* 2000). Nevertheless, the development of a multisensor ACB system improved the spatial resolution allowing us to monitor the disintegration process of tablets and simultaneous gastrointestinal motility under physiologic conditions (Corá *et al* 2003, 2005).

In addition, multisensor ACB showed sensitivity and temporal resolution to obtain magnetic images. This system remains over the area of interest during all the recording time, not requiring repositioning and, consequently, there is no noise from vibrations. These are the important features of the multisensor ACB system that allows evaluation of the dynamic process that occurs in brief periods of time.

In order to obtain a profile of the disintegration process of tablets an *in vitro* study was carried out aiming to qualitatively compare the photographs and the corresponding magnetic images. Analysing the image sequences shown in the figures 5 and 6, it was possible to verify the MM in the initial instances, while the tablet remains intact during the dissolution of the coating layer by the action of the acidic solution. When the coating layer was reduced the onset of disintegration (from instant t_3) could be observed, continuously, until the spreading of the magnetic material in the glass vessel (instant t_6).

This study was focused on the investigation of the disintegration process of tablets in the human stomach through magnetic imaging. The disintegration (figure 7(a)) was visualized solely by the magnetic method. By segmentation of the imaging area, it was possible to quantify the spreading of the magnetic material to characterize the transition between the MM and MT due to the disintegration process. Our data demonstrated that multisensor ACB was capable of identifying differences in the profile of the disintegration process.

From the results presented, it was observed that the onset of disintegration occurred in a short time interval (1.1 $\pm$ 0.4 min), indicating that this process once initiated promotes the dispersion of the ferrite continuously.

Pharmacoscintigraphy is an important method to investigate the gastrointestinal performance of pharmaceutical dosage forms and to provide information about the release and subsequent drug absorption (Wilding *et al* 2001). As an alternative to scintigraphy, biomagnetic methods have become feasible to monitor the dosage forms in the human gastrointestinal tract (Weistchies *et al* 2001). Although this multisensor ACB does not have sensitivity, the spatial resolution of the SQUID systems with a larger number of detectors was able to characterize efficiently the disintegration of tablets through magnetic images (Corá *et al* 2005). More reliable data will be obtained in combination with pharmacokinetics studies, since the magnetic material is devoid of harmful effects.

Despite the difficulties, the multisensor ACB system was able to obtain images with reasonable quality. However, the blurring in the magnetic images due to the differences in the sensitivity profile could be corrected by applying the point-spread function for each sensor. Moreover, the application of restoration techniques could improve image quality and suppress noise simultaneously (Kondo *et al* 1977, Gravel *et al* 2004).

More extensive studies are required to obtain a comprehensive knowledge of the behaviour of pharmaceutical forms in the human gastrointestinal tract. Moreover, it is essential that the development of sophisticated and specified delivery systems can improve and control the bioavailability and effectiveness of administered drugs. In the future, ACB with a larger number of channels as a non-invasive and radiation-free imaging tool might achieve the same importance as other techniques in pharmaceutical and physiological research. In summary, our study showed that multisensor ACB, a completely safe and harmless device, demonstrated enough sensitivity and spatial resolution to evaluate pharmaceutical dosage forms in the human gastrointestinal tract.

Acknowledgments

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