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Research paper

Disintegration of magnetic tablets in human stomach evaluated by alternate current Biosusceptometry

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Abstract

Oral administration is the most convenient route for drug therapy. The knowledge of the gastrointestinal transit and specific site for drug delivery is a prerequisite for development of dosage forms. The aim of this work was to demonstrate that is possible to monitor the disintegration process of film-coated magnetic tablets by multi-sensor alternate current Biosusceptometry (ACB) in vivo and in vitro. This method is based on the recording of signals produced by the magnetic tablet using a seven sensors array and signal-processing techniques. The disintegration was confirmed by signals analysis in healthy human volunteers' measurements and in vitro experiments. Results showed that ACB is efficient to characterize the disintegration of dosage forms in the stomach, being a research tool for the development of new pharmaceutical dosage forms.

Keywords: Disintegration time; Tablets; Biomagnetic measurement; Magnetic marker; Biosusceptometry

1. Introduction

Oral route is commonly used for drug administration and solid pharmaceutical dosage forms are the most utilized, since they present advantages such as: stability, ease ingestion and commodity for the patients when compared with other formulations [1].

The disintegration process consists in the release of therapeutic agents contained in the solid dosage forms to be absorbed and produces an effect in organism. This process is dependent of time, pharmaceutical form, excipients and it is related to the bioavailability of the drug. Therefore, if any failure occurs, the dissolution and absorption of active substance will be affected, damaging the pharmacological effect [2].

Due to extreme importance for absorption of the drugs, the disintegration must be evaluated before the commercialization of a new product. Although, routinely in vitro tests are carried out a significative correlation between these results and the biological situation is difficult [3].

In vivo studies provide other informations about the behavior of solid dosage forms in the gastrointestinal (GI) tract since physiological variables, such as pH, motility, GI transit and prandial state can interfere with the release profile and absorption of many drugs [4,5]. Besides that, specific sites for drug delivery assure the maximum therapeutic usefulness, contributing to the rational development of new formulations [6].

To follow the transit and release characteristics of pharmaceutical dosage forms in GI tract the γ-scintigraphy is the standard method. However, it must be emphasized that the use of radioisotopes requires precaution to manipulate and to prepare the dosage forms, besides the risks of exposition to ionizing radiation in repeated studies. In addition, some countries established restrictions to the use of radiation in studies with human volunteers [7–10]. The endoscopy also is another method that can be used to observe the disintegration of dosage forms in the stomach but

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provides a discomfort to the volunteer because of its invasiveness method [11].

As an alternative to the methodologies traditionally utilized biomagnetic techniques are being employed to study the behavior of solid pharmaceutical forms in the human GI tract. The technique of magnetic marker monitoring combined with the most sensitive magnetic detector system, the superconducting quantum interference device (SQUID) has been used to characterize, with great accuracy, the GI transit and disintegration of magnetically marked capsules [12–15]. A multichannel-SQUID system is precise, non-invasive and possesses high sensitivity, but the need for liquid helium and a magnetically shielded environment, as well as specially trained personnel makes it difficult to be use in large scale.

Another biomagnetic system, the alternate current Biosusceptometry (ACB) is being utilized in investigations that focus on studies about GI motility, such as: determination of the orocaecal transit time, gastric emptying, esophageal transit time, pharynx clearance and the gastric activity contraction (GAC) through the ingestion of a test meal magnetically marked [16–20]. This methodology is based on recordings obtained from a high magnetic susceptibility material (ferrite – $MnFe_2O_4$) response to the application of an alternated magnetic field. In this way, the signals originating from the magnetic tracer and magnetic markers are detected and analyzed using signals processing techniques.

A new instrumental approach through a multi-sensor Biosusceptometric system allowing signal acquisition from different positions was used. Comparative analysis between the signals from magnetic markers (non-disintegrating tablets) and magnetic tracers (disintegrating tablets) was performed, thus making possible to follow the transition between these magnetic forms, due to disintegration process. This non-invasive method has the advantage of high signal/noise ratio and low cost, with reasonable spatial resolution.

Thus the main objective of this study was to employ a multi-sensor biomagnetic system to characterize and determine the disintegration time of a special solid dosage form (magnetic tablets) in vivo and in vitro.

2. Materials and methods

2.1. Fundamentals of ACB

The ACB, with a single sensor, used in previous studies involving the GI motility, consisted of two pair of coils separated by a distance (baseline). Each pair of coils is composed of the excitation coil (external) and a detection coil (internal), this arrangement is also referred as a first-order gradiometric configuration (Fig. 1a) [16–20]. The working principle, according to Faraday's Induction Law, is based on a double magnetic flux transformer with an air nucleus, in which the pair (excitation/detection), located more distant from magnetic material (ferrite), acts as reference. Thus, the output signal is given by Eq. (1).

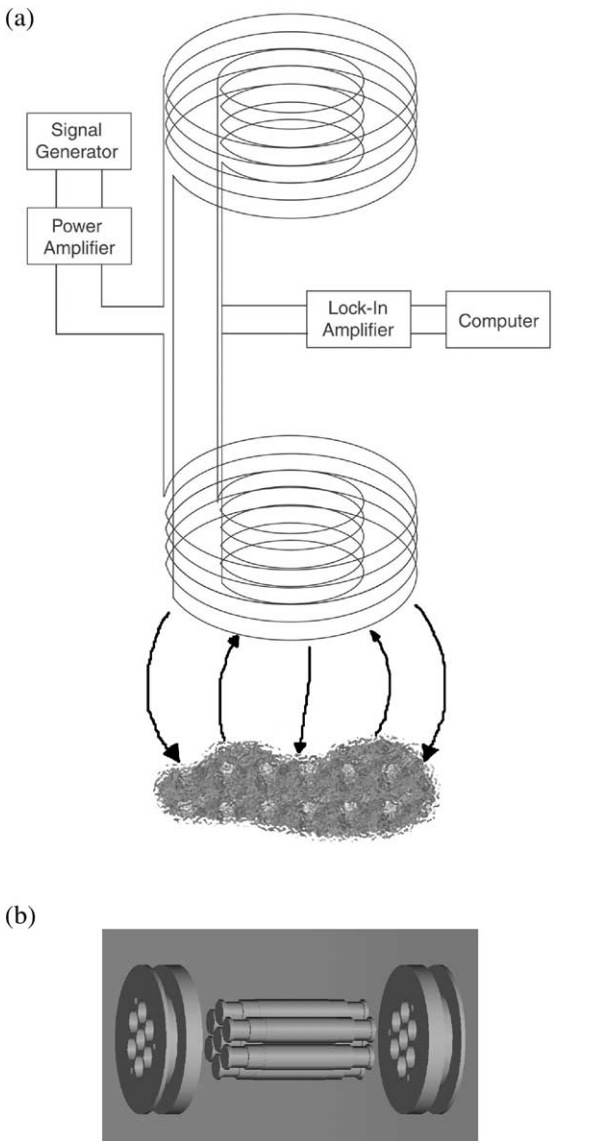

Fig. 1. (a) Schematic diagram of ACB single sensor. The excitation and detection coils are shown as well as the electronic equipment associated. (b) Multi-sensor Biosusceptometry System showing the individual detection coils and the single excitation coil.

$$\Delta\Phi = \Delta\Phi_m - \Delta\Phi_r \quad (1)$$

where

$\Delta\Phi$ = total flux;

$\Delta\Phi_m$ = measuring coil flux;

$\Delta\Phi_r$ = reference coil flux.

Due to this configuration, when there is no magnetic material near the system, the output signal is minimized. With the approximation of any magnetic mass, an unbalance in the output signal occurs and the temporal variation of the magnetic flux is detected as an electromotive force, a phase sensitive detection ('lock-in') is used to improve

the sensitivity (Fig. 1a). This system is sensitive to distance variations between the detector coil and the magnetic material, thus this technique is very sensitive to movement of the ferrite inside the organ as showed in the studies of GAC [17].

2.2. Multi-sensor ACB

The difference between the multi-sensor system and the previously utilized is that the new arrangement uses only a pair of excitation coil ($\phi = 11$ cm) and seven pairs of detection coils ($\phi = 3.5$ cm) in the first-order gradiometric configuration, coaxially arranged (Fig. 1b). This system is fixed in a vertical support with adjustment to be positioned on the area corresponding to the gastric projection of human subject.

The signals were acquired through the use of seven 'lock-in' amplifiers (Stanford Research Systems) digitalized to an A/D board of 16 bits (PCI-MIO-16XE-10, National Instruments Inc.) with a microcomputer.

The signals generated by the magnetic tablets were acquired in seven distinct points distributed on the abdominal wall (gastric projection). The real time visualization of these signals allows the knowledge of ferrite distribution in the stomach.

The study of disintegration is based in the fact that, after the swallowing, the signals of magnetic tablets are given by a punctual source (magnetic marker) that, when disintegrating, it will be interpreted as a magnetic tracer in which the particles are dispersed in a larger volume. Thus, changes in the magnetic signals recorded simultaneously by the sensors provide temporal data about spatial localization and also disintegration process in the gastric region. These modifications can be observed through a change in the baseline level between the sensors and in intensity of GAC in each sensor before and after the disintegration process. Consequently, this will cause more sensors to recording the contraction activity, indicating the distribution of magnetic material. Hence, by analysis of simultaneous recordings, the coating dissolution time (CDT) and the disintegration time (DT) can be determined.

2.3. Preparation of magnetic tablets

The tablets used in this study can be considering a new pharmaceutical dosage due its characteristics. These dosage forms were obtained by direct compression from 1.0 g of ferrite powder ($MnFe_2O_4$; $80 \leq \phi \leq 125$ μm) mixed with 0.5 g of microcrystalline cellulose (Merck, Germany), 0.01 g of magnesium stearate (Merck, Germany) and 0.1 g of effervescent mixture (SmithKline Beecham, Brazil). The ferrite is an inert material that is not absorbed by the GI tract, harmless to the organism and, therefore without side effects, endowing the tablet as a magnetic marker [21]. The effervescent mixture was the choice to provide fast disintegration. Magnetic tablets weighing 1.52 g, 1.0 cm of diameter and density of 2.03 g/cm^3 were coated by spray-drying with a solution of gastrosoluble polymer – Eudragit® E100 (Röhm, Germany) [22].

2.4. In vitro study

For this experiment 12-coated magnetic tablets were used. Initially a beaker was immersing in a glass vessel containing 4.0 l of water prewarming. This beaker containing 1.5 l of acid solution (pH = 1.2; 0.1 Eq.l^{-1} HCl) was maintained at 37°C with the aid of a thermostat. After that, the apparatus was positioned in front of the multi-sensor Biosusceptometry system. A video camera (Samsung®, Japan) was used to obtain the correspondent images of the tablets in the solution, aiming to correlate the digitalized images with acquired signals. Each of the magnetic tablets was introduced in the solution, simulating the swallow by the volunteer, and signals were acquired until the complete disintegration. The acid solution was replaced before each measurement.

To observe the response to the movement of punctual sources in the multi-sensor system magnetic, gastroresistent tablets were moved along the axis and transversal to the gradiometer.

2.5. In vivo study

The study was done in the Biomagnetism Laboratory, Department of Physics and Biophysics – Institute of Biosciences after approval by the Ethic Committee in Research of the Medical School – Universidade Estadual Paulista (UNESP). Non-symptomatic 12 healthy volunteers,

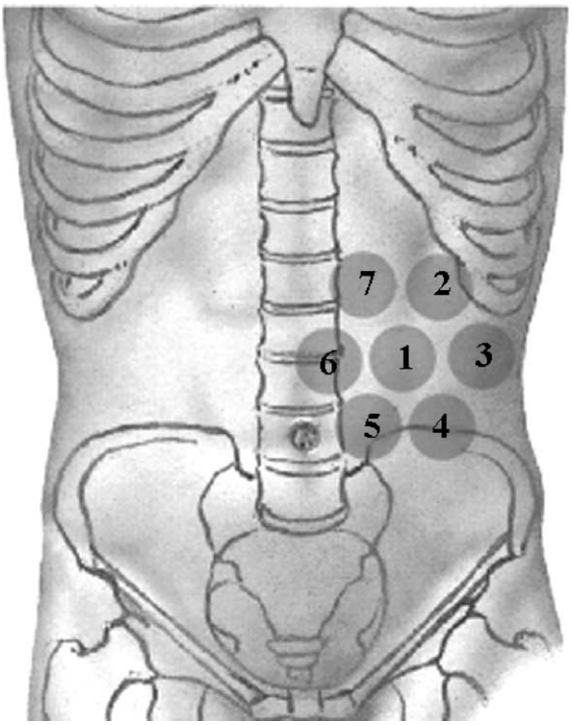

Fig. 2. Schematic positioning of sensors in gastric projection in the volunteers (Modified of Netter – Atlas of Human Anatomy – CD ROM 1998).

of both sex and aged between 21 and 40 years old were selected. Informed consent was obtained from all of them.

The multi-sensor Biosusceptometry System was positioned on the volunteers abdomen, in orthostatic position, in the correspondent region to gastric projection, considering the xiphoid process and the umbilicus as anatomic references (Fig. 2). The human volunteers, after an overnight fasting, already positioned, swallowed a magnetic dosage with 200 ml of water. The acquisition of signals was done, concomitantly, during 15 min.

2.6. Data analysis

The magnetic signals, recorded with acquisition frequency of 10 Hz/channel and stored in ASCII format, were analyzed in MatLab (Mathworks, Inc.) using bi-directional Butterworth filter with 150 mHz cutoff frequency. The frequency analysis was done by fast fourier transform.

To quantify the disintegration process in vitro and in vivo the CDT and DT were determined.

The interval that corresponds to the CDT indicates the period in which there is no release of magnetic material (ferrite) and was determined from the arrival of the magnetic tablets in the acid solution or in the volunteers' stomach, until the onset of disintegration process.

DT corresponds to the interval between the onset and complete disintegration of the magnetic tablet. To dissolve the coating, the dosage form remains in contact with the acid solution or gastric fluid that promotes a fast disintegration, by the action of the excipients.

3. Results

3.1. In vitro measurement

The Fig. 3 shows the image sequence correlated with magnetic signals acquired during the magnetic tablet

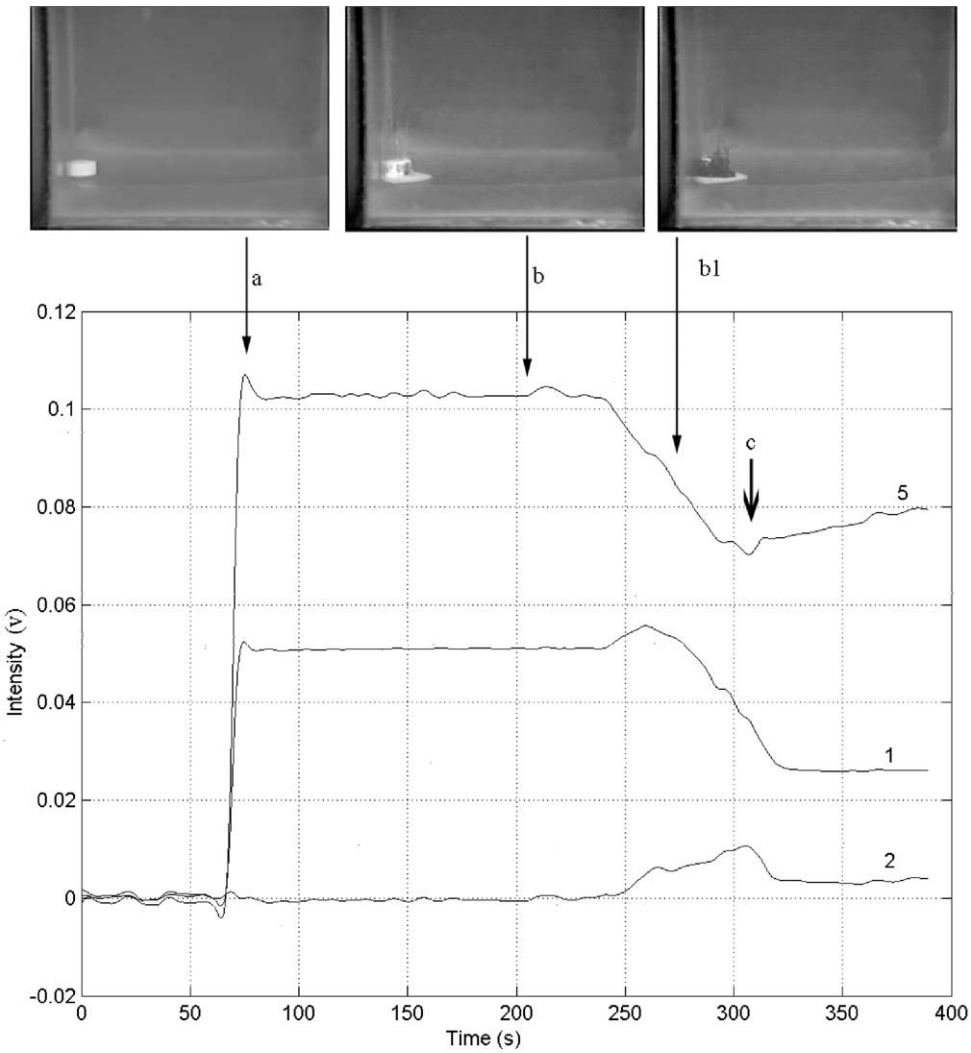

Fig. 3. Illustration of image sequence correlated with magnetic signals of tablet disintegration process in vitro. Each image has an instant correspondent in recording and the arrows a, b, c, indicated respectively, the arrival, onset and complete disintegration. The arrow b1 indicate an intermediary instant of disintegration process. The numbers of sensors followed the same configuration showed in Fig. 2.

disintegration process in acid solution. The arrows a, b, c indicates respectively, the arrival, the onset and complete disintegration of magnetic tablets.

The CDT was determined by the time interval between the arrows a, b and corresponds to the period in which the pharmaceutical dosage form remains solid. DT was determined for the interval between arrows b, c.

The arrival of magnetic dosage form in the acid solution (arrow a) shows that the sensor located near the tablet presents high intensity of magnetic signal (sensor 5). In the recorded signal, it was observed a period of stability during the CDT in which does not occur the ferrite release, indicating a lag time until the beginning of magnetic tablet disintegration.

With the reduction of coating layer, caused by action of the acid solution, the tablet disintegration begins (arrow b). At this moment, a strong decline of intensity of magnetic signal at the nearer sensors (sensors 1 and 5) is observed, while the signal intensity at the more distant sensor (sensor 2) increases quickly. This occurs because the spreading of ferrite in the recipient. The DT was calculated in this period of magnetic signals alterations. The arrow c indicates the complete disintegration process and the signal return to stability, but with different basal level compared with initial phase. All this process can be followed by the correspondent images (Fig. 3).

The Fig. 4 presents the CDT and DT for all the in vitro measurements and inset illustrates the CDT and DT obtained. The averages were significantly different for $P < 0.01$ (Student's *t*-test).

3.2. In vivo measurement

The Fig. 5 is a typical example of magnetic signals obtained in a measurement with human volunteers.

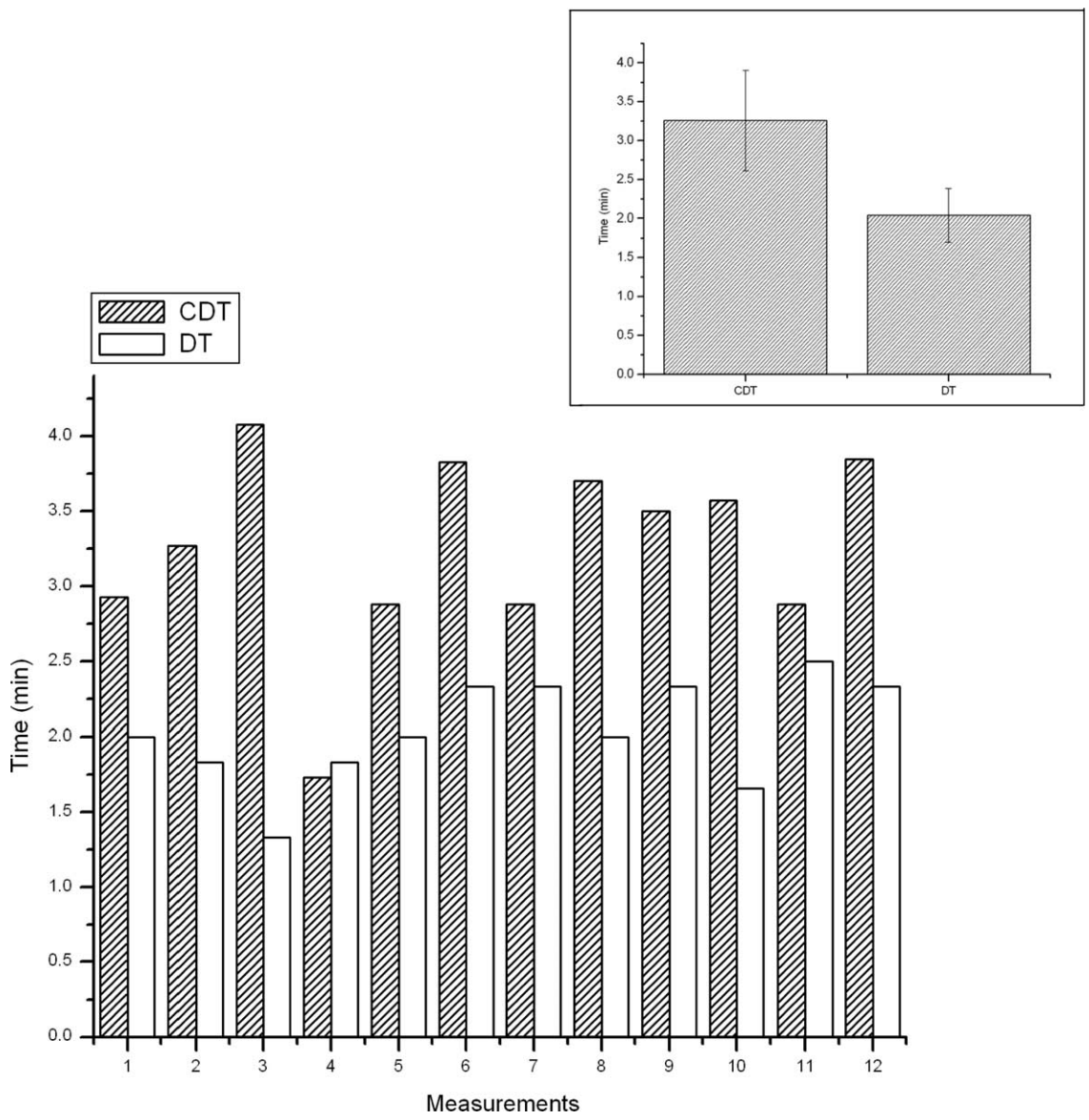

Fig. 4. CDT and DT of the magnetopharmaceutical in vitro experiments. The inset illustrates the average values for times.

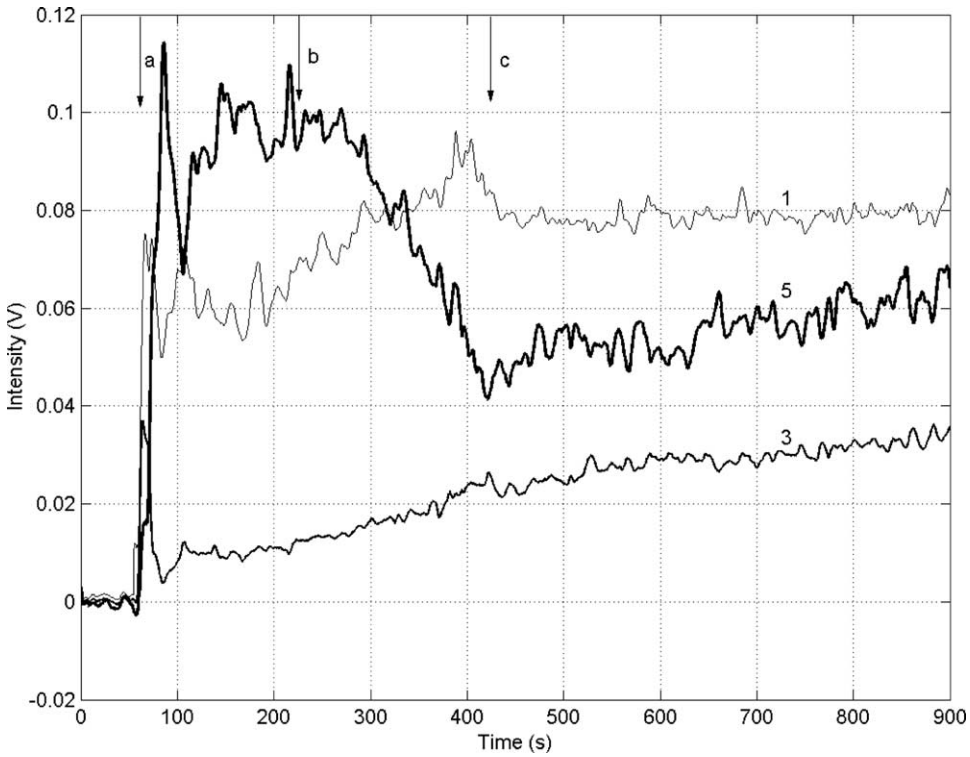

Fig. 5. Example of magnetic signals acquired in subject measurement. Observe basal level variation between the sensors and the recording of GAC in real time. The numbers of sensors followed the same configuration illustrated in Fig. 2. The arrows a, b and c indicate, respectively, the arrival, onset and complete disintegration.

The arrows a, b, c indicate respectively, the arrival, the onset and complete disintegration. The determination of CDT and DT for in vivo measurements followed by the same parameters used in vitro measurements.

Based on the position of the sensors (Fig. 2), it was observed in all the volunteers that the magnetic tablet was deposited in the projection region of the distal stomach. The arrival of magnetic tablet (arrow a) was verified through the intense alteration of basal level in the signal of the sensor positioned in that region (sensor 5) and confirmed by the transit recording of magnetic dosage during its passage to the sensor in the proximal region (sensor 3).

Arrow b indicates the onset of magnetic tablet disintegration. The magnetic signal of the sensor located near the tablet (sensor 5) had strong decline of intensity and in the most distant sensors (sensors 1 and 3) occurs an increase of intensity indicating the distribution of magnetic material in the organ. The complete disintegration process is indicated by arrow c and the magnetic signal remain stable, but as observed in the in vitro measurement, there was different basal level characterizing the distribution of ferrite for the disintegration process.

The GAC with typical frequency of three cycles/minute also is an important indication of magnetic tablet disintegration. The GAC was registered in real time showing that, before the disintegration process the amplitude of contractions was more intense in the distal sensors (1 and 5) than the proximal sensor (sensor 3). After the complete disintegration, must be observed that the recorded signal by proximal sensor (sensor 3) shows the GAC with a quick increase of amplitude due to distribution of ferrite. The GAC and the basal level variation between the sensors characterize the tablet disintegration, indicating the transition between a magnetic marker to magnetic tracer.

In Fig. 6 are presented the CDT and DT for all the human measurements and the inset shows the mean values obtained for these times. The averages were not significantly different to $P < 0.05$ (Student's t-test).

4. Discussion

The new multi-sensor biosusceptometric system provided a significative improvement in the sensitivity and in the spatial resolution, compared to the system used in the previous investigations [16–20]. This is the first study using multi-sensor ACB to investigate the behavior of punctual sources and through the recording of alterations in the basal level and the intensity of the magnetic signal originating from different sensors, being able to characterize the magnetic tablets disintegration. The performance of magnetic signals indicating the ferrite release was similar to the in vitro experiments and for the in vivo measurement, showing accuracy of ACB to record the disintegration process.

Film coating is much used in conventional dosage forms and the CDT indicated how long the pharmaceutical form

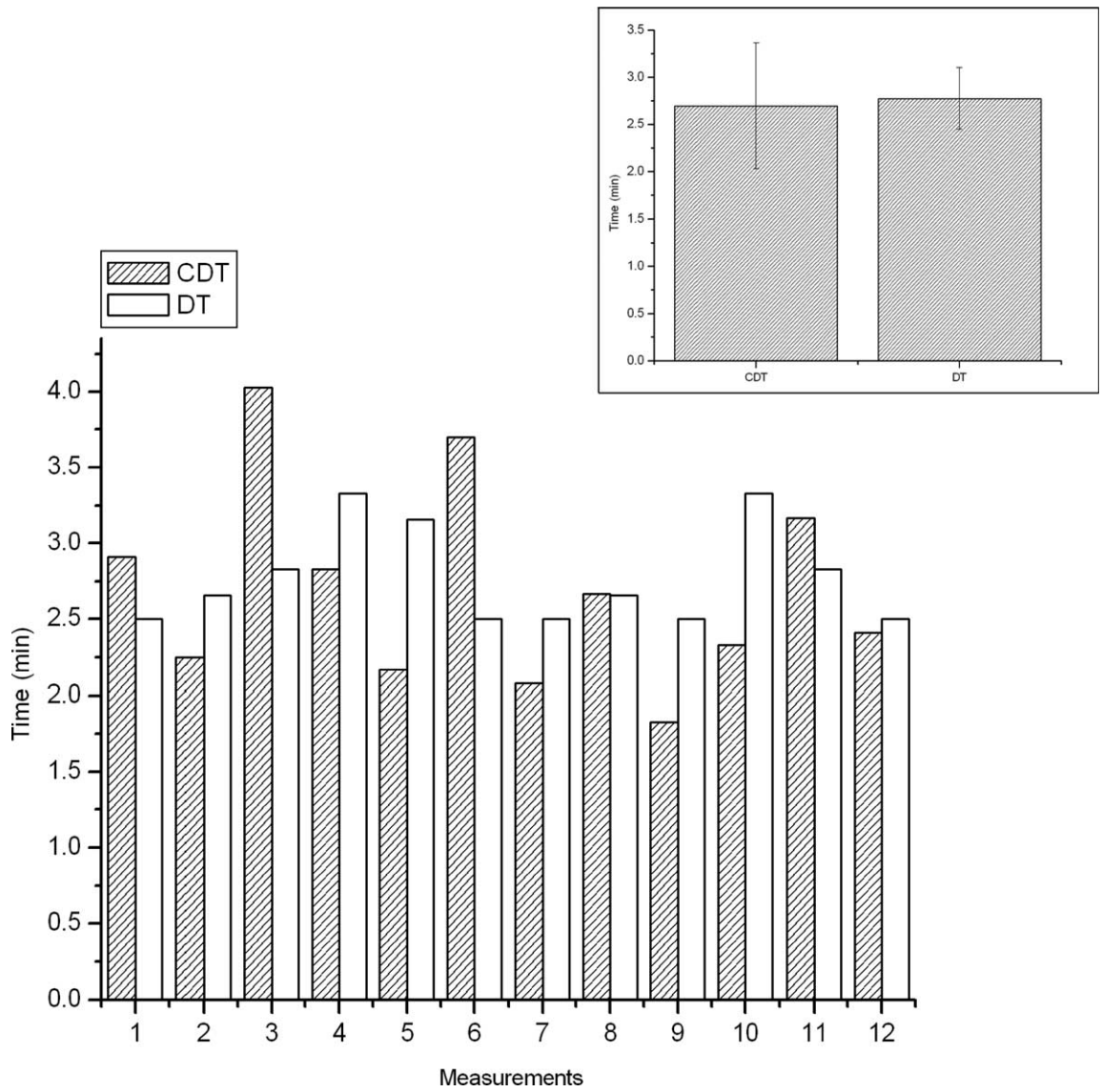

Fig. 6. CDT and DT of the magnetopharmaceutical in vivo measurements. The inset illustrates the average values for times.

remained solid in the gastric fluid or acid solution. It is an important parameter in the development of a drug delivery system, including gastroretentive dosage forms and colon-specific drug delivery [23]. In these cases, an adequate and uniform coating is indispensable to promote the drug delivery in a specific site at the GI tract [24]. The CDT of magnetic tablets verified in both the in vitro and in vivo measurements were equivalent.

Another parameter with important consequences in the drug delivery of solid dosage forms is the DT that can be influenced by GAC in the subject measurements. The destructive action of the motility interferes in the solid forms disintegration and can affect the bioavailability of the drug [4]. The motility pattern is characterized according to the prandial state and the presence or absence of food can affect considerably the release and absorption of many therapeutic agents. In this manner, the ACB could be employed in future studies to evaluate the behavior of magnetic dosage forms in different prandial state, to compare the effects of fasting and postprandial motility in disintegration process.

The success for the rational development of new formulations depends on the knowledge of physiological variables of GI tract that act in the behavior of the release systems [25]. It is indispensable the use of methodologies to investigate the solid dosage forms in GI tract without interfere the organ normal physiology.

For this reason, the pharmacoscintigraphy is a standard methodology used for assessing the disintegration rate of capsules and tablets besides allowing the correlation with pharmacokinetics data [11]. Recently, the development of new technologies like the multichannel-SQUID systems make possible the monitoring and the study of disintegration of magnetic dosage forms allowing to obtain information about those formulations in the GI tract [14].

This study shown that the multi-sensor ACB is another biomagnetic technique that, although, does not have the sensibility and the spatial resolution of the SQUID was able to characterize efficiently the magnetic tablets disintegration with the advantage of having a lower cost, easier operation and portability.

The multi-sensor ACB can be used in tests to evaluate efficacy of super-disintegrants potentials in new pharmaceutical dosage contends magnetic material. Besides that, this technique in combination with pharmacokinetic studies could be providing information about the GI transit and disintegration of oral dosage forms and subsequent drug absorption.

The development of a system involving more sensors will contribute for new applications of multi-sensor ACB and an association of new magnetic devices, like magnetoresistive magnetometer, can improve the accuracy and sensitivity of this methodology. The multi-sensor ACB also is a research tool that can be used in future acquisition of magnetic images allowing to visualize the disintegration process in vivo.

In this way, the physical characteristics that impaired the comparison between the magnetic tablet and the conventional solid form could be overcome. This improvement would elevate the magnetic dosage to the condition of 'magnetopharmaceuticals' in analogy to the radiopharmaceuticals utilized by scintigraphy.

In summary, our data showed that multi-sensor ACB has a great capability to study the dosage forms disintegration both in vitro and in vivo. Moreover, ACB is a non-invasive technique and radiation-free, that a new approach for investigation of drug delivery systems in the human GI tract.

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