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Research paper

Determination of the disintegration behavior of magnetically marked tablets☆

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Abstract

The disintegration behavior of different tablets that were marked as magnetic dipoles by the incorporation of ferromagnetic black iron oxide and subsequent magnetization was studied using a specially developed measurement setup. This novel apparatus records the magnetic induction generated by the magnetic dipole moment of the tablets during their disintegration. It was found that the observed decrease of the magnetic induction can be used for a quantitative determination of the disintegration of tablets. In particular, it could be shown that the magnetic data provide information about the disintegration mechanism. For tablets with a minor influence of swelling on the disintegration mechanism a linear decline of the magnetic fluxes was observed. After addition of swelling disintegrants (crospovidone) the decline of the magnetic flux could be fitted by an exponential function, indicating the involvement of a disintegration force. Furthermore, the data demonstrate that using modern multichannel biomagnetic measurement equipment the monitoring of the disintegration behavior of magnetically marked tablets in humans will be possible.

Keywords: Disintegration; Disintegration force; Black iron oxide; Magnetic tablet; Magnetic dipole; Magnetic marker monitoring

1. Introduction

Solid dosage forms that are labeled as magnetic dipoles can be localized within the organs of the gastrointestinal tract by means of magnetic measurements, a procedure that is called magnetic marker monitoring (MMM) [1]. Magnetic labeling of solid dosage forms is achieved by the incorporation of remanent magnetic particles and their subsequent magnetization in order to create one single magnetic dipole moment. After ingestion components of the dosage form's dipole field are measured at multiple positions outside the body using extremely sensitive biomagnetic measurement equipment. Then, the dipole field is reconstructed from the recorded field components. The localization procedure is carried out as an approximation, where the deviation between the measured dipole field and the dipole field of an assumed magnetic dipole with variable orientation and position is minimized.

So far, mainly nondisintegrating dosage forms have been applied for in vivo investigations. This has the advantage that the magnetic dipole remains stable during the gastrointestinal passage. Thus, the magnetic moment of such a nondisintegrating dosage form can be determined in a separate experiment prior to the in vivo measurements and can be taken as a constant value in the localization procedure. This reduces the parameters to be fitted to five: the three position coordinates x, y, z and two angles describing the orientation of the dipole in space. We were already able to demonstrate that using modern biomagnetic measurement equipment which records components of the magnetic field in several planes and orientations the localization procedure also yields valid results for monitoring of the in vivo behavior of disintegrating magnetically marked capsules, in which the magnetic moments are decreasing with time [2]. Thereby, the application of MMM can be extended to the determination of the in vivo behavior of disintegrating dosage forms.

It was the purpose of the presented experiments to investigate the in vitro behavior of magnetically marked tablets with respect to the temporal development of their magnetic moments during disintegration. Using biomagnetic measurement equipment, such in vitro investigations are hampered by serious difficulties. The magnetic flux densities measured in biomagnetic experiments are extremely

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Table 1
Composition of tablets

	Ingredient	Supplier[a]	Type A (mg)	Type B (mg)	Type C (mg)	Type D (mg)	Type DE (mg)
Inner phase (granules)	Riboflavin	Caelo	20	20	20	20	20
	Black iron oxide	Caelo	10	10	10	10	10
	Lactose	Caelo	212	44	44	–	–
	Potato starch	Caelo	53	188	188	–	–
	Crospovidone	BASF	–	7.5	7.5	–	–
	Gelatin solution (10%)	Caelo	q.s.	q.s.	q.s.	–	–
Outer phase	Magnesium stearate	Caelo	3	3	3	7.5	7.5
	Silicon dioxide	Caelo	2	2	2	4.5	4.5
	Potato starch	Caelo	–	7.5	–	–	–
	Cellulose (microcryst.)	Rettenmaier	–	18	18	–	–
	Crospovidone	BASF	–	–	7.5	–	–
	Cellulose (Elcema G250)	Degussa-Hüls	–	–	–	213	213
	Cellulose (Elcema P100)	Degussa-Hüls	–	–	–	45	45
	Eudragit E	Röhm					3.9[b]

[a] Caelo, Hilden, Germany; BASF, Ludwigshafen, Germany; Rettenmaier, Rosenberg, Germany; Degussa-Hüls, Frankfurt, Germany; Röhm, Darmstadt, Germany.
[b] mg/cm$^{2.}$.

weak. For MMM they are usually in the range of some nT to some pT, i.e. a factor 10^3–10^6 below the earth's magnetic induction. In order to be able to measure such weak magnetic fluxes, the influence of external fields (e.g. the earth's field and magnetic fields generated by electrical currents or by moving magnetic objects like vehicles or elevators) has to be strongly reduced. Therefore, biomagnetic measurement devices are installed in special environments, so called magnetically shielded rooms, where external magnetic fields are strongly reduced by several layers of special magnetic materials. Within these rooms, any source of a magnetic field (e.g. iron, electricity) must be avoided. Accordingly, the usual components in laboratory equipment for the characterization of dosage forms (e.g. thermostated water baths, stirrers) cannot be used within these shielded rooms. In order to overcome this problem, we developed a special equipment for the measurement of the magnetic fluxes produced by magnetically marked dosage forms that can be operated outside of magnetically shielded environments.

2. Materials and methods

2.1. Preparation of tablets

Four different tablets (types A, B, C and D) were pressed on an excenter tableting machine (Nagema KB2, Germany). The compositions of the tablets are given in Table 1. The tablets of the types A, B and C, respectively, were prepared after granulation of the components of the inner phase with a solution of gelatin in water as binder. The tablets of type D were prepared by direct compression of the powder mixture. Furthermore, some of the tablets of type D were coated with 3.9 mg/cm^2 of Eudragit E (tablets type DE).

2.2. Magnetic measurements

The magnetic flux $\vec{B}$ generated by the tablets was measured using a magnetoresistive magnetometer (HMR 2300, Honeywell Inc., USA) connected to a personal computer. The data sampling rate was 20 Hz. The magnetometer contains three sensors that record the three axial components B_x, B_y and B_z of $\vec{B}$. The magnetometer was mounted within a plastic shielding against water on the outer bottom of a nonmagnetic beaker made from poly(vinyl chloride). For every disintegration experiment one tablet was placed in a nonmagnetic basket located at the outer end of a stirrer (Fig. 1). The stirrer was mounted on a

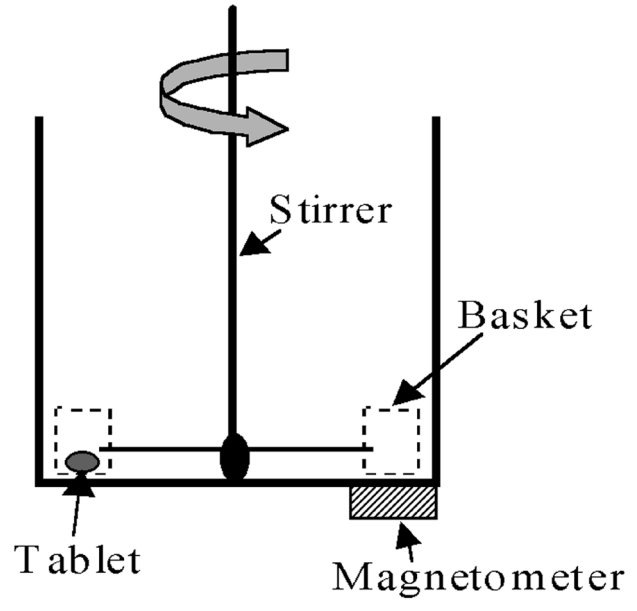

Fig. 1. Schematic drawing of the experimental setup for magnetic disintegration measurements.

conventional dissolution tester (Erweka GT, Germany). In order to have a strong signal, the stirrer with the basket was adjusted in a position where the tablet was as close to the bottom of the beaker as possible. The disintegration experiments were performed in 0.1 N hydrochloric acid at 37°C. The stirring rate was 20 rpm. The measurement device was operated in a regular laboratory. No shielding against the magnetic field of the earth or environmental magnetic noise was employed.

2.3. Data evaluation

The recorded magnetic fluxes were evaluated using a self-made computer program. The different steps of the data evaluation procedure are demonstrated in Fig. 2a,b on hand of experimental data obtained for a tablet of type A. First, the absolute value of $\vec{B}$ (Fig. 2a) was calculated from the three measured components B_x, B_y and B_z according to Eq. (1).

$$B = \left|\vec{B}\right| = \sqrt{B_x^2 + B_y^2 + B_z^2} \quad (1)$$

Then, the maximal values of B for every turn of the stirrer (inset of Fig. 2a) were extracted from the data sets. In order to eliminate magnetic fluxes generated by other sources than the tablet (especially the earth's magnetic field), for every turn the median of B was subtracted. Hence, it is possible to calculate the magnetic flux generated by the tablet (B_{peak}, Fig. 2b) for every turn of the stirrer even in a magnetically unshielded environment.

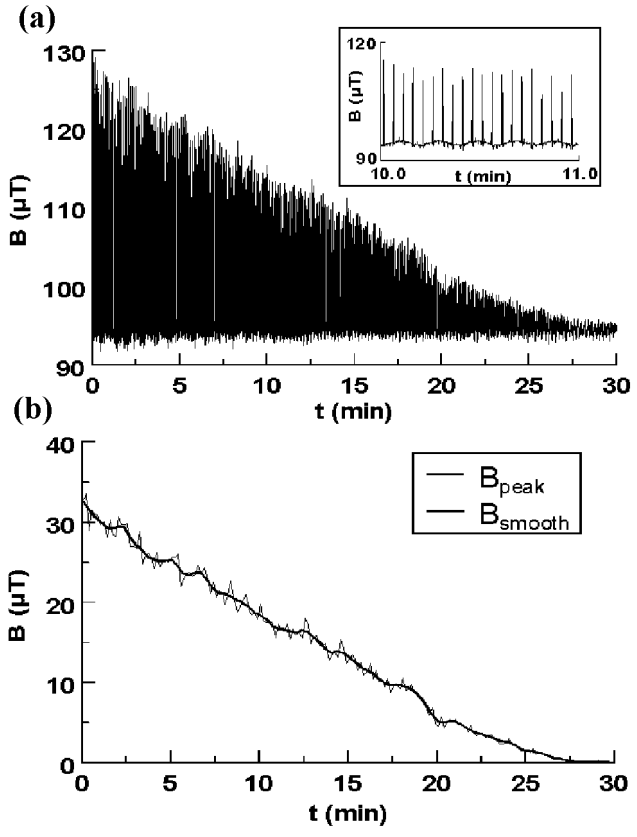

Fig. 2. Examples for the data evaluation process. (a) Magnetic flux B generated by the magnetic dipole moment of a magnetically marked tablet of type A during disintegration. The inset shows individual peaks of the magnetic flux recorded during one minute of disintegration. Every peak indicates one passage of the tablet above the magnetometer (stirring rate: 20 rpm). (b) Peak values of B (B_{peak}) after subtraction of the background signal and smoothed values (B_{smooth}) calculated by locally weighted regression.

The data acquisition rate of the magnetometer used is limited to 20 Hz. This frequency is rather low compared to the stirring rate of 20 rpm. Therefore the maximal values measured for subsequent turns of the stirrer fluctuate due to the positioning of the tablets relative to the magnetic sensor at the time points of data acquisition (inset Fig. 2a,b). This variability could be reduced by the calculation of a locally weighted regression using the Cleveland–Devlin algorithm [3] (B_{smooth}, Fig. 2b). Thereafter, the normalized values B/B_0 were extracted from the smoothed data sets. Every disintegration experiment was performed six times and the mean and the standard deviation (SD) of $B(t)/B_0$ were calculated.

As the last step of the data evaluation procedure regression analysis was performed assuming either a linear decay or an exponential decay. The linear decay was fitted by linear regression, the exponential decay was fitted to Eq. (2) using the Levenberg–Marquardt algorithm [4]. During the fitting procedure, the variable c was calculated without restrictions, whereas d was restricted to values between 0 and 5 and calculated in steps of 0.5.

$$\frac{B}{B_0} = e^{-ct^d} \quad (2)$$

3. Results

All tablets were tested for their drug content, tablet mass and disintegration time, respectively, according to Ph. Eur. 1997, appendix, 2000. All required parameters were within the limits. The visually determined disintegration times in water were 11 min for the tablets of type A, 8 min for the tablets of type B and C, respectively, and 2 min for the tablets of type D. Film coating of the tablets of type D with Eudragit E prolonged disintegration (tested in 0.1 N HCl) marginally to 3 min.

In order to simulate in vivo conditions of tablet disintegration in an empty stomach, the magnetic disintegration experiments were performed at pH 1. All measured data could be evaluated. The end points of disintegration as determined by the magnetic measurements and simultaneous visual inspection were identical for all tablets investigated.

In comparison to the disintegration behavior observed in water according to the European Pharmacopoeia, the disintegration velocity of the tablets of type A was strongly reduced to a total disintegration time of about 26 min. By visual inspection a continuous decrease of the tablets' sizes was observed. The magnetic measurements yielded a

continuous decline of the magnetic flux during this time that can be well fitted by a linear function (Fig. 3a).

In the magnetic measurement setup, the tablets of type B disintegrated within about 12 min. Again, a continuous decrease of the size of the tablets was observed by visual inspection. The magnetic measurements yielded a linear decline of the magnetic flux, too (Fig. 3b).

Complete disintegration of the tablets of type C was observed within about 11 min. The visual inspection provided an initial phase of approximately 2 min duration without any visible signs of disintegration, followed by volume expansion due to swelling and thereafter a continuous release of particles. The magnetic measurements yielded a nonlinear decrease of the magnetic flux that can be fitted assuming an exponential function as shown in Fig. 3c.

As in water, the tablets of type D disintegrated in the magnetic measurement setup very fast within about 3 min. Visually, it could be observed that the tablets disintegrated immediately after contact with the fluid. The magnetic data were fitted best assuming an exponential relationship as shown in Fig. 3d. After coating with Eudragit E (tablets type DE) the total disintegration time remained unchanged. The visual inspection yielded a very rapid disintegration after an initial phase of about 30 s duration without any observable changes. The magnetic measurements corroborate this observation (Fig. 3d). Again, the magnetic data could be fitted best assuming an exponential decay.

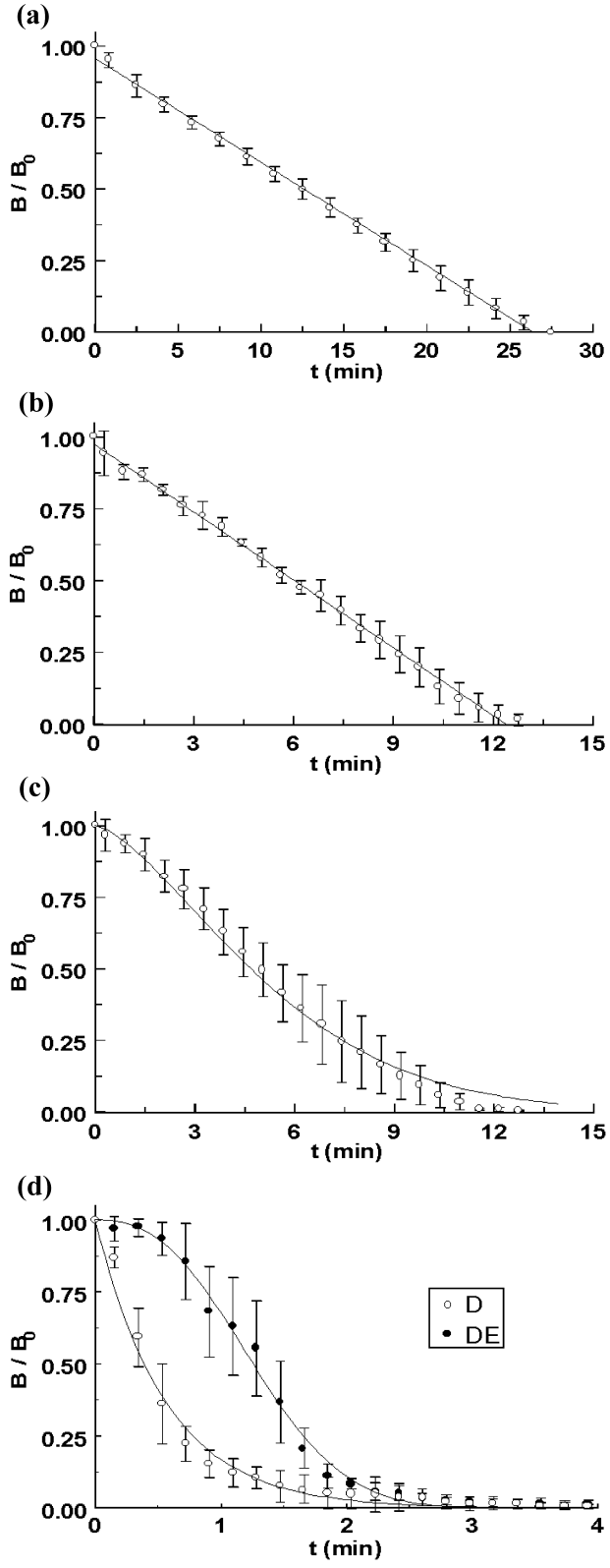

Fig. 3. Normalized magnetic fluxes of tablets measured during disintegration ($n = 6$, mean ± SD) and best-fitting curves. (a) Tablets type A. The decay was fitted as $B/B_0 = -0.036\ \text{min}^{-1}\ t + 0.958$ ($r^2 = 0.997$). (b) Tablets type B. The decay was fitted as $B/B_0 = -0.079\ \text{min}^{-1}\ t + 0.976$ ($r^2 = 0.997$). (c) Tablets type C. The decay was fitted according Eq. (2) with $c = 0.07\ \text{min}^{-1.5}$ and $d = 1.5$ ($r^2 = 0.991$). (d) Tablets type D (○) and DE (●). The decays were fitted according Eq. (2). Tablets type D: $c = 1.78\ \text{min}^{-1}$, $d = 1$ ($r^2 = 0.986$). Tablets type DE: $c = 0.39\ \text{min}^{-2.5}$, $d = 2.5$ ($r^2 = 0.995$).

4. Discussion

The measured magnetic fluxes are generated by the magnetic dipole moments of the magnetized tablets. The magnetic moment of a dipole is determined by the amount of magnetic material incorporated, the magnetic properties of this material (most of all its remnant magnetization) and the magnetization process itself. Ferromagnetic iron oxides (Fe_3O_4, γ-Fe_2O_3) have a remanent magnetization of about 0.4–0.6 T, a value far below the magnetic flux of at least 2 T that was applied during the magnetization of our tablets. Therefore, we can assume that the tablets were magnetized until saturation, i.e. the magnetic moments of all magnetic particles were aligned during magnetization into the direction of the applied magnetic field. Hence, the tablets consist of an ensemble of particles with a stable magnetic dipole moment in the direction of the short axes (Fig. 4a).

This dipole moment can in principle be reduced by several mechanisms: the loss of magnetism induced by temperature, the dissolution of the magnetic particles in the simulated gastric fluid, the loss of magnetic particles due to their release from the tablet core or the loss of

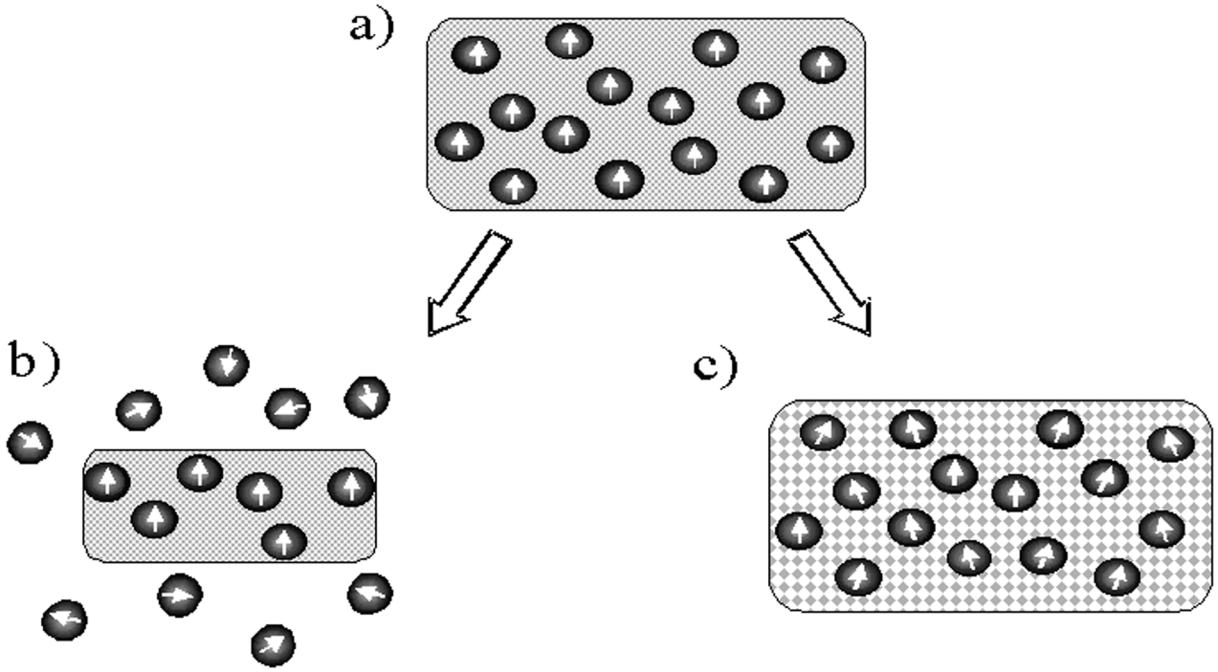

Fig. 4. Schematic representation of the orientations of the individual magnetic dipole moments of magnetic particles. (a) Tablet after magnetization: All magnetic moments are aligned in the direction of the short axis of the tablet. They create as an ensemble the net magnetic moment of the tablet. (b) Decrease of tablet's magnetic moment due to release of particles by surface erosion. The released particles are freely movable in the surrounding fluid. Therefore, they do not contribute longer to the net magnetic moment of the tablet. (c) Decrease of tablet's magnetic moment due to swelling by water uptake. The alignment of the direction of the magnetic moments of the particles is disturbed.

magnetic moment due to decreased alignment of the magnetic particles, respectively. The first two mechanisms can be ruled out: the susceptibility of all ferromagnetic materials decreases with increasing temperature until reaching paramagnetic behavior at a characteristic temperature, the so-called Curie point. The Curie points of ferromagnetic iron oxides are in the range of about 700–1100 K, far above the 37°C of the thermostated water bath. Therefore, in our experiments, temperature cannot be regarded as a cause for the observed decline of the magnetic fluxes. Furthermore, iron oxides are indeed soluble in inorganic acids but, in our experience, there is no measurable dissolution of the magnetic particles that we used in our experiments in 0.1 N hydrochloric acid within the observed time windows (up to 30 min).

Therefore, we can assume that the two remaining mechanisms that were mentioned above cause the observed decline of the magnetic flux during disintegration. The first mechanism is the release of particles into the surrounding fluid (Fig. 4b). As the released particles are freely movable, they loose their magnetic orientation due to rotational movements (Brownian movements). The directions of these rotational movements are statistically distributed. Accordingly, the net magnetic moment of the released magnetic particles equals zero. Therefore, released particles do not longer contribute to the magnetic dipole moment of the tablet. The second mechanisms for a decline of the magnetic moment is caused by the swelling of the tablet's core that is initialized by water uptake (Fig 4c). Within a swelling tablet, the alignment of the magnetic moments of the particles will be disturbed and, thereby, the net magnetic moment of the dipole decreases, too.

Examples for tablet compositions where the decrease of the magnetic moment is predominantly caused by the first mechanism were found for the tablets of type A and B, respectively. These two types of tablets do not contain a strong disintegrant in the outer phase. The time course of their loss of magnetic flux could be well fitted by a linear function. To our interpretation, this indicates that under the chosen experimental conditions the disintegration of these two tablet formulations is mainly driven by surface erosion.

The temporal decrease of the magnetic fluxes generated by the tablets of types C, D and DE could be fitted by an exponential function. To our understanding, this indicates that these tablets disintegrated by further mechanisms besides surface erosion. The tablets of type C contained crospovidone as a strong disintegrant in the outer phase. In comparison to the tablets of type B, this portion of crospovidone is better accessible for water molecules that are entering the core by diffusion. Accordingly, in comparison to the tablets of type B the disintegration of the tablets of type C was additionally driven by swelling of crospovidone, resulting in an altered mechanism of disintegration. The tablets of type D and DE were prepared by direct compression of a powder mixture. With respect to the magnetic data, the disintegration of the tablets of type D started immedi-

ately after water contact due to swelling and surface erosion. After coating with Eudragit E (tablet type DE) there was an initial delay of disintegration due to the time span needed for dissolving the coating. Afterwards, the tablets disintegrated very quickly. This might be caused by water molecules that had already passed the coating layer by diffusion.

Ferrari et al. [5] classified disintegration processes by two main mechanisms: a passive mechanism of disintegration and an active mechanism of disintegration. The passive mechanism is due to the weakening or even annihilation of intermolecular bonds and no force is developed. The active mechanism is always characterized by the development of a disintegration force that is due to the swelling of components of the tablet. The visual inspection of the tablets of type A showed no sign of swelling during disintegration and the tablets of type B showed only minor swelling during disintegration, respectively. As swelling is always present in the active disintegration mechanism, the observed disintegration behaviors of the tablets of types A and B might be taken as examples for the passive mechanism of disintegration.

For the active disintegration mechanism Caramella et al. [6] proposed a mathematical model, with a normalized disintegration force F/F_∞ that can be calculated according to Eq. (3) [6].

$$\frac{F}{F_\infty} = 1 - e^{-kt^n} \tag{3}$$

In this approach for the description of active disintegration processes k is an expansion rate constant, whilst the exponent n is indicative for the mechanism of the disintegration process. According to Colombo et al. [7] active disintegration processes can be divided into two classes, disintegration with orders of $n < 1$ and disintegration with orders of $n > 1$. For $n < 1$ disintegration is mainly caused by processes that occur within the tablets (driven by diffusion of water molecules into the tablets), whilst for $n > 1$ disintegration should be dominated by interface-derived processes.

In the case of the tablets of type C, D and DE, respectively, the visual inspection yielded that swelling occurred during disintegration. If one assumes, that the development of such a force is the driving mechanism for disintegration, one might expect, that in our experiments the effect of the disintegration force on the tablets was determined, which should result in the decreasing exponential function (Eq. (2)) and simultaneously in the increasing exponential function describing the disintegration force (Eq. (3)).

The magnetic disintegration data of the tablets of type C, D and DE, respectively, could indeed be fitted by exponential decays. For the exponent n values with $n \geq 1$ were calculated. According to Colombo et al. [7] this result might indicate that the disintegration of these tablets was mainly driven by interface derived swelling processes.

In conclusion, we were able to demonstrate that using our magnetic measurement setup the in vitro disintegration behavior of tablets can be determined quantitatively. We are now looking towards determining the disintegration behavior of magnetically marked tablets in humans using a biomagnetic measurement device.

References

[1] W. Weitschies, R. Kötitz, L. Trahms, D. Cordini, High resolution monitoring of the gastrointestinal transit of a magnetically marked capsule, J. Pharm. Sci. 86 (1997) 1218–1222.
[2] W. Weitschies, D. Cordini, M. Karaus, J. Breitkreutz, W. Semmler, L. Trahms, Magnetic marker monitoring of the esophageal transit and disintegration of capsules, Proc. Med. Biol. Eng. Comp. 37 (1999) 1474–1475.
[3] W.S. Cleveland, Locally weighted regression: An approach to regression analysis by local fitting, J. Am. Statist. Assoc. 83 (1988) 596–610.
[4] D.W. Marquardt, An algorithm for least squares estimation of nonlinear parameters, SIAP 2 (1963) 431–441.
[5] F. Ferrari, M. Bertoni, M.C. Bonferoni, S. Rossi, C. Caramella, C. Nyström, Investigation on bonding and disintegration properties of pharmaceutical materials, Int. J. Pharm. 136 (1996) 71–79.
[6] C. Caramella, P. Colombo, U. Conte, F. Ferrari, A. Gazzaniga, A. La Manna, N.A. Peppas, A physical analysis of the phenomenon of tablet disintegration, Int. J. Pharm. 44 (1988) 177–186.
[7] P. Colombo, F. Ferrari, A. Gazzaniga, C. Caramella, U. Conte, A. La Manna, N.A. Peppas, Simulation of the disintegration process of pharmaceutical tablets, Pharm. Acta Helv. 63 (1988) 221–223.