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Magnetic marker monitoring of esophageal, gastric and duodenal transit of non-disintegrating capsules

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Dedicated to Prof. Dr. Hans-Hartwig Otto, Greifswald, on the occasion of his 60th birthday

The purpose of the study was to investigate in detail the esophageal, gastric and duodenal passage of non-disintegrating capsules in a fasted, healthy volunteer using Magnetic Marker Monitoring (MMM). Five independent experiments were performed. In each case the same healthy male volunteer ingested one magnetically marked capsule after fasting for at least 8 h. The magnetic dipole fields of the capsules were recorded by biomagnetic multichannel measuring equipment. The positions of the capsules were calculated from the recorded data by methods established in magnetic source imaging. The esophageal, gastric and duodenal passages of the capsules were successfully reconstructed from all recorded data sets. The spatial resolution of the capsules' three-dimensional positions in the organs of the gastrointestinal tract was within a range of several millimeters, with a chosen temporal resolution of up to four milliseconds. The esophageal transit times were between 3–13s, the gastric residence times were between 14–133 min and the duodenal transit times were between 7–245 s. The data demonstrate that Magnetic Marker Monitoring permits the detailed investigation of the gastrointestinal transit of solids.

1. Introduction

The number of diagnostic methods based on the detection and application of magnetic fields and their clinical application have increased rapidly during the last twenty years. The origin of the measured magnetic signal can either be a natural source or a magnetic material introduced into the body. Examples of diagnostics methods based on magnetic measurements are determination of relaxing magnetic moments of atomic nuclei in magnetic resonance imaging (that may be enhanced by the application of paramagnetic or ferromagnetic contrast agents), magnetic field effects generated by paramagnetic iron in liver susceptometry [1] or by ferromagnetic particles deposited in the lung due to dust inhalation in magnetopneumography [2], or biomagnetic fields generated by ionic currents in magnetocardiography [3] and magnetoencephalography [4].

Currently, the behavior of pharmaceutical dosage forms in the gastrointestinal tract is mostly investigated by γ-scintigraphy, i.e. scintillation measurements of the abdomen of healthy volunteers who have ingested drug dosage forms containing γ-emitting radioisotopes. Meanwhile, magnetic methods are also increasingly used for this purpose. This includes determination of gastric emptying by susceptometry [5], magnetic resonance imaging of microtablets containing contrast material in rats [6] and development of a novel magnetic method for the determination of the gastrointestinal transport velocity of a magnetically labeled object [7].

During the last few years we have developed a novel method called Magnetic Marker Monitoring (MMM) for monitoring the gastrointestinal passage of solid pharmaceutical dosage forms. MMM is based on a measurement of the spatial magnetic field distribution of an ingested magnetically marked dosage form, reconstruction of the magnetic dipole field from the measured data and, finally, estimation of the six parameters characterizing location, orientation and magnitude of the magnetic dipole (three spatial coordinates, two polar angles and magnetic dipole moment) from the field distribution. The labeling of the dosage form as a magnetic dipole is achieved by incorporation of ferromagnetic material in the dosage form and its subsequent magnetization. Due to the use of extremely sensitive biomagnetic measuring instruments the amount of magnetic required as ferromagnetic material for the labeling of the drug dosage form ranges from about 50 μg to a few milligrams [8]. After the magnetically labeled dosage form is ingested its magnetic field distribution is continuously measured at several positions above the abdomen. In order to calculate the six parameters of the magnetic dipole from the magnetic field distribution in the presence of rapid movements of the dosage form in the gastrointestinal organs, multiple magnetic field sensors (channels) and a sufficiently high data sampling frequency are needed [9].

In a former experiment it was demonstrated that using biomagnetic multichannel measuring equipment with a planar arrangement of 37 magnetic field sensors at a data sampling frequency of 250 Hz, MMM shows the position of an insoluble, magnetically marked capsule in the organs of the gastrointestinal tract with a three-dimensional resolution of several millimeters, and a temporal resolution of its movement in the range of milliseconds [10].

The aim of the present study was to use MMM to investigate in detail the esophageal and gastric passage of an insoluble capsule ingested by a fasted, healthy volunteer. In order to determine intraindividual variations of gastric transport and gastric emptying and, furthermore, to demonstrate the reproducibility of MMM, five independent measurements were performed, each after ingestion of one of the magnetically marked capsules by the same volunteer.

2. Investigations and results

For each experiment the same male, healthy volunteer (35 y, 65 kg, 1.70 m) who had fasted for at least 8 h ingested one magnetically marked capsule together with 50 ml of water while lying beneath the SQUID-based magnetic field detector that was positioned approximately 5 cm above the abdomen of the volunteer. The exact position of the detector relative to the jugulum of the volun-

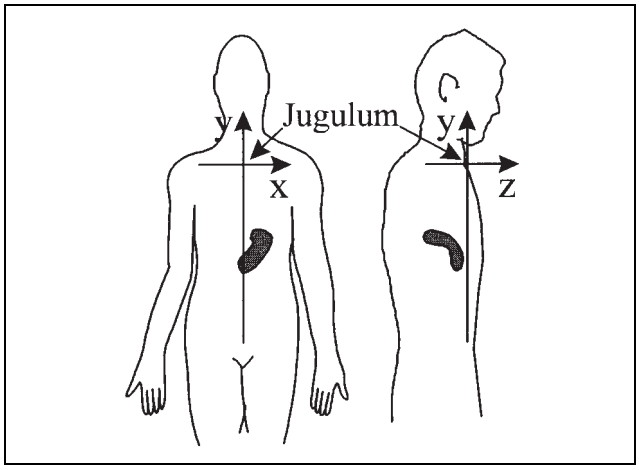

Fig. 1: Coordinate system used for determination of the capsule's positions. The origin of the coordinate system is at the jugulum of the volunteer.

teer was determined before each measurement in order to relate the localized positions of the capsule to the chosen coordinate system, with x pointing to the volunteer's left side, y pointing in the cranial direction and z pointing in the ventral direction (Fig. 1).

In addition, the respiration pattern of the volunteer was simultaneously recorded during the magnetic measurements by a non-magnetic piezoelectric pressure sensor that was mounted on the volunteer's abdomen by a plastic belt.

The positions of the capsules were calculated successfully for all recorded data with typical standard deviations of 2% to 15% between the measured and the recalculated magnetic field distributions, an exception being the first one to two seconds of exophageal passage, where the standard deviations sometimes even exceeded 30%. These deviations are caused by noise and magnetic signals generated by the heart and the gastointestinal organs. The errors obtained for the first 1–2 s of esophageal passage are due to the unfavorable position of the sensor area at a distance of more than 30 cm above the abdomen.

A comparison of the localized positions with the signal of the breathing sensor shows that the positions of the capsules are modulated by the breathing-induced motion of the abdomen relative to the fixed magnetic field sensors. These breathing-related motions of the capsules typically range from several millimeters up to 2 cm. In a few cases modulations of up to 5 cm were observed. The predominant direction of these movements depends on the position of the capsule in the gastrointestinal organs.

The motion of the heart also modulates the localized position of the capsules by typical amounts of 1 mm to 10 mm, the most pronounced direction of the modulation again being dependent on the position of the capsule in the organs of the gastointestinal tract.

As an example of these findings, Fig. 2 shows the movements of the capsule in the x-, y- and z-direction as well as the localization errors and the signal of the breathing sensor for a time interval of 230 s to 290 s during a measurement sequence that started 120 min after ingestion of the capsule in the fourth experiment. During this time interval the capsule was in the region of the antrum of the stomach. The volunteer stopped breathing within the time interval between 240 s to 270 s. For this example the breath-induced motions are pronounced in the x- and y-direction with an amplitude of about 1 cm to 2 cm, whereas breathing-induced motion in the z-direction is below 2 mm. The heart-induced motions of the capsule are clearly discern-

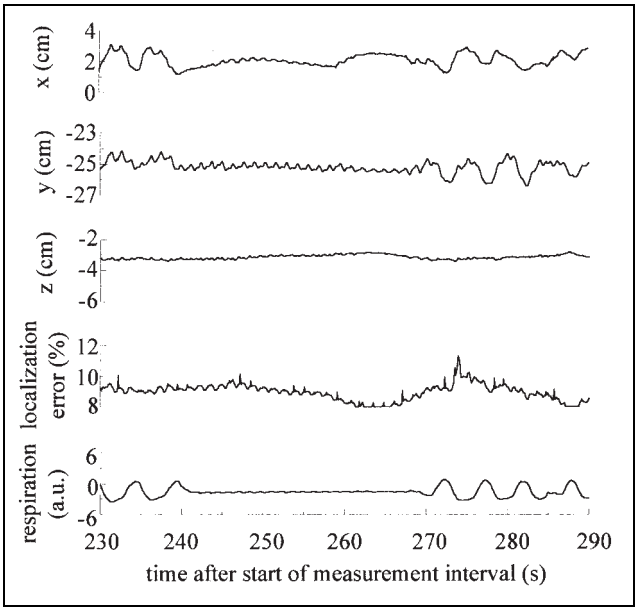

Fig. 2: Capsule's positions within the stomach (calculated in steps of 80 ms), localization errors and respiration pattern derived for a time interval of 230 s to 290 s during a measurement sequence that started 120 min after ingestion of the capsule in the fourth experiment. Here, the volunteer stopped breathing in the time interval between approximately 240 s to 270 s.

ible while the breath is being held. They are predominant in the y-direction with an amplitude of about 0.5 cm.

An example for the passage of a capsule through the esophagus is shown with a temporal resolution of 4 ms in Fig. 3. The esophageal transit times varied between 3 and 13 s (Table).

Two of the gastroduodenal passages, including transit through the terminal esophagus are shown in Figs. 4a and 4b. The transit times through the different regions of the stomach for all five experiments are given in the Table. In the first two experiments, the capsules remained in the proximal stomach for 21 min 50 s and 18 min 10 s respectively. In the other three experiments, the capsules passed the proximal stomach within at least 3 s and entered directly into the distal stomach. The transit times of all five capsules through the proximal stomach were between 1 s and 21 min 50 s (Table).

The residence times of the capsules within the distal stomach were also highly variable. In the first two experiments the capsules passed the distal stomach within less than 3 min (Table) and were almost directly emptied from

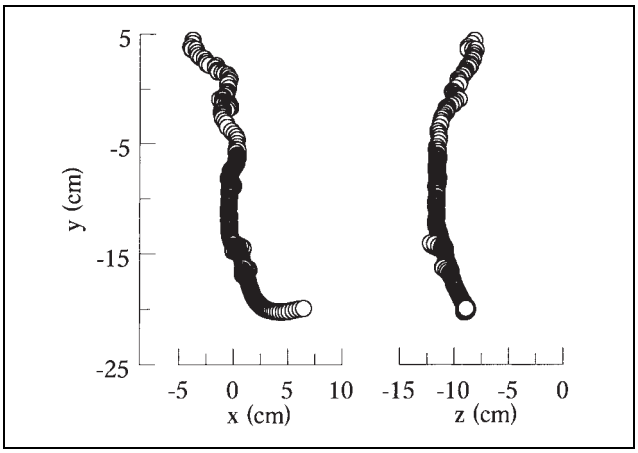

Fig. 3: Esophageal transit of a capsule monitored in experiment 3 (temporal resolution 4 ms)

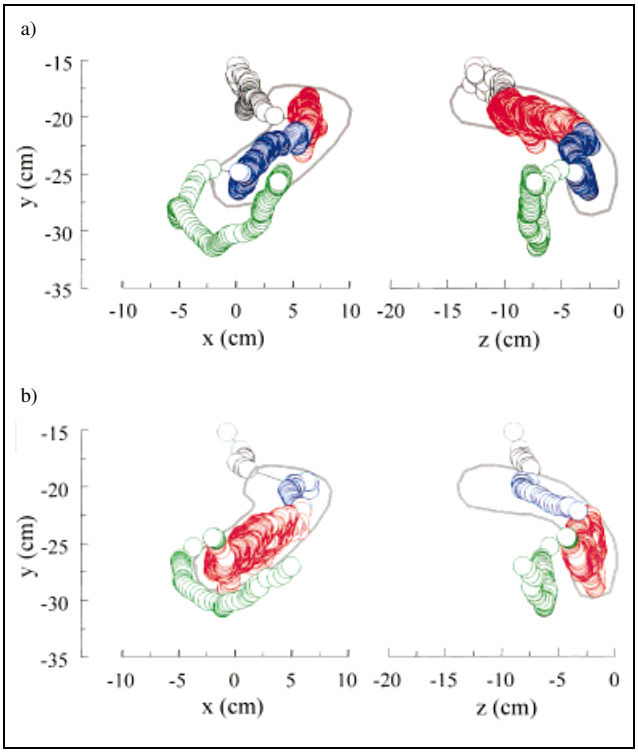

Fig. 4: Plots of positions of capsules in steps of 100 ms showing with reference to a schematic drawing of the stomach their passage through the terminal esophagus (black circles), the proximal stomach (red circles), the distal stomach (blue circles) and the duodenum (green circles). a) Experiment 2, b) Experiment 5

the stomach after arriving at the pylorus. In the third and fifth experiment the capsules remained in the distal stomach for about 14 min and 25 min, respectively, before being emptied from the stomach. In these two experiments the capsules reached the pylorus several times before being emptied from the stomach.

In the fourth experiment, the capsule remained within the stomach for at least 125 min. At the beginning of the measurement interval between 140 min to 145 min the capsule was found in the region of the jejunum. Accordingly, in this experiment the capsule was emptied from the stomach in the measurement break between 126 min to 140 min (mean 133 min) after ingestion. In all five experiments transport of one of the capsules from the distal stomach back into the proximal stomach was not observed.

The duodenal transit times varied between 7 s and 245 s (Table). The calculation of the velocities of the capsules before and during duodenal transit showed that the capsules were accelerated to velocities of up to 50 cm/s during emptying (Fig. 5). In contrast, during gastric residence the capsules moved mostly slowly with a velocity that was typically in the range of some cm/s.

Table: Transit times of a capsule through the esophagus, the different parts of the stomach and the duodenum

Experiment no.	Transit times				Gastric residence time
	Esophagus	Proximal stomach	Distal stomach	Duodenum	
1	8 s	21 min 50 s	2 min 30 s	39 s	24 min 20 s
2	13 s	18 min 10 s	1 min 20 s	15 s	19 min 30 s
3	3 s	1 s	13 min 56 s	245 s	13 min 57 s
4	4 s	2 s	133 min*	–**	133 min*
5	3 s	3 s	24 min 30 s	7 s	24 min 33 s

* between 126–140 min, ** not monitored

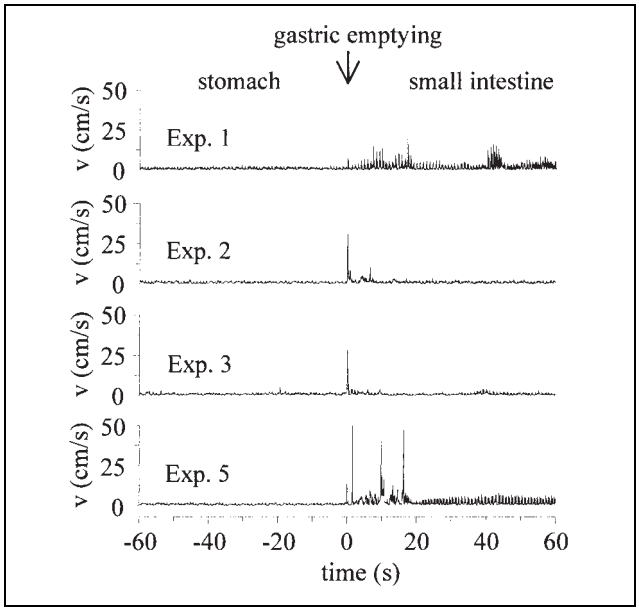

Fig. 5: Velocities of capsules calculated for the last 60 s of their residence in the stomach and the first 60 s of their transit through the small intestine

3. Discussion

The study presented demonstrates that MMM yields a very detailed picture of the gastrointestinal transit of magnetically marked objects with high reproducibility. The spatial resolution achieved for determination of the capsules' positions in the organs of the gastrointestinal tract was within a range of a few millimeters. This is in good agreement with the results obtained in a previous study, where magnetic monitoring of the gastrointestinal transit of a pellet enclosed in a capsule was performed in one healthy volunteer using a 37-channel SQUID magnetometer with a planar arrangement of the field sensors as the measuring device [10]. Compared to this tudy, employment of an 83-channel SQUID-based measuring device – with an arrangement of magnetic field sensors in three planes and with the ability to additionally determine vertical components of the magnetic dipole field – in combination with the higher amount of magnetite used for the labeling of the capsules yields better localization of the capsules at positions that are not close to the sensor plane. Therefore, we were now even able to monitor the esophageal transit of the capsules with the sensor planes fixed above the volunteer's abdomen.

The interindividual variability of esophageal transit times from 3 s to 13 s found in this study seems rather small compared to the high variability found for the transit times through the stomach and the duodenum. A comparison of these data with esophageal transit times that are considered normal for capsules containing ^{131}iodine and that have been determined in 41 patients within a range of 4 s to 51 s [13] shows that the esophageal transit times yielded by MMM correspond well to data obtained by γ-scintigraphy for capsules of comparable size. Any abnormal prolongation of the esophageal transit of the capsules due to the supine position that has been reported to hinder sometimes esophageal transit of solid oral dosage forms [14] was not observed in this study.

Gastric transit times were highly variable. The observed gastric residence times of approximately 14 min to 133 min are within the normal range reported for gastric emptying of large solids in a fasted state [15, 16]. The total duration

of gastric residence was not dependent on the residence times in particular segments of the stomach.
It could further be demonstrated that due to the high temporal and spatial resolution of MMM the investigation of duodenal transit times becomes possible. Here, we found that the capsules entered the duodenum with very high velocities. This may indicate that the capsules were emptied during the so-called 'housekeeper wave', which has been shown to be responsible for the emptying of large solids from the stomach during phase III of the interdigestive migrating motor complex (MMC) [18]. However, simultaneous recording of MMC and monitoring of capsule movements are required to prove this hypothesis.
The simultaneous recording of the breathing-induced motions of the abdomen makes it possible to distinguish movements of the capsules caused by breathing from movements that are due to active transport of the capsules in the gastrointestinal organs. This might in particular be interesting for a detailed analysis of transit patterns of solid material in the gastrointestinal tract. This combination of MMM with a recording of the breathing pattern may also help to explain effects of respiration on gastrointestinal passage of contents. An example of such an influence of respiration on the gastrointestinal transport was probably seen during esophageal transit monitored in the second experiment. Here, in contrast to the other four experiments, the volunteer breathed very pronounced starting approximately 2 s after swallowing. The observed short retention of the capsule in the esophagus might be due to this pronounced breathing. This interpretation is corroborated by the finding that the breathing pattern indeed influences esophageal transit [17]. The high spatial and temporal resolution of MMM provides further evidence of movements of the gastrointestinal organs induced by the heartbeat.
At the current stage of development we see the following main technical limitations with respect to the use of MMM: It is currently limited to the detection of one single magnetically marked object at a time. This restriction can partly be overcome by increasing the number of magnetic field sensors. Furthermore, MMM is in principle restricted to the monitoring of the gastrointestinal passage of solid or at least semi-solid objects. (This is due to the fact that the magnetic micro- or nanoparticles used as magnetic lebels lose their orientation soon after magnetization due to rotation within the surrounding fluid when they are dispersed in low-viscosity fluids or materials. Therefore, a magnetized ensemble of magnetic particles dispersed in a fluid or semi-solid does not produce a single dipole moment that is sufficiently stable over the time span of gastrointestinal passage).
The data presented show that MMM is a novel and very powerful tool for the investigation of the gastrointestinal transport of solid particles. The high temporal and spatial resolution of MMM provides several advantages compared to established methods like γ-scintigraphy. It is now possible to monitor in detail the behavior of solid drug dosage forms during their passages through the organs of the gastrointestinal tract. This provides an insight into the profiles of transport within distinct segments of the gastrointestinal organs and the calculation of transport velocities.

4. Experimental

4.1. Preparation of the magnetically marked capsules

Magnetite (FE_2O_4, 98% $<5\,\mu m$, Aldrich, USA; 20 mg) was dispersed in 6 g of silicone rubber (Kreulosil, Kreul, Germany). Hardener (Kreulosil Härter, Kreul, Germany; 200 µl) was added, and the dispersion was filled in gelatin capsules (volume 0.37 cm^3, length 16.1 mm, diameter 5.7 mm, capsulae operculatae, Pohl, Germany). Each capsule contained approximately 410 mg of silicone rubber and 1.3 mg of magnetite. After the silicone rubber hardened for 24 h the gelatin capsules were additionally coated with poly(methyl methacrylate) (PMMA, Grünberg Kunststoffe, Germany). The capsules were proven to be insoluble for at least 120 h in water, 0.1 M hydrochloric acid and phosphate buffer with a pH of 7.4. At least 24 h before the experiments each capsule was magnetized for 60 s along its longitudinal axis between the poles of an electromagnet in a field of approximately 100 mT.

4.2. Measurement procedure

The measurements were performed in a magnetically shielded room using a homemade Biomagnetic 83-SQUID (Superconducting Quantum Interference Device) Detector System [11]. The data were collected in 1st-order gradiometer mode with 70 mm baseline and with a sampling frequency 250 Hz in a bandwidth ranging from DC to 64 Hz.
Magnetic measurements of 30 min duration were started 60 s before ingestion of the capsule with the volunteer just lying below the detector and the capsule being placed on a chair at his left hand side, approximately 0.6 m away from the sensor area. The reference signal measured within these first 60 s served to calibrate the offset of the measured data. After a rest of 30 min duration further measurements, each of 6 min to 15 min duration, were performed with rests of approximately 15 min to 20 min between these measurement intervals. During the last 60 s of each of these consecutive measurements intervals, the volunteer moved to a position approximately 1.5 m away from the sensor area. The data recorded within the last seconds, when the volunteer was distant from the magnetic sensors were taken as base line signals in order to determine the absolute value of the measured data for the whole measurements interval. The volunteer left the magnetically shielded room during the rests and was allowed to walk around.
This experiment was repeated five times with a time interval between the experiments of at least one week. This rest between the experiments was chosen in order to ensure that during each experiment only one capsule was present within the organs of the gastrointestinal tract. In advance of each experiment a noise data acquisition with several minutes duration was started that was invoked to improve the signal-to-noise ratio in the further data processing.

4.3. Calculation of the capsule positions

The biomagnetic inverse problem for the magnetic capsule is solved on basis of a single dipole estimation least squares with use of the Gauss-Seidel algorithm [10], where the capsule parameters are derived by minimizing the cost function specified by:

$$\sigma = \sqrt{\frac{\sum_j \left(G_{calc,j} - G_{meas,j}\right)^2}{\sum_j \left(G_{meas,j}\right)^2}} \tag{1}$$

Eq. 1 contains the 1st-gradient components G_j that represent the magnetic signal for each sampling point and magnetic channel j contributing to the localization procedure. Their relation to the capsule position $r = (x, y, z)$ and the magnetic dipole moment $m = m\,(\sin\theta \sin\varphi, \sin\theta \cos\varphi, \cos\theta)$, the latter expressed in polar coordinates, has been described in detail previously [12] and is given in Eq. 2:

$$B_{calc,k} = B_{calc,k} \cdot n_{s,k} = \frac{\mu_0\, 3(r - r_{s,k})\,((r - r_{s,k}) \cdot m) - m(r - r_{s,k})^2}{\sqrt{(r - r_{s,k})^2}^5} \cdot n_{s,k} \tag{2a}$$

and finally

$$G_{calc,j} = \sum_k W_{jk} B_{calc,k} \tag{2b}$$

where W_{jk} represents the combination matrix for gradiometer forming, and $r_{s,k}$ and $n_{s,k}$ denote the position and orientation of SQUID-sensor k, respectively, in the volunteer's coordinate system (Fig. 1).
We introduced polar coordinates for the magnetic moment in order to separate its absolute value that is constant in the whole course of a measurement. As a consequence, only five parameters $(x, y, z, \theta, \varphi)$ had to be fitted.
The recorded data were digitally re-filtered with a Kayser-Bessel lowpass filter when extracting a new set of regular sampling points for the localization procedure, except for highly resolved particular localization segments of gastric entering with unchanged sampling step (4 ms).
The velocities of the capsules were calculated as given in Eq. 3 with a time interval $\Delta t = 0.040$ s:

$$v = \sqrt{\left(\frac{x_t - x_{t-\Delta t}}{\Delta t}\right)^2 + \left(\frac{y_t - y_{t-\Delta t}}{\Delta t}\right)^2 \left(\frac{z_t - z_{t-\Delta t}}{\Delta t}\right)^2} \tag{3}$$

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References

1 Brittenham, G. M.; Farrell, D. E.; Harris, J. W.; Feldman, E. S.; Danish, E. H.; Muir, W. A.; Tripp, J. H.; Bellon, E. M.: N. Engl. J. Med. **307**, 1671 (1982)
2 Huvinen, M.; Oksanen, L.; Kalliomaki, K.; Kalliomaki, P. L.; Moilanen, M.: Sci. Total. Environ. **199**, 133 (1997)
3 Baule, G. M.; McFee, R.: Amer. Heart. J. **66**, 95 (1963)
4 Cohen, D.: Science **161**, 784 (1968)
5 Miranda, J. R.; Baffa, O.; Oliveira, R. B.; Masuda, N. M.: Medical Physics **19**, 445 (1992)
6 Christmann, V.; Rosenberg, J.; Seega, J.; Lehr, C. M.: Pharm. Res. **14**, 1066 (1997)
7 Andrä, W.; Eitner, K.; Hergt, R.; Zeisberger, M., in: Häfeli, U.; Schütt, W.; Teller, J.; Zborowski, M. (Eds.): Scientific and clinical applications of magnetic carriers, p. 419, Plenum Press, New York 1997
8 Weitschies, W.; Wedemeyer, J.; Stehr, R.; Trahms, L.: Pharm. Pharmacol. Lett. **1**, 45 (1991)
9 Weitschies, W.; Wedemeyer, J.; Stehr, R.; Trahms, L.: IEEE Trans. Biomed. Eng. **42**, 192 (1994)
10 Weitschies, W.; Kötitz, R.; Cordini, D.; Trahms, L.: J. Pharm. Sci. **86**, 1218 (1997)
11 Drung, D.: IEEE Trans. Appl. Sup. **5**, 2112 (1994)
12 Model, R.; Trahms, L.: Numerical Algorithms **5**, 603 (1993)
13 Garcia-Pena, E.; Caravalho, J.; Watkins, J. W.: J. Nucl. Med. Technol. **25**, 55 (1997)
14 Hey, H.; Jorgensen, F.; Sorensen, K.; Hasselbach, H.; Wamberg, T.: Br. Med. J. **285**, 1717 (1982)
15 Park, H. M.; Chernish, S. M.; Rosenek, B. D.; Brunelle, R. L.; Hargrove, B.; Wellman, H. N.: Dig. Dis. Sci. **29**, 207 (1984)
16 Davis, S. S.; Christensen, F. N.; Khosla, R.; Feely, L. C.: J. Pharm. Pharmacol. **40**, 205 (1988)
17 Mittal, R. K.; Shaffer, H. A.; Parollisi, S.; Baggett, L.: Am. J. Physiol. **269**, G577 (1995)
18 Coupe, A. J.; Davis, S. S.; Evans, D. F.; Wilding, I. R.: Pharm. Res. **10**, 1281 (1991)

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