34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

# Dissolution of Magnetically Marked Tablets: Investigations in a Physical Phantom*

S. Biller, J. Domey, P. Fiedler, R. Holzhey, H. Richert, and J. Haueisen, *Member, IEEE*

*Abstract*— **Pharmacological research is strongly driven by maximizing the bioavailability of new pharmaceuticals. For orally applied drugs the bioavailability highly depends on the process of dissolution in the gastrointestinal tract and is affected by numerous physiological and environmental factors. Available techniques for in vivo monitoring of the dissolution process are very limited and not applicable for large studies. The technique of magnetic marker monitoring provides new prospects for these investigations. However, it is currently limited due to low fields common magnetic markers produce. Hence, only highly sensitive sensors are applicable. In this paper, we performed dissolution tests of novel markers in a physical phantom with magnetoresistive sensors in an unshielded environment. The markers were continuously localized and the movement through the phantom was tracked. By analyzing the changing magnetic moment of the markers we were able to monitor the progress of dissolution in the phantom. We conclude that our proposed phantom and tracking technique is an important step towards new systems for in vivo monitoring of pharmaceutical dissolution processes.**

## I. Introduction

Since millennia the therapy with pharmaceuticals is of high importance for the treatment of different diseases. Besides active ingredients, particularly their bioavailability affects the biologic effects of pharmaceuticals [1]. Thus, the evidence of the bioavailability is a mandatory precondition for the approval of new pharmaceuticals and generic medicaments [2]. Studies showed that an insufficient bioavailability is the main reason for 40 % of the failures during the accreditation of new pharmaceuticals [3]. Since most pharmaceutical drugs are applied orally [1], understanding the process of the liberation of the tablets and capsules in the gastrointestinal tract is highly relevant for pharmaceutical research. This process, which involves the disintegration of the pharmaceutical into smaller pieces as well as the dissolution in the intragastric medium, can be controlled with coating technologies in order to influence the place of liberation in the gastrointestinal tract [4]. It is well known that this process strongly depends on individual characteristics such as gender, sports activities, nutrition, stress as well as functional disorders or interactions with other pharmaceuticals [5]. Consequently, the understanding of these relations is of high importance for pharmaceutical research and hence field studies are necessary. Unfortunately, the applicability of available techniques to monitor the in vivo dissolution process are very limited. The gold standard for such investigations, a szintigraphic technique in which the pharmaceuticals are radioactive labeled [5], is not applicable in large studies due to the irradiation of the subjects.

A new possibility for the in vivo observation of the dissolution behavior of pharmaceutical tablets and capsules is the technique of magnetic marker monitoring [6], [7]. The magnetic field outside of the patient is measured after ingesting a magnetically marked capsule. The position of the marker can be calculated by solving the inverse problem and hence the marker can be tracked continuously in the gastrointestinal tract. For dissolution testing markers of pure magnetized magnetite are commonly used. These markers change their external magnetic induction while the magnetite is dispersed during the dissolution process [7]. Since the current markers produce very weak magnetic fields in the range of a few pico Tesla [7] only highly sensitive sensor technologies (e.g. superconducting quantum interference devices) are applicable. In conjunction with active and passive shielding technologies this yields to very restrictive measurement setups (e.g. a supine position of the patient). Hence, the potential for extensive studies using this conventional technique is very limited.

In order to overcome these restrictions we recently presented a novel concept for magnetic marker design which enables the investigation of the dissolution process with stronger magnetic fields and less sensitive sensor technologies [8]. These markers consist of one permanent magnet and a compartment of iron powder in a magnetically unstable configuration. During dissolution of the pharmaceuticals, the powder is redistributed around the magnet, thereby altering the externally measured magnetic induction. This effect enables easier investigations of the dissolution process.

In the study presented in this paper we tested the novel markers in a physical phantom and monitored the dissolution process using an array of magnetoresistive sensors.

* This work was supported in part by the German Research Council (GRK 1567/1).

S. Biller is with the Institute of Biomedical Engineering and Informatics, Ilmenau University of Technology, D-98684 Ilmenau, Germany (phone: +49-3677-691310; fax: +49-3677-691311; e-mail: sebastian.biller@tu-ilmenau.de).

J. Domey is with the Institute of Biomedical Engineering and Informatics, Ilmenau University of Technology, D-98684 Ilmenau, Germany (email: joerg.domey@tu-ilmenau.de).

P. Fiedler is with the Institute of Biomedical Engineering and Informatics, Ilmenau University of Technology, D-98684 Ilmenau, Germany (email: patrique.fiedler@tu-ilmenau.de).

R. Holzhey is with the Innovent e.V., D-07745 Jena, Germany (email: rh2@innovent-jena.de).

H. Richert is with the Matesy GmbH, D-07745 Jena, Germany (email: h.richert@matesy.de).

J. Haueisen is with the Institute of Biomedical Engineering and Informatics, Ilmenau University of Technology, D-98684 Ilmenau, Germany and the Biomagnetic Centre, University Hospital Jena, D-07740, Germany.

## II. Materials And Methods

### A. Magnetic markers

The raw material for the magnetic markers were conventional tablets with a size of approx. 22 × 9.1 × 6.7 mm (length × width × height) and a weight of 2 g. Along the longitudinal axis a hole with a diameter of 3 mm and a depth of 18 mm was drilled and subsequently a neodymium magnet was inserted. This magnet had a cylindrical shape (diameter 3 mm, height 2 mm) and was magnetized in axial direction with a residual flux density $B_R$ between 1.40 T and 1.45 T (magnetization grade N50). Subsequently, 450 mg of conventional iron powder was inserted into the tablet and the tablet was closed by means of a fragment of the drilled tablet hole.

### B. Physiological phantom

The physical phantom of the gastrointestinal tract is designed to enable the investigation of the dissolution process of the tablet in an environment that is as physiologically correct as possible. Any magnetically influencing metallic material must be avoided in order to allow for later measurements of the magnetic field of the tablets inside the phantom. Consequently a meander-shaped tube with a diameter of 16 mm, a size of 25 × 31.5 cm and an overall path length of 101.4 cm was fabricated based on non-magnetic glass material. This glass tube was mounted using nonmagnetic shells on top of an acrylic base plate with a size of 50 × 50cm (see Fig. 1). In order to simulate the intestinal contents a solution of Cyamopsis tetragonoloba flour (3 g Cyamopsis tetragonoloba flour to 100 ml water) was used resulting in a viscosity of 186.25 mPa. Drive of the fluid was provided by a peristaltic pump (Masterflex 7520-47, Cole-Parmer Ltd., Vernon Hills, Illinois, USA) connected to the glass tube using a silicone tube system.

### C. Sensor system

The measurements of the magnetic field produced by the magnetic marker in the phantom were performed using the high-resolution three-dimensional magnetic detection system 3D-MAGMA (Matesy GmbH, Jena, Thuringia, Germany) [9]. This device consists of 27 anisotropic magnetoresistive sensors which are arranged in nine sensor triplets (separated on three sensor board modules) enabling the detection of the magnetic field in three dimensions at room temperature. The sensitivity of the system concerning the magnetic induction B covers a range of $10^{-8}$ T up to $10^{-5}$ T and the primary internal measurement rate is 500 samples per second. In addition, the movement of the marker was monitored using a USB-connected video camera with a resolution of 640 × 480 pixels (Logitech Ltd., Romanel-sur-Morges, Switzerland) which was positioned below the phantom at a distance of 52.5 cm (see Fig. 1).

### D. Measurement setup

The phantom was completely filled with the prepared solution using the peristaltic pump. During this process the system was continuously de-aerated in order to reduce air bubbles inside the liquid, possibly influencing the movement and the process of dissolution. Subsequently, the sensor system was placed in a central position above the phantom resulting in a distance of 5 cm, 8 cm and 6 cm between the three sensor boards and the glass tube (see Fig. 1). The magnetic field was measured for the purpose of determining the offset resulting from the earth magnetic field and other interfering signals. Following this procedure the magnetic marker was placed inside the phantom's glass tube. After this preparation procedure the system was ready to start the intended investigation of the dissolution process. The fluid and the magnetic marker within were driven via the peristaltic pump. The direction of pumping was inverted shortly before the marker reached the end of the glass tube. This operation sequence was repeated until the tablet was dissolved completely. During the whole procedure the magnetic field was measured using the 3D-MAGMA system described above and the movement of the marker was monitored using the video camera. Up to now two magnetic markers were analyzed with this procedure.

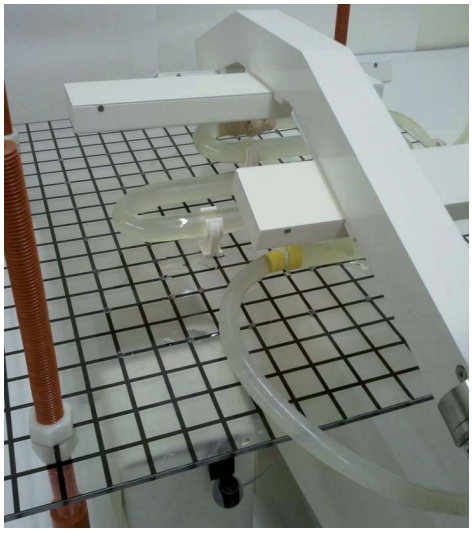

Figure 1 Overview of the measurement setup. The meander-shaped glass tube was mounted on top of an acrylic base plate. The 3D-MAGMA sensor system was centrally positionend above the phantom. The movement of the magnetic marker was monitored using a camera below the phantom.

### E. Data analysis

The sensor signals were recorded and analyzed using the provided software package of the sensor system (Mfield, Matesy GmbH, Jena, Thuringia, Germany). This software enables the real-time determination of the position and orientation of the marker as well as its velocity, the distance covered and the path and duration of the passage. For source localization the software uses a magnetic dipole model in conjunction with a Levenberg-Marquardt localization algorithm. The provided localization accuracy is ±5 mm [9]. The sampling rate was set to 4 samples per second. Hence, 125 samples of the internal measurement rate were automatically averaged in order to obtain one measurement point. Video acquisition was controlled using Deput Video Capture Software (NCH Software, Canberra, ACT, Australia). Both software tools saved time stamps according to the system clock. These were used for synchronization of the video and the results of the localization. For further data

analysis and visualization we used Matlab (The MathWorks Inc., Natick, Massachusetts, USA).

## III. Results

### A. Characteristics of the magnetic field and the velocity

Fig. 2 shows a section of the magnetic moment and the velocity of the marker during the motion in the phantom. During the movement through the phantom the velocity was not constant (cp. Fig. 2b). As expected, the velocity was zero at the points where the direction of pumping was inverted. The magnetic moment was very stable at these points and only fluctuation occurred which were of the size of $\pm$ 0.00045 Am$^2$. Based on these fluctuations the signal-to-noise ratio was estimated to be approx. 33dB. From time to time the tablet stuck at the wall of the phantom resulting in a steady change of acceleration und deceleration. In consequence of these irregular movements larger variations of the magnetic moment can be noticed (see Fig. 2a). These variations occurred especially at positions where the sensor had a larger distance to the phantom (see Fig. 2a at the period between 75 min to 76 min and 82 min to 83 min).

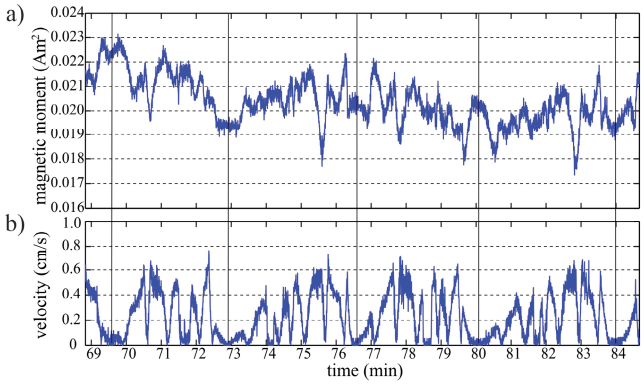


Figure 2 Example sequence of the aquired data (69 min to 85 min after the marker was placed into the phantom). The vertical lines indicate the invertion of the pumping shortly before the marker reached the respective end of the glass tube: a) magnetic moment of the marker, and b) velocity of the marker

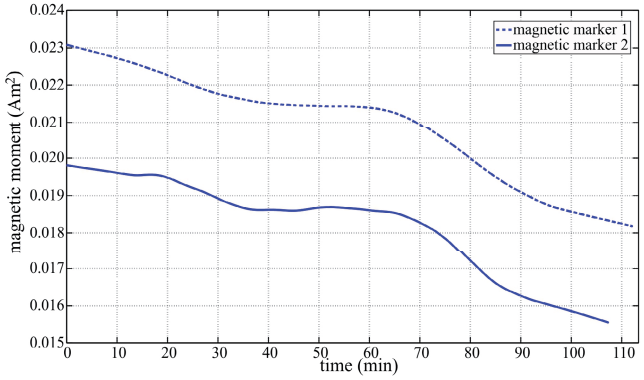


Figure 3 Magnetic moment during the dissolution process in the phantom for both investigated magnetic markers after smoothening the data.

For determining the overall behavior of the magnetic moment the data was smoothed using a weighted linear least square regression model with a span of 0.25 % of the data. During the dissolution process the iron powder is gradually released and reallocates around the magnet. Hence the external magnetic field is decreasing (cp. Fig. 3). In order to determine the magnetic moment the mean value of the first and the last three minutes (720 data points) before and after the dissolution were used. The magnetic moments of marker 1 were calculated with 0.0230 Am$^2$ and 0.0182 Am$^2$ which causes a reduction of 20.87 %. A similar decrement during dissolution of 21.21 % was found for marker 2 with slightly lower magnetic moments of 0.0198 Am$^2$ and 0.0156 Am$^2$.

### B. Localization of the magnetic markers

During the measurement the 3D-MAGMA system continuously calculated the position of the magnetic marker in three dimensions. The result of this localization is presented for three distinct time steps in Fig. 4. The comparison with the real position which was obtained by analyzing the gathered video shows a good agreement during the whole dissolution process. These calculated positions can be used for further evaluation. The overall path length of the motion (irrespective of its direction) is determined by tracking the whole movement of the marker. For the performed measurements path lengths of 10.2 m and 29.5 m were covered within the phantom in 108 min and 112 min respectively until the tablets were dissolved completely. Accordingly, the average velocities were 9.4 cm/min and 26.3 cm/min which were influenced by chosen power of the peristaltic pump as well as short periods of time wherein the tablet was sticking at the wall of the glass tube.

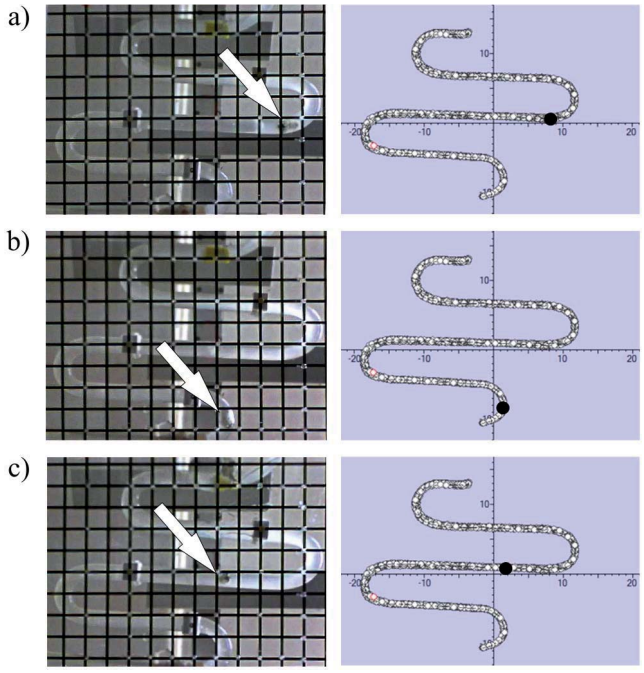


Figure 4. Comparison of the location of the tablet based on the video camera (left column, position ist marked with an arrow) and the result of the localization using the 3D-MAGMA system (right column, position is marked with a dot) after a) 39 s, b) 3304 s, and c) 6694 s.

## IV. Discussion

We successfully monitored the dissolution process of novel magnetic markers in a physical phantom. Since the magnetic induction of the used markers is in the range of a few micro Tesla at a distance of 10 cm [8] a commercially available sensor system with magnetoresistive sensors was applicable. During dissolution the iron powder redistributed around the magnet and hence the external magnetic field is altered. The obtained reductions of approx. 21 % were slightly higher compared to the 17 % of our recently published work [8]. These differences could be caused by a larger quantity of iron powder that was used (450 mg vs. 250 mg). The whole process of dissolution was observable with the used sensor system.

The order of magnitude of the magnetic fields enabled continuous localization of the marker. Thus, the place of dissolution can be investigated by analyzing the distance covered. The distances covered in our phantom were relatively large and not physiologically correct. The reason was the technical restriction that by choosing a slower flow rate of the pump the tablet stuck completely at the wall and did not started moving again. In the human gastrointestinal tract tracking the marker could by triggered by the marker leaving the stomach. This process can easily be detected by analyzing the frequencies of the marker movement. These frequencies are dominated by slow waves of 3 cycles per minute in the stomach [9] while 12 cycles per minute will dominate in the duodenum. Afterwards the tracked path is used to determine the place of dissolution in the small intestine or the colon.

## V. Conclusion

For the first time we demonstrated the possibility of monitoring the dissolution process of pharmaceuticals using magnetoresistive sensor technologies. These sensors are applicable at room temperature and can be used without laborious and expensive passive shielding. Since the sensors are small and easy to handle they offer a wide field of applications. This will enable smaller and less expensive devices for analyzing dissolution processes in pharmaceutical research. Furthermore, the patients or volunteers are not irradiated or otherwise stressed. Hence, large studies concerning influencing factors of the dissolution process (e.g. gender, sports activities, nutrition, stress as well as functional disorders or interactions with other pharmaceuticals) are be enabled by our proposed novel markers using. Further investigations using the physiological phantom will be performed in order to analyze the influence of different velocities and viscosities of the medium on the dissolution process of the novel magnetic markers. Afterwards, first in vivo investigations on animals will be carried out.

## Acknowledgment

The authors want to thank Innovent e.V. (Jena, Germany) and Matesy GmbH (Jena, Germany) for the great cooperation, for providing the measurement system and for many helpful discussions concerning technical issues.

## References

[1] A. Ruiz-Garcia, M. Bermejo, A. Moss, and V.G. Casabo, "Pharmacokinetics in Drug Discovery," *J Pharm Sci.*, vol. 97, pp. 654–690, February 2008

[2] M.-L. Chen, V. Shad, R. Patnaik, W. Adams, A. Hussain, D. Connor, M. Mehta, H. Malinowski, J. Lazor S.-M. Huang, D. Hare, L. Lesko, D. Sporn, and R. Williams, "Bioavailability and Bioequivalence: An FDA Regulatory Overview," *Pharm Res.*, vol. 18, pp. 1645–1650, December 2001

[3] H. Kubinyi, "Drug research: myth, hype and reality," *Nat Rev Drug Discov.*, vol. 2, pp. 151–154, August 2003

[4] F. Liu, P. Moreno, and A.W. Basit, "A novel double-coating approach for improved pH-triggered delivery to the ileo-colonic region of the gastrointestinal tract," *Eur J Pharm Biopharm.*, vol. 74, pp. 311–315, February 2010

[5] J. Davis, J. Burton, A.L. Connor, R. Macrae, and I.R. Wilding, "Scintigraphic study to investigate the effect of food on a HPMC modified release formulation of UK-294,315," *J Pharm Sci.*, vol. 98, pp. 1568–1576, April 2009

[6] W. Andrä, H. Danan, K. Eitner, M. Hocke, H.-H. Kramer, H. Parusel, P. Saupe, C. Werner, and M.E. Bellemann, "A novel magnetic method for examination of bowel motility," *Med Phys.*, vol. 32, pp. 2942–2944, September 2005

[7] W. Weitschies, O. Kosch, H. Mönnikes, and L.Trahms, "Magnetic Marker Monitoring: An application of biomagnetic measurement instrumentation and principles for the determination of the gastrointestinal behavior of magnetically marked solid dosage forms," *Adv Drug Deliv Rev.*, vol. 57, pp. 1210–1222, June 2005

[8] S. Biller, D. Baumgarten, and J. Haueisen, "A Novel Marker Design for Magnetic Marker Monitoring in the Human Gastrointestinal Tract," *IEEE Trans Biomed Eng.*, vol. 58, pp. 3368–3375, December 2011

[9] M. Hocke, U. Schöne, H. Richert, P. Görnert, J. Keller, P. Layer, and A. Stallmach, "Every slow-wave impulse is associated with motor activity of the human stomach," *Am J Physiol Gastrointest Liver Physiol.*, vol. 296, pp. 709-716, April 2009