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Research paper

Influence of compression forces on tablets disintegration by AC Biosusceptometry

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Abstract

Analysis of physical phenomena that occurs during tablet disintegration has been studied by several experimental approaches; however none of them satisfactorily describe this process. The aim of this study was to investigate the influence of compression force on the tablets by associating the AC Biosusceptometry with consolidated methods in order to validate the biomagnetic technique as a tool for quality control in pharmaceutical processes.

Tablets obtained at five compression levels were submitted to mechanical properties tests. For uncoated tablets, water uptake and disintegration force measurements were performed in order to compare with magnetic data. For coated tablets, magnetic measurements were carried out to establish a relationship between physical parameters of the disintegration process. According to the results, differences between the compression levels were found for water uptake, force development and magnetic area variation measurements. ACB method was able to estimate the disintegration properties as well as the kinetics of disintegration process for uncoated and coated tablets. This study provided a new approach for *in vitro* investigation and validated this biomagnetic technique as a tool for quality control for pharmaceutical industry. Moreover, using ACB will also be possible to test these parameters in humans allowing to establish an *in vitro*/*in vivo* correlation (IVIVC).

Keywords: AC Biosusceptometry; Compression force; Disintegration force; Water uptake; Magnetic tablets; Disintegration

1. Introduction

Despite increasing interest in modified release systems, conventional tablets are still the most popular solid dosage forms due to ease of manufacture, convenience of dosing and stability [1,2].

Drug release from tablets occurs by disintegration process promoting a fast fragmentation of the dosage form under the action of the disintegrant [3]. If this process is slow or incomplete the bioavailability of a drug will be inadequate. Appropriate choice of a disintegrant and its consistency of performance have critical importance to the formulation development [4].

Disintegration of compressed tablets is an important quality parameter and it is strongly influenced by the properties of the excipients, such as particle size distributions and the compression force [5,6]. It is well established that the compression force is essential for the tablet manufacturing process since an increase in the compression force causes a reduction of tablet porosity and, as a consequence, a linear increase of the disintegration time [7,8].

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In experimental determination of tablet disintegration an official *in vitro* apparatus is used; however, it does not describe satisfactorily the disintegration properties. Notwithstanding, tablet disintegration has been studied by several research groups by developing novel experimental approaches for analysis of physical phenomena occurring during this process [9–11].

A mathematical model based on measurements of the disintegration force developed as a result of water uptake provided an interesting parameter to quantify and to compare the efficiency of disintegrants [12–15]. Moreover, it can be useful to determine the better relationship between the compression force and the force developed during the disintegration process.

In the past few years, Alternate Current Biosusceptometry (ACB) has been innovative in this application field and has become an alternative method for pharmaceutical research. Disintegration of compressed magnetic tablets has been evaluated *in vitro* and *in vivo* through signals and images employing a multisensor ACB system [16–20]. Biosusceptometry demonstrated versatility not only for human studies but also the capability to be used as a tool in quality control for pharmaceutical products.

The aim of this study was to investigate the influence of compression force on the tablets by associating the AC Biosusceptometry with consolidated methods, water uptake and disintegration force, in order to validate the biomagnetic technique as a tool for quality control in pharmaceutical processes.

2. Materials and methods

2.1. Materials

Materials used in this study were ferrite powder ($MnFe_2O_4$; 80–125 μm) as the magnetic marker (Thornton, Brazil), effervescent mixture (SmithKline Beecham, Brazil), microcrystalline cellulose PH101 (Valdequímica, Brazil), Eudragit® E100 (Röhm GmbH, Germany), magnesium stearate (Valdequímica, Brazil), talc (Valdequímica, Brazil), titanium dioxide (Valdequímica, Brazil), triethyl citrate (Scandiflex, Brazil), and isopropyl alcohol (Sigma–Aldrich, Brazil).

2.2. Preparation of tablets

Tablets were directly compressed on a single punch tablet machine (Marconi, MA-098/1CPE, Brazil) at five different force levels (10, 20, 30, 40, and 50 kN), using 11 mm concaved punches. The tablets had the following composition: 71% ferrite, 21.5% microcrystalline cellulose, 7% effervescent mixture, 0.5% magnesium stearate. Sample tablets at each compression force were taken and were stored in glass bottles before physical tests. A chemical characterization for magnetic material has been provided, as described previously [19].

Hardness testing of 10 tablets at each compression force was determined with a model THB 220 (Erweka Hardness Testers, Brazil). Friability of the tablets was determined using an Automated Friabilator EF-2 (Electrolab, Brazil) at 25 rpm/min for 4 min. The tablets were weighed and loss in weight (%) was calculated.

Coating dispersion was prepared by dissolving 6% (w/w) Eudragit E100, 2% (w/w) talc, 1% (w/w) triethyl citrate, 1% (w/w) magnesium stearate, and 2% (w/w) titanium dioxide in 88% isopropyl alcohol. Coating was performed with a coating machine (PCCA, Brazil) under the following conditions: spray air pressure, 1.5 mg/cm^2; inlet temperature, 40–45 °C; rotating speed, 20 rpm. Acid-soluble coating dispersion was applied to 16 g of tablets at each compression force.

2.3. AC Biosusceptometry

AC Biosusceptometry bases its functioning on induction coils for recording the magnetic flux variation obtained from the response of a magnetic material when an alternating magnetic field is applied.

Essentially, the multisensor ACB system has one pair of excitation coils ($\phi = 11$ cm) and seven pairs of detection coils ($\phi = 2$ cm) separated by a fixed distance (baseline), coaxially arranged in a first-order gradiometric configuration for acquisition of magnetic signals in distinct points [18]. The sensor is mounted as a couple of magnetic flux transformers with an air nucleus in which the pair (excitation/detection) that is located more distant from the magnetic material that will be detected acts as a reference transformer and the pair closest of the sample as a measurement transformer.

The excitation coils induce equal magnetic flux in the detection coils, hence, when a magnetic sample is nearest of the measurement system an imbalance in the voltage occurs, due to the change in the differential flux between the detection coils. Consequently, the gradiometric system detects the magnetic flux variation between the detection coils. Magnetic signals have been acquired employing lock-in amplifiers (Stanford Research Systems, Inc., USA), digitized by an A/D board of 16 bits (PCIMIO-16XE-10, National Instruments Inc., Austin, TX, USA) and stored in the computer for further analysis.

The multisensor ACB system has been developed to improve spatial resolution and sensitivity for pharmaceutical applications [16–20].

2.4. Water uptake and disintegration force measurements

Water uptake and disintegration force measurements were carried out using an apparatus modified from Catellani et al. [14]. A glass container filled with 80 ml of distilled water and covered by a quantitative filter paper was positioned on an electronic precision balance. A force transducer (Model CI-6746, PASCO® Scientific, USA) was connected to the upper side of a cylindrical frame passing

through a slide guide locked by an arm which assured that the set always stopped at a fixed level. Samples of uncoated tablets at each compression force were then placed into the lower side of this slide guide. A schematic representation of the measurement apparatus is shown in Fig. 1.

When the tablet started absorbing water it was pressed against the cylindrical frame allowing to monitor the force developed during liquid uptake. Water uptake data corresponded to the weight decreases recorded by the precision balance. Water uptake and disintegration force data were acquired (sample rate at 10 Hz) and stored in a personal computer for analysis.

2.5. Magnetic measurements

Experimental determination of disintegration process was performed using a glass vessel positioned in front of the multisensor ACB system, as shown in Fig. 2. For uncoated tablets, the apparatus without the precision balance and the force transducer was positioned in front of the multisensor ACB system in order to acquire the magnetic signals during water uptake by the tablet.

As regards the relevance of coating process on drug delivery, the disintegration of magnetic coated tablets has also been evaluated. The recipient was filled with 900 ml of fasted state simulated gastric fluid without pepsin (0.1 N HCl; pH 1.2) prepared according to the USP XXII method. A tablet was added in the recipient test and the magnetic signals were acquired simultaneously for at least 20 min. The solution was replaced between each measurement.

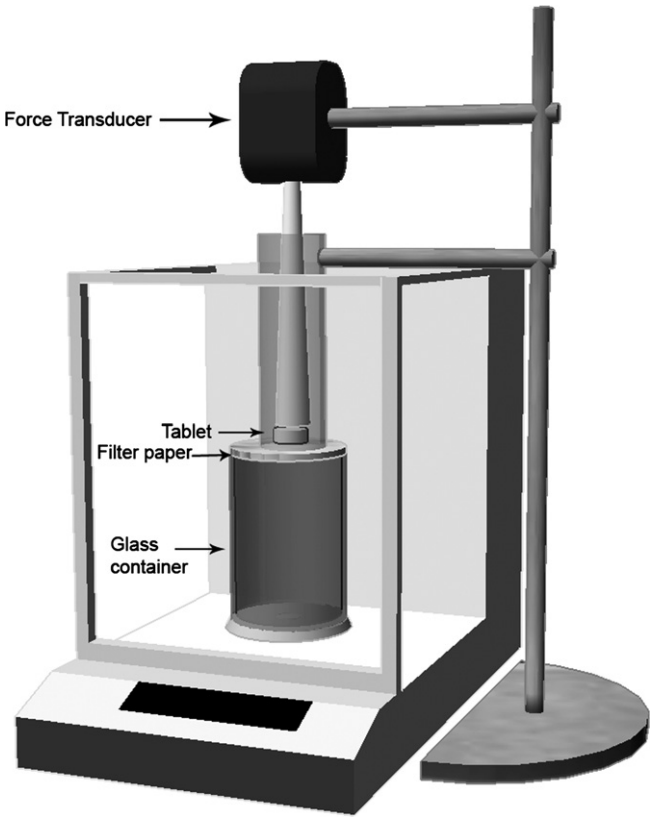

Fig. 1. Water uptake and disintegration force apparatus. When water was taken up by the uncoated tablet, the force developed was measured by the transducer placed on the upper side of the cylindrical frame.

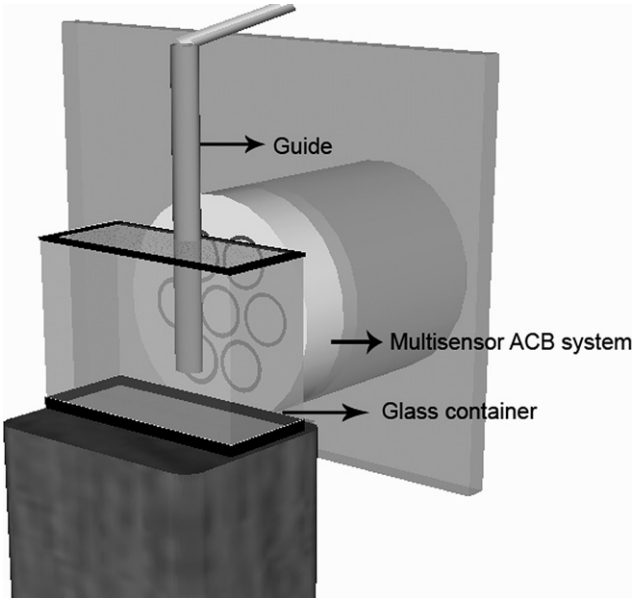

Fig. 2. Magnetic apparatus mounted for disintegration measurement. A coated tablet was inserted by a guide in the glass container placed in front of the multisensor AC Biosusceptometry system. The disintegration process was monitored in real time by seven magnetic sensors.

The disintegration process may be characterized by the transition of a magnetic marker, MM (non-disintegrated tablet), to a magnetic tracer, MT (disintegrated tablet). Hence, when the tablet is a MM, the magnetic signals were detected with high and located intensity values. As soon as the tablet started absorbing water the disintegration process occurred and the magnetic signals detected a distribution of the intensity values. For coated tablets, the interval between the transition has been delayed by the coating layer.

Magnetic signals were acquired with a sample rate of 10 Hz/channel and were stored as ASCII format for analysis.

2.6. Magnetic images

A detailed description about the principles of biomagnetic images from ACB for pharmaceutical applications was reported by Corá et al. [17]. Briefly, magnetic signals recorded by the multisensor ACB system are represented by a time series matrix. From these signals, imaging sequences have been calculated by computing an average in regular time interval of 3 s (sample rate at 0.33 Hz). Image processing techniques had included background subtraction, brightness and contrast adjustment. Once processed, the images were submitted to a segmentation process aiming to quantify, in the number of pixels, the magnetic area on each time interval.

2.7. Data analysis

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. Water uptake *versus* time, *versus* time and magnetic area *versus* time profiles were fitted using the classical exponential Weibull distribution [21] modified from Pena Romero et al. [15], as shown by Eq. (1).

$$F = F_{\max}\left(1 - e^{-\left(\frac{t-t_0}{t_{63.2}}\right)^{\beta}}\right) \quad (1)$$

where F is the force developed (N) at time t (min), $F_{\max}$ is the maximum force developed, t_0 is the lag time, $t_{63.2}$ is the time needed to reach 63.2% of the maximum force developed, and β is the shape parameter. In analogy, $Q_{\max}$ and $A_{\max}$ were used to calculate the maximum amount of water uptake (mg) and the maximum magnetic area variation (pixel), respectively. This model allowed plotting a set of parameters involved in the overall tablet disintegration and the coefficient of determination (R^2) was the statistical parameter established to assure the integrity of fit.

For uncoated tablets, magnetic imaging area variation ($A_{\max}$) was calculated during the water uptake aiming to establish a correlation with the force measured. All of these analyses were performed using Origin® (OriginLab Corporation, Northampton, MA, USA).

To evaluate the disintegration process of coated tablets, the following parameters were considered: coating dissolution time (CDT) was the time interval between the arrival of the magnetic tablet into the solution until its initial disintegration time; initial disintegration time (t_{10}) represented the 10% increase of pixels in the imaging area; complete disintegration time (t_{90}) was the time needed for calculating the 90% increase of pixels in the imaging area; disintegration time (DT) was calculated by subtracting t_{90} from t_{10}. DT was defined according to previous quantification parameters for *in vivo* measurements [16]. Plotting imaging area values *versus* time and particularly the first derivative of the curve was calculated and it was used for describing the disintegration kinetics.

Similarly, imaging area *versus* time profiles were fitted using Weibull distribution and the sigmoidicity of curves and time parameters ($t_{63.2}$ and DT) were also evaluated. Magnetic signals and images were processed and analyzed using MatLab® (Mathworks, Inc., Natick, MA, USA) according to procedures described previously [17].

All graphs plotted represent the mean value for the 10 tablets at each compression force applied without error bars for the sake of clarity.

3. Results and discussion

This study showed that the AC Biosusceptometry associated with conventional analysis methods could be proposed as a novel approach to investigate some physical parameters involved in the phenomenon of tablet disintegration. Hence, by using an alternative disintegrant, different compression force levels were chosen to investigate the disintegration properties of uncoated as well as coated magnetic tablets.

As expected, tablet hardness and friability were typically compression force dependent. It was observed that at higher compression forces the hardness of the tablets increased (ranging from 104 to 487 N) and the friability decreased (ranging from 2.4% to 0.02%). Increases in the hardness hasten the disintegration time, since the tablets become harder and, consequently, less friable.

Hardness and friability are strictly related to the liquid penetration into solid dosage forms. Water uptake promotes the development of a force inside the tablet responsible for its disintegration and the rate of this process may be related to the rate of liquid penetration into the dosage form [22]. Therefore, there is a substantial relationship between formulation parameters and the disintegration efficiency since the force developed depends on the water uptake, the presence of the disintegrant and the compression force applied to the tablets.

Combined measurements of water uptake and force development have been extensively exploited to provide parameters to quantify the disintegration process of tablets [23,24]. ACB technique was proposed to investigate the relationships among these parameters and disintegration properties of tablets aiming to verify its ability to quantifying the efficiency of an effervescent disintegrant transforming liquid uptake into force through the magnetic image area.

Fig. 3 shows profiles of water uptake, disintegration force and magnetic area obtained for measurements using uncoated tablets at different compression forces. It may be observed that for different compression forces tablets differ more on the amount of water uptake (a), than on the disintegration force developed (b) and also on the magnetic area variation (c) during liquid penetration.

In order to demonstrate the performance of ACB technique to measure the physical parameters of the disintegration process, examples of magnetic area variation, water uptake and disintegration force developed profiles obtained for a tablet compressed at 30 kN are shown in Fig. 4.

Individual plots (Fig. 4a) indicated that there was a similarity particularly evident in the magnetic and force developed data. A linear relationship between magnetic area against disintegration force (Fig. 4b) at a higher significance level ($R = 0.987$) has been found. Despite a short non-linear region between these parameters that could be explained by a preload force applied to the tablet due to the positioning of transducer, the results could suggest that the area variation may be related to force measurements.

Plotting magnetic area variation against water uptake and disintegration force (Fig. 4c) was possible to observe that despite absorbing a substantial amount of water, the magnetic area as well as disintegration force remained constant when they reached the maximum value.

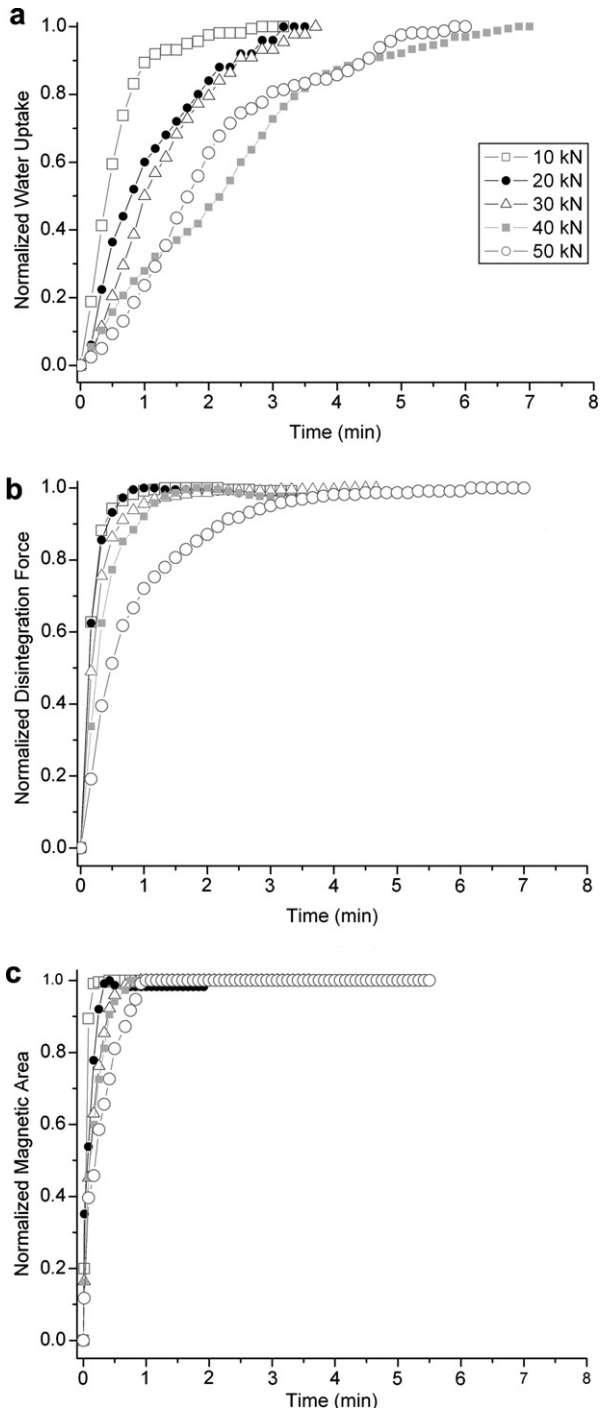

Fig. 3. Time-dependent profiles of water uptake (a), disintegration force (b) and magnetic area variation (c) for uncoated tablets at different compression forces.

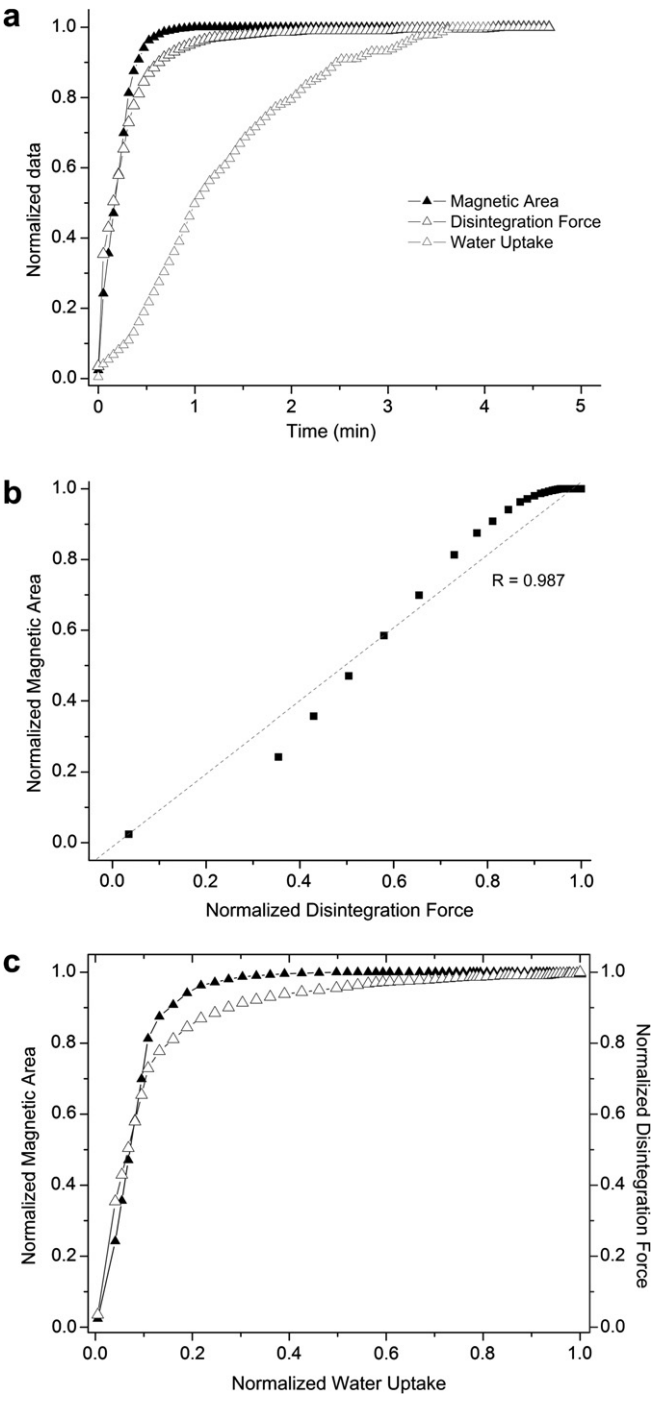

Fig. 4. Plots of physical parameters of the disintegration process for tablets compressed at 30 kN. (a) Temporal magnetic area variation and disintegration force developed during water uptake. (b) Correlation between magnetic area and force developed ($R = 0.987$). (c) Relationship between magnetic area, water uptake and disintegration force.

The most relevant water uptake, force developed and magnetic area data are summarized in Table 1. As expected, the time interval needed to achieve 63.2% of the total water amount (Q_{max}), of the maximum force developed (F_{max}) and of the maximum area variation (A_{max}) was directly influenced by compression force applied to the tablets. In general, tablets obtained at lower compression force developed a high disintegration force as well as an expressive magnetic area variation and disintegrated in a shorter time.

Several studies investigated the relationship between the liquid penetration rate and the disintegration force and had concluded that the force increases linearly with the amount of water absorbed and, as a result, contributes to the disintegration of tablets with swelling disintegrants [9,13,23].

Table 1
Fit parameters of water uptake, disintegration force and magnetic area profiles for uncoated tablets according to Weibull model, expressed as mean ± SD

Compression force (kN)	Water uptake (mg)			Disintegration force (N)			Magnetic area (pixel)		
	$t_{63.2}$ (min)	β	Q_{max} (mg)	$t_{63.2}$ (min)	β	F_{max} (N)	$t_{63.2}$ (min)	β	A_{max} (pixel)
10	0.55 ± 0.14	1.23 ± 0.11	1.60 ± 0.05	0.17 ± 0.04	1.00 ± 0.12	16.20 ± 0.6	0.06 ± 0.012	1.43 ± 0.1	1150 ± 98
20	1.13 ± 0.13	0.92 ± 0.13	1.57 ± 0.04	0.18 ± 0.03	1.13 ± 0.10	13.30 ± 0.9	0.11 ± 0.014	1.73 ± 0.15	1118 ± 108
30	1.39 ± 0.19	1.27 ± 0.15	1.62 ± 0.06	0.26 ± 0.04	0.88 ± 0.11	13.03 ± 1.1	0.16 ± 0.012	0.99 ± 0.16	1011 ± 88
40	2.02 ± 0.26	1.51 ± 0.09	1.61 ± 0.08	0.34 ± 0.08	1.03 ± 0.15	11.82 ± 1.8	0.20 ± 0.024	0.97 ± 0.11	975 ± 112
50	2.65 ± 0.35	1.67 ± 0.12	1.65 ± 0.05	0.77 ± 0.07	0.77 ± 0.09	11.5 ± 0.9	0.30 ± 0.022	1.03 ± 0.09	885 ± 76

Regarding our data, in general, the maximum liquid penetration occurred at a constant rate; however the disintegration force developed, magnetic area variation and the time interval defined as $t_{63.2}$ were clearly dependent on the compression force applied (Table 1).

It could be partially explained by the disintegrant used, since effervescent tablets disintegrate by means of a reaction that promotes the disruption of the tablet due to the pressure of the gas formed [6,22]. The concept of effervescence is utilized in several dosage forms and the efficiency of this reaction depends on several factors, including the quantity of the disintegrant and its efficiency to react to water.

In addition, the shape of curves represented by β parameter seems to be related to the disintegration process of tablets since it provides information on compression behavior [10]. For magnetic tablets, different shapes characterized the curves evaluated, however, a certain discrepancy has been found and it may be related to the kind of disintegrant used. Further relationship between shape parameters and disintegration properties of swelling materials might be investigated by ACB method.

Whereas the time needed to absorb the maximum amount of water, to develop the maximum disintegration force and the maximum magnetic area variation, may be observed differences in relation to the compression force applied, as illustrated in Fig. 5. Comparing the curves, it was observed that for a same level of compression force a higher time interval ($t_{63.2}$) was needed for the amount of water absorbed to be able to promote the development of a force as well as a variation in the magnetic area resulting in the disintegration of tablet. Meanwhile, despite absorbing water continuously, not even the disintegration force or magnetic area had been affected which could be mainly attributed to the effervescent property. In our data this phenomenon continues to be evident while the compression forces increase confirming that the compression forces clearly exerted an expressive effect on several formulation parameters.

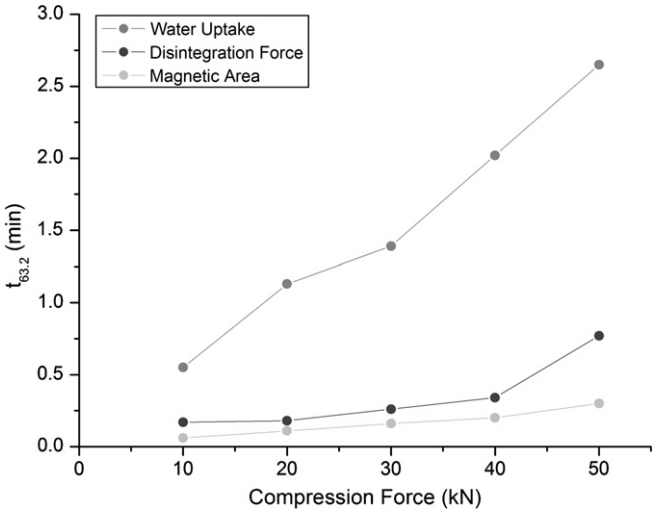

Fig. 5. Relationship between compression force and $t_{63.2}$ parameter. The time interval needed for the maximum amount of water to be able to promote the development of disintegration force and magnetic area was higher for a same level of compression force.

Aiming to establish a possible relationship between compression force, disintegration time and magnetic area variation, measurements having been performed for coated tablets. Nowadays, film coatings are important pharmaceutical excipients to control the drug release and, despite film-forming polymers have been widely used for film coating of solid oral dosage forms, there are few techniques able to verify *in vitro* and *in vivo* its uniformity properties. Typical examples of such curves are given in Fig. 6.

As discussed early, magnetic area variation was markedly influenced by compression force applied to the tablets (Fig. 6a). As expected, tablets obtained with higher compression forces tend to develop a slower area variation which could be explained by the decrease in porosity that would contribute to delay the water uptake and, consequently, to the development of a strong disintegration force.

The overall kinetics of tablet disintegration has been evaluated through the first derivative of magnetic area variation curves (Fig. 6b). This parameter, called *input* [10], was determined at time $t_{63.2}$ of area curves and allowed describing the maximum capability of the effervescent agent to promote the disintegration of the tablets. In fact, input depends on the compression forces used: when the tablets became more resistant the variation rate was smaller than for the tablets prepared at lower compression levels. A magnetic measurement device for the *in vitro* determination of tablet disintegration kinetics has been previously employed [25].

The sigmoidicity of curves and time parameters of the magnetic measurements are reported in Table 2. The time

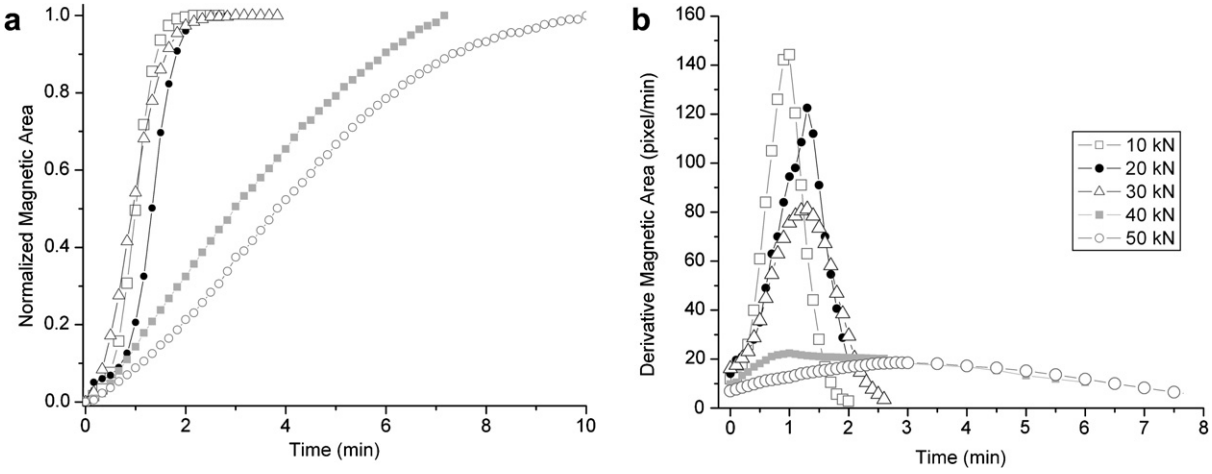

Fig. 6. Magnetic data profiles for coated tablets. (a) Temporal effect of compression force on the magnetic area variation. (b) First derivative of magnetic area variation curves for compression force with respect to time.

Table 2
Fit parameters of magnetic area profile for coated tablets according to Weibull model, expressed as mean ± SD

Compression force (kN)	Magnetic data					
	$t_{63.2}$ (min)	β	A_{max} (pixel)	DT (min)	CDT (min)	Input (pixel/min)
10	1.11 ± 0.13	3.57 ± 0.22	755 ± 35	1.24 ± 0.10	0.78 ± 0.23	120 ± 25
20	1.48 ± 0.11	4.46 ± 0.11	732 ± 29	1.69 ± 0.53	1.54 ± 0.47	103 ± 29
30	1.65 ± 0.19	2.32 ± 0.32	715 ± 42	2.33 ± 0.48	1.05 ± 0.30	61 ± 17
40	3.82 ± 0.28	1.31 ± 0.18	690 ± 33	3.85 ± 0.31	1.50 ± 0.55	17 ± 12
50	4.82 ± 0.26	1.39 ± 0.26	665 ± 46	5.26 ± 0.64	2.88 ± 0.56	14 ± 7

parameters ($t_{63.2}$ and DT) as well as A_{max} and input values were dependent on the compression forces. An inverse relationship among A_{max} and time parameters was found, since tablets showing higher A_{max} values exhibited shorter disintegration times. A similar behavior has been observed for uncoated tablets (Table 1) which can also be attributed to compression force used for tablet preparation.

Indeed, for uncoated tablet $t_{63.2}$ related to A_{max} values was faster than for coated tablets at each compression force applied. ACB may be useful to characterize the functionality of coating systems, since it has been demonstrated as appropriate to determine the performance for the product.

Concerning the shape parameter (β) it can be observed that the values calculated were higher than 1 and could indicate the presence of an initial obstacle to water penetration linked to the surface conditions of the coated tablet. However, as discussed above, shape parameters need further investigation.

Compression force plays an important role for tablet manufacturing process, since it is a well-known parameter influencing the disintegration time. Disintegration time of coated tablets ranged from 0.7 to 5.2 min. It has been reported that compression forces are related to the porosity of tablets [8], therefore, when the compression force was increased, the hardness increased resulting in tablets of low porosity. Besides compression forces, the coating layers had also interfered in the water uptake and, consequently, delaying the disintegration time.

4. Conclusions

The ACB technique associated with standard methods allowed evaluating the relationship between compression forces and magnetic area on the disintegration process of tablets. The parameters evaluated showed that ACB technique satisfactorily was able to estimate the disintegration properties as well as the kinetics of disintegration process for uncoated and coated tablets. Thus, this study was able to provide an alternative approach to investigate *in vitro* disintegration and also to validate a low-cost magnetic method as a tool for quality control for pharmaceutical industry.

On the basis of this study, further characterization of functionality of superdisintegrants can be made in predicting the mechanisms of action on the basis of compression data.

Regarding the importance of physiological parameters on the pharmaceutical processes, attention has been focused on dosage forms that have been tested in humans. In this research field, ACB technique has demonstrated promising results and has become an alternative to the conventional methods.

In summary, AC Biosusceptometry might be able to characterize a number of parameters related to drug delivery, deserving the same importance as conventional techniques for pharmaceutical research. Furthermore, ACB method will be especially powerful when combined with classical pharmacokinetic data (''magnetopharmacokinetic'') allowing establishing an *in vitro/in vivo* correlation (IVIVC).

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