Application of a Biomagnetic Measurement System (BMS) to the Evaluation of Gastrointestinal Transit of Intestinal Pressure-Controlled Colon Delivery Capsules (PCDCs) in Human Subjects

Zhaopeng Hu,[1] Shunsuke Mawatari,[1] Nobuhito Shibata,[1] Kanji Takada,[1,4] Hiroshi Yoshikawa,[2] Akira Arakawa,[3] and Yoshikazu Yosida[3]

Received September 30, 1999; accepted November 2, 1999

Purpose. For determination of the transit time through various parts of the gastrointestinal (GI) tract, we developed a method that provides the location of disintegration and drug release. This method involves GI magnetomarkergraphy (GIMG) using a 129-channel Shimadzu vector biomagnetic measurement system (BMS).

Methods. To magnetically label the pressure-controlled colon delivery capsule (PCDC) containing 75.0 ± 0.5 mg of caffeine as a tracer drug, small capsule caps containing 90 mg of ferric oxide powdered magnetite (Fe_2O_3) were attached to PCDCs. After orally administration to fasted human volunteers, saliva samples were collected hourly and salivary caffeine concentration was measured. At the same time, locations of the magnetic PCDC were detected by BMS just after the PCDCs were magnetized with the coils of a magnetic resonance imaging (MRI) system. The magnetic field distributions were analyzed and the estimated positions were shown on the MRI picture of the same subject's abdominal structure.

Results. We magnetized PCDC with permanent magnets or an electromagnet before ingestion and the estimated locations of PCDC in the GI tract exhibited high estimation error. In order to increase the precision of estimated localization of PCDCs, PCDCs were magnetized within the coils of the MRI. As a result, these PCDCs had strong magnetic dipoles that were parallel to the sensor unit of BMS in every measurement, and therefore the spatial resolution of the PCDC's two-dimensional positions in the organs of the GI tract was within a range of several millimeters.

Conclusions. GIMG is a powerful tool for the study of colon delivery efficiencies of PCDCs. The main advantage of GIMG is the capability to obtain even more detailed knowledge of the behavior and fate of solid pharmaceutical formulations during GI passage.

KEY WORDS: Colon delivery; gastrointestinal transit; pressure-controlled colon delivery capsules (PCDC); biomagnetic measurement system (BMS); superconductive quantum interference device (SQUID); gastrointestinal magnetomarkergraphy (GIMG).

[1] Department of Pharmacokinetics, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607-8414, Japan.

[2] Department of Drug Dosage Form Design Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-01, Japan.

[3] Technology Research Laboratory, Shimadzu Corporation, Nakagyo-ku, Kyoto 604-8511, Japan.

[4] To whom correspondence should be addressed. (e-mail: takada @mb.kyoto-phu.ac.jp)

INTRODUCTION

Colon delivery systems have attracted the interest of both pharmaceutical scientists and clinicians because they are a useful technology for treating colon specific diseases such as constipation, irritable bowel syndromes, and serious diseases including ulcerative colitis, Crohn's disease, and colorectal carcinomas (1,2). In addition, the colon is considered a preferable site for the absorption of oral protein drugs because the hydrolytic enzyme activity of the colon is lower than that of the small intestine (3–7). Therefore, much effort has been focused on the colon as a potential delivery site for protein drugs (8,9). We have been exploring the use of intestinal luminal pressure-controlled colon delivery capsules (PCDCs) to treat colon specific diseases (10,11). This delivery system holds promise for effective and convenient administration of anti-inflammatory drugs, chemotherapeutic drugs, or anti-cancer drugs that are expected to exhibit their effects topically (12,13).

PCDCs were directly prepared from capsular shaped suppositories, which were spray coated with a water-insoluble polymer, ethylcellulose (EC), by a pharmaceutical coating machine, Hicoater-mini® (14). After oral administration to subjects, the PCDCs behave like an EC balloon containing drug solution; since the suppository base liquifies at body temperature. In the upper part of the gastrointestinal (GI) tract, the fluidity is such that the EC balloon is not directly subject to intestinal luminal pressures. However, reabsorption of water occurs in the colon and the viscosity of the luminal content increases there. As a result, intestinal pressures due to peristalsis directly affect the EC balloon. Since the EC balloon cannot tolerate these pressures, it disintegrates in the colon. However, it is necessary to confirm the colon delivery efficiency of PCDCs in human subjects directly.

γ-scintigraphy is a standard method to investigate the GI transit characteristics of orally administered preparations (15,16). Wilson et al. studied the colon delivery efficiency of CTDCs (Colon-Targeted Delivery Capsules) using this method, which was developed by a pharmaceutical group at Tanabe Pharmaceutical Industry (17). As this method requires the use of radioisotopes which are well known to be harmful to humans, human volunteers cannot participate in repeated γ-scintigraphy studies during a short time period. In addition, in some countries, this method is disallowed on human subjects, since the application of γ-scintigraphy is restricted by radiation protection requirements (18). Therefore, to study the transit characteristics of PCDCs in the human GI tract, we introduced a 129-channel vector biomagnetic measurement system (BMS) which we called gastrointestinal magnetomarkergraphy (GIMG). This system is safe for investigating the GI transit of magnetic PCDCs in healthy human volunteers.

The BMS is an established tool for the study of ionic currents generated by nervous and muscular tissue, and is used for the diagnosis of epileptic patients, where it is called magnetoencephalography (MEG). It is generally understood that one of the particular advantages of the biomagnetic methodology is the ability to localize the current sources with high accuracy and reliability (19–21). This is the first trial using BMS to investigate the delivery efficiency of a colon delivery system, PCDC, in healthy human volunteers.

0724-8741/00/0200-0160$18.00/0

MATERIALS AND METHODS

Materials

Gelatin capsules (#0) were obtained from Elanco Japan Co. Ltd. (Yamatokouriyama, Japan). Caffeine anhydrous, methanol, ethanol, acetonitrile, and chloroform were obtained from Kanto Chemical Co., Ltd. (Tokyo, Japan). Polyethylene glycol (PEG) 1000 was obtained from Nacalai Tesque Inc. (Kyoto, Japan). Ethylcellulose (EC, 7G grade) was a gift from Shin-Etsu Chemical Industrial Co., Ltd. (Tokyo, Japan). Talc was obtained from Maruishi Pharmaceutical Co. Ltds. (Osaka, Japan). Ferric oxide (Fe_2O_3) was a gift from Morishita Bengara Industrial Co. Ltd. (Ueno, Japan). All other materials were of reagent grade and were used as received.

The 129-Channel Shimadzu Vector Biomagnetic Measurement System (BMS)

Figure 1 depicts a schematic drawing of the instrument. BMS recordings were performed in a magnetically shielded room made of high-permeability materials, in which the noise level is lower than 10 $fT/Hz^{1/2}$ in order to eliminate outside magnetic noise. Thus, it was confirmed that the system had sufficient sensitivity for biomagnetic measurement. The outputs of flux locked loop (FLL) were filtered, amplified, and digitized by an A/D converter and stored in a computer for analysis. The sensor unit is composed of a dewar, detection coils, and a superconductive quantum interference device (SQUID) that was mounted on a counter-balanced gantry. This allows one to move the sensor unit up and down as well as to rotate and tilt it in order to detect magnetic fields over an area of interest. The bed can also be moved toward the sensor unit perpendicularly. Forty-three vector garadiometers were arranged at intervals of 25 mm over the area with a diameter of nearly 230 mm (22). At each measuring point magnetic fields in three directions could be measured. A radial magnetic field and two tangential magnetic fields could be calculated from the measured three values at each experimental point.

Preparation of Magnetic PCDCs

Coating of Capsular Shape Suppositories Containing Caffeine by a Coating Machine

Initially, 9.4 g of caffeine was dissolved with 100 g of PEG 1000 solution at 50°C and was introduced into a stainless steel mold the size of which was the same as the #0 gelatin capsule. The caffeine content was 75.0 ± 0.5 mg for a single capsule. A steel stick was inserted into the mold to make an air space to prevent volume change, which occurs with the melting of the suppository base after oral administration to human volunteers. After the caffeine solution in warm PEG 1000 was hardened at 10°C in a freezer, PEG 1000 capsules were removed from the mold. Thereafter, the steel stick was removed and a small solid mass of PEG 1000 was used to smoothly seal the surface of the air space. Next, the capsular shaped suppositories were coated with 5.0 %w/v EC solution by a Hicoater-mini™ (Freund Industries, Tokyo, Japan) to produce PCDCs. The coating method is precisely described in our previous report (14). Coating time determines the thickness of the fabricated EC membrane, which is important for PCDC to disintegrate in the human colon due to luminal pressure.

Preparation of Magnetic PCDCs Containing Caffeine

The aim of our investigation was to develop a non-invasive method to study the transit characteristics of PCDCs in the GI

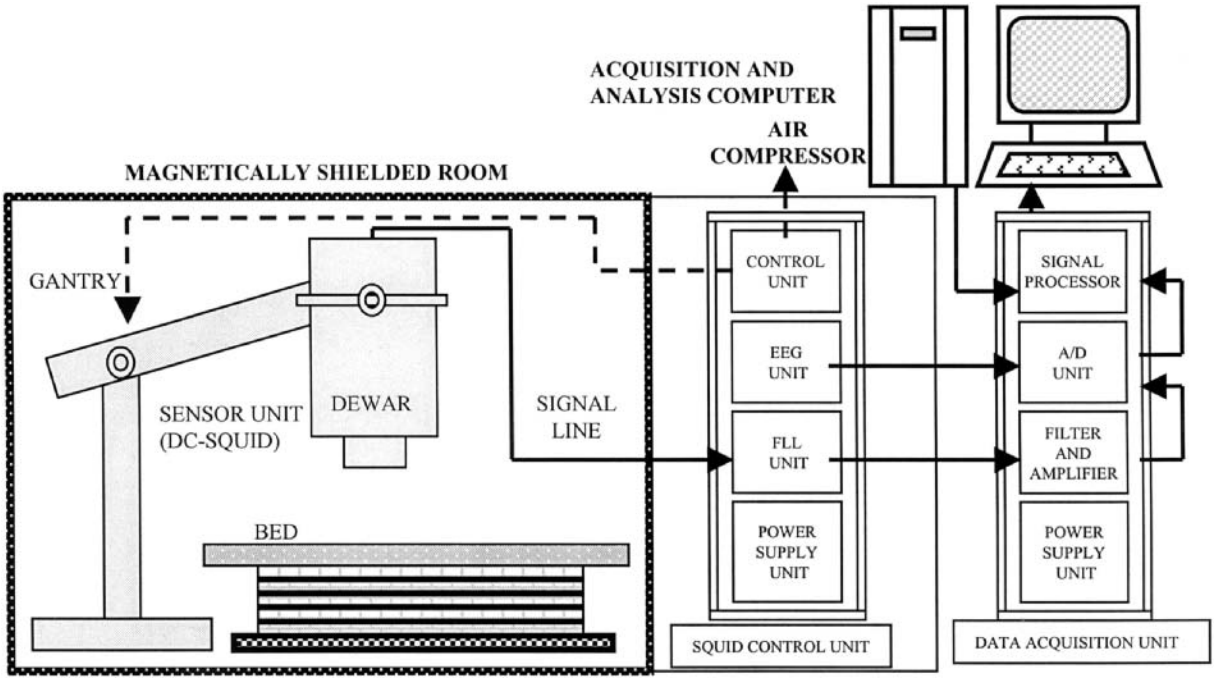

Fig. 1. Structure of 129 channel vector biomagnetic measurement system (BMS) used for monitoring the gastrointestinal transit of PCDCs. To eliminate the outside magnetic noise, the sensor unit was placed in a magnetically shielded room. The outputs of flux locked loop (FLL) are filtered, amplified digitized by an A/D converter and stored in a computer for analysis.

tract using GIMG which required magnetically labelled PCDCs. In order to magnetically label the PCDCs, 90 mg of powdered ferric oxide (Fe_2O_3) was suspended with 0.02 ml of 25 w/v% EC solution and was introduced into the head of #3 gelatin capsule caps. Ferric oxide has a density which is almost the same as the caffeine-PEG 1000 suppositories, and was solidified by evaporating the solvent. The ferric oxide cap was then stuck to the head of the PCDC. After comparing a number of methods, we chose the use of a 0.5 Tesla MRI system for magnetizing PCDCs.

Subjects

The GIMG study in healthy volunteers was conducted at Sakazaki Hospital at Kyoto city, Japan. The study followed the tenets of the Declaration of Helsinki (1964). Two of the male authors, S. M. and Z. H., were enrolled as human subjects in this study after informed consent was obtained. The age, body weight, and height of the two subjects were 23 years, 64.5 kg, 178 cm and 26 years, 66.5 kg, 174 cm, respectively. Good health was determined by medical history and physical examinations conducted within 2 weeks prior to the start of the study. Medication or drug use of any kind within 1 week of the start of dosing, and use of any agent known to induce or inhibit drug-metabolizing enzymes within 1 month prior to study initiation was prohibited. Use of alcohol and caffeine within 24 h prior to dosing, smoking of any degree within 12 h prior to start and throughout this study were not allowed. At the completion of the study, the subjects were given a post study physical and laboratory examination. Except during monitoring of the magnetic signal by BMS which was carried out under conditions of lying on a bed in the shielded room, subjects were allowed free movement in the laboratory. Following satisfactory completion of these tests, the subjects were discharged from the study.

Biomagnetic Measurement Procedure

To reduce the environmental magnetic noise, the measurements were performed in a magnetically shielded room with a BMS, which measures the magnetic field over a plane with a diameter of 230 mm. Volunteers who had fasted for 12 h ingested a magnetically labelled PCDC together with 50 ml room temperature water at 9 AM. At 4 h after ingestion, volunteers were instructed to eat a standard meal (23) over 20 min. In addition, just before administration, blank saliva samples were collected over 1 min, and serial salivary samples were collected at 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 h. After oral administration, the GI transits of the magnetic PCDCs were monitored with BMS for 7 h between 3 h and 10 h after ingestion. The BMS detector, i.e, a SQUID sensor unit, was positioned above the volunteer's abdomen, essentially measuring the magnetic field component, while volunteers were lying beneath the sensor unit for approximately 5 min for every measurement. The first measurement of BMS was performed at 3 h after oral administration of the magnetic PCDC, because it was confirmed in our previous report that the first-appearance time of caffeine into the systemic circulation was greater than 4 h (10). To determine the first-appearance time of caffeine into the systemic circulation, saliva samples were also collected over 1 min immediately after finishing each measurement by BMS. To monitor caffeine excretion rate in the saliva, the caffeine content in the saliva samples were analyzed by a HPLC method (10), because caffeine appears in the saliva as soon as PCDCs disintegrate in the GI tract. Except during the time of monitoring the magnetic PCDC signal by BMS, the volunteers could leave the shielded room and freely move about in the laboratory. The volunteers took their lunch at 4 h after administration. The volume of the saliva samples was measured and the samples were stored in a freezer at -20°C until analysis.

Estimation of the Positions of PCDCs in the GI Tracts of Human Volunteers

The position of the magnetic PCDC was estimated with a coordinate system chosen with x pointing to the volunteers left side, and y pointing cranially. To localize the position of the magnetic PCDCs in the volunteers' GI tract, three positioning coils were attached to their abdomen, where each was 6 cm away from the navel above, right and left. The coordinates of the three positioning coils were determined during measurement with the SQUID sensor unit. As shown in Fig. 2, relative positions between the PCDCs and positioning coils were calculated from an isofield contour map which shows outflux, influx and extrema of magnetic field. Between outfluxes and influxes, there is a heavy line which shows zero magnetic field. The crossing of the zero magnetic field line and the line that connects extrema of outflux and influx showed the location of the PCDC in the volunteer's GI tract. At each time point, the position of the PCDC within the GI tract was determined from the measured field distribution assuming a magnetic dipole model. The results calculated from isofield contour maps were shown on the MRI pictures of the volunteer's abdominal structure, an image of which was taken after measurement with the BMS.

Recording and analysis were performed as follows: (1) Three positioning coils were set on the subject's abdomen and fed tiny currents. The magnetic field distributions from the coils were measured by the sensor unit and analyzed later by a nonlinear least-squares analysis method in order to obtain the position of the abdomen on the coordinate of the sensor unit. (2) Evoked fields or spontaneous fields were measured. (3) MR images of the subject were taken with three MRI markers made of NiCl set at the same position as the positioning coils. (4) Positions of the three MRI markers were determined on the MR image manually. (5) The parameters of a current dipole were calculated by nonlinear least-squares analysis. (6) The calculated current dipoles were displayed on the MRI picture of the subject's abdominal structure.

Saliva Caffeine Assay

The concentrations of caffeine in the saliva samples were determined by a HPLC method as described in our previous report (10). Briefly, the human saliva samples were deproteinized by heating at 80°C for 5 min. After centrifuging for 10 min at 4000 g, supernatants were obtained. To 1 ml of the saliva, 200 μl of saturated sodium chloride solution and 5 ml of chloroform were added and caffeine was extracted. Four ml of the organic phase was evaporated to dryness under a flow of nitrogen gas. The residue was dissolved with 200 μl of the mobile phase, acetonitrile: water (1:4), and 100 μl of the reconstituted sample was injected into the HPLC system. A set of six or seven calibration standards was run with each series

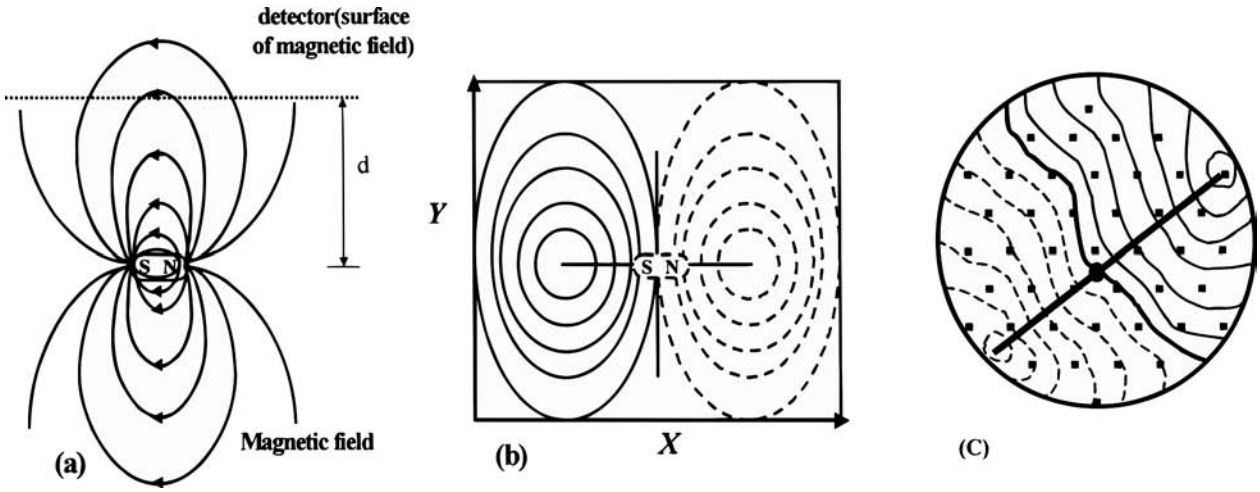

Fig. 2. Schematic representation of magnetic field (a) from magnetic dipole, where d is the distance from the observe surface to magnetic dipole; and contour maps (b). Under the crossing of the zero magnetic field line and the line that connected extrema of outflux and influx, the location of the magnetic dipole is shown (c).

of unknown samples. The standard curve of caffeine added to each human volunteer's saliva was linear over the range of 0.2–10.0 μg/ml and passed through the origin.

RESULTS

In Vitro Experiment of Magnetic PCDC Monitored with BMS

To investigate the magnetic dipole pattern, we performed *in vitro* experiments first. Fig. 3. shows the results of *in vitro* experiment of magnetic, which were magnetized by strong permanent magnets for 2 days monitored with BMS. In the section of magnetic strength maps, MEG-19-R to MEG-26-R show the vector gradiometers of No. 19–26 of a total of 43 vector gradiometers. From this data it is clearly demonstrated that there was a good relation between the magnetic strength and the transmutation of the contour maps because they are localized in the centerline of the 43 vector gradiometers. In the contour maps, the same colour class shows the same magnetic strength, and the hyper-chromic gray and hypo-chromic gray show magnetic dipole concentration gradients. The black field shows magnetism was not detected.

Initially we set the detecting surface, the bed of BMS, at a distance of 10 cm from the sensor unit surface. A magnetic PCDC was positioned 20 cm away from center of the sensor unit's projection on the bed. As the magnetic PCDC was slowly moved toward the projection point of the sensor unit's center on the bed plane, the detected magnetic strength increased as shown in the magnetic strength maps (Fig. 3). When the PCDC was moved just under the center of the sensor unit, the peak of the magnetic signal was observed and the magnetic dipole was clearly divided equally into two sections in the contour maps (Fig. 3. point (a)). Thereafter, when the magnetic PCDC was rotated along its longitudinal axis beneath the sensor unit of the BMS, the magnetic strength did not change appreciably and the contour map did not show any diversification (Fig. 3. point (b) and (c)). Meanwhile, by rotating the magnetic PCDC along its latitudinal axis, the magnetic strength showed a sharp fluctuation and the pattern of the magnetic dipole was regularly transformed. When the head of the magnetic PCDC was vertically pointed towards the detector, only one magnetic pole was observed in the contour map; when the opposite head of the capsule pointed towards the detector, the opposite magnetic pole was shown in the contour maps as illustrated in Fig. 3. i e., points (d), (e) and (f). From the entire detecting course, we selected 6 time points from (a) ~ (f) that best illustrates the relation between the location of the magnetized PCDC and magnetic strength or contour maps pattern. In other words, a magnetic dipole has multiple detected magnetic patterns with different attitude angles as shown by *in vitro* magnetic dipole attitude determinations. Therefore, it is essential to determine which attitude information responds with which contour maps pattern. Finally, we can conclude that only six kinds of contour map patterns reflect PCDC location in the GI tract.

GI Transit of a Magnetic PCDC in Human Subjects Detected by BMS

The data obtained from the SQUID sensor unit was analyzed by magnetic dipole calculator software. The estimated locations of PCDC were recorded in the MRI picture of individual volunteer's abdominal structure. The three closed circles show positioning coils in Figs. 4. and 5. that were affixed to the volunteer's abdomen. Fig. 4. shows the GI transit of a magnetic PCDC in volunteer S. M., which was estimated from the isofield contour maps during 3 to 10 h. The magnetic sources at 3 and 4 h were detected in the middle portion of volunteer S. M.'s abdomen. From 5 to 9 h, the magnetic sources changed to the right side of the volunteer's body. By judging from his abdominal anatomy obtained by MRI, the magnetic PCDC was localized in the ascending colon. The magnetic PCDC was delayed approximately 5 h in the ascending colon and the magnetic signal was detected in the upper middle of the abdomen at 10 h, i e., in the transverse colon. In the case of volunteer Z. H., as shown in Fig. 5., the magnetic signal was detected in the right side of the abdomen between 4 to 10 h, which was in the ascending colon by judging from his abdominal anatomy

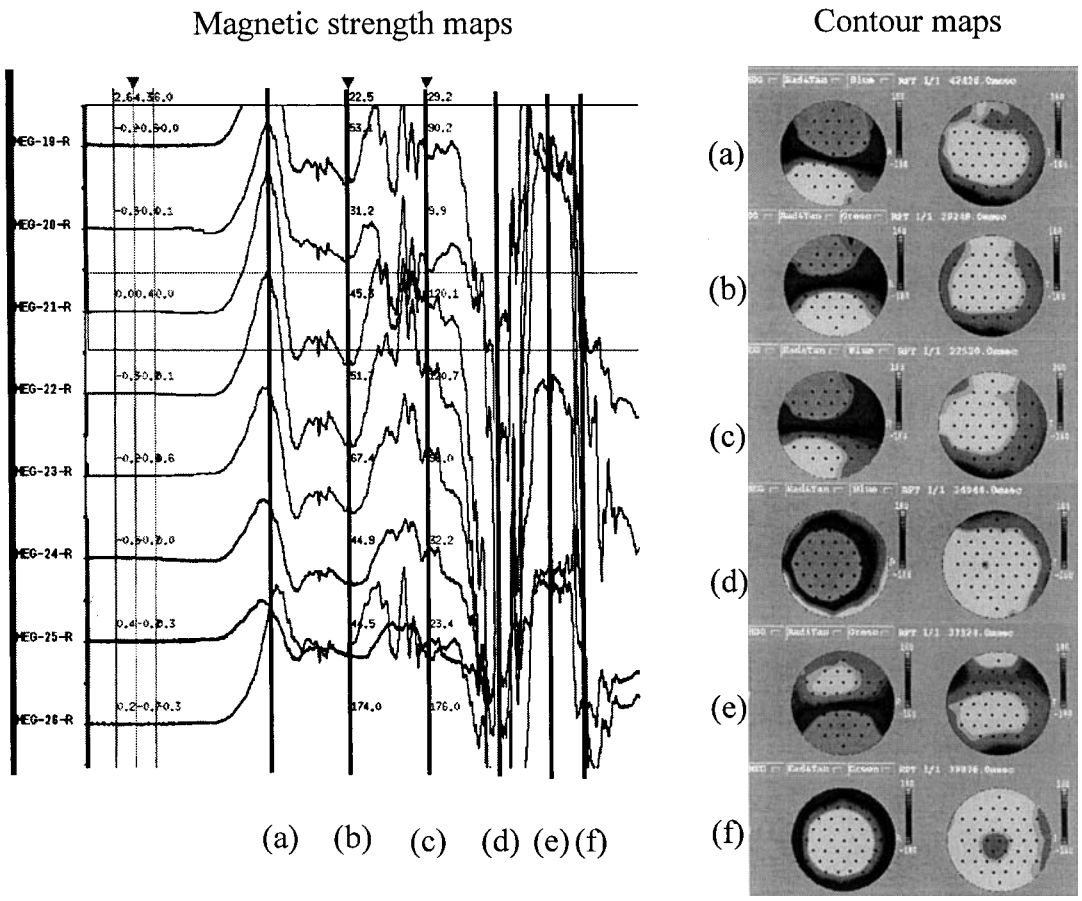

Fig. 3. *In vitro* magnetism monitoring of PCDC with BMS. (a) PCDC is left just under the detector. (b, c) when the magnetic PCDC was rotated along its long axis, not only magnetic strength but also magnetic pole did not show any change. (d, e. f) when the magnetic PCDC was rotated along its short axis, the magnetic strength showed a sharp fluctuation and the pattern of the magnetic dipole was regularly transformed.

as determined by MRI. Feces are formed by reabsorption of water in the ascending colon, and as a result the PCDC changed its position following the movement of intestinal fluid upward and downward in the ascending colon.

The magnetic PCDC was also filled with caffeine, the mean content of which was 75.0 $\pm$ 0.5 mg. The first-appearance times of caffeine in the saliva, Ti, were about 6 h and 5 h after oral administration in the case of volunteer S. M. and Z. H. as shown in Fig. 6. These results suggest the PCDC disintegrated between 5–6 h in volunteer S. M. and disintegrated between 4–5 h in volunteer Z. H.

Combining the results of the caffeine test with the estimated position of PCDCs in volunteer S. M. and Z. H.'s GI tract, we can state that the test PCDC disintegrated in the colon, where the tracer drug, caffeine, was released into the intestinal fluids, absorbed into the blood and excreted into the saliva.

DISCUSSION

The magnetic PCDCs in this study had a relatively feeble magnetism of approximately 10^{-10} Tesla. If the distance between the dewar of the SQUID sensor unit and the PCDC was more than 20 cm, the extrema of the magnetic dipole could not be observed from the isofield contour map. As the magnetic-flux density diverged into rarefaction, the accuracy of the measurement rapidly decreased. Therefore, the SQUID sensor unit was positioned 1 cm from the surface of the abdomen to bring the magnetic PCDC as close to the dewar as possible. In addition, because the position of the magnetic PCDC was not known before computer analysis of the data obtained from the SQUID sensor unit, the human volunteers' abdomen was divided into three sections: the left, center, and right. To detect the magnetic signal from the PCDC, the center of the dewar of the SQUID sensor unit was shifted along these three lines between the volunteers' sternum and femur.

In the experimental section, we described the spatial resolution of the PCDC's within the isofield contour maps of two-dimensional organs of GI tract as shown in Fig. 2. We used BMS in an attempt to investigate the delivery efficiency of solid preparations in the human GI tract, although this technique was originally developed as a diagnostic instrument for cranial nerve disease. Therefore, it was necessary to first resolve the problem of the relation between the different patterns of isofield contour maps and the position of magnetic PCDCs. Second, it was necessary to clarify the precision of the BMS method for the estimation of location of PCDCs in the human GI tract.

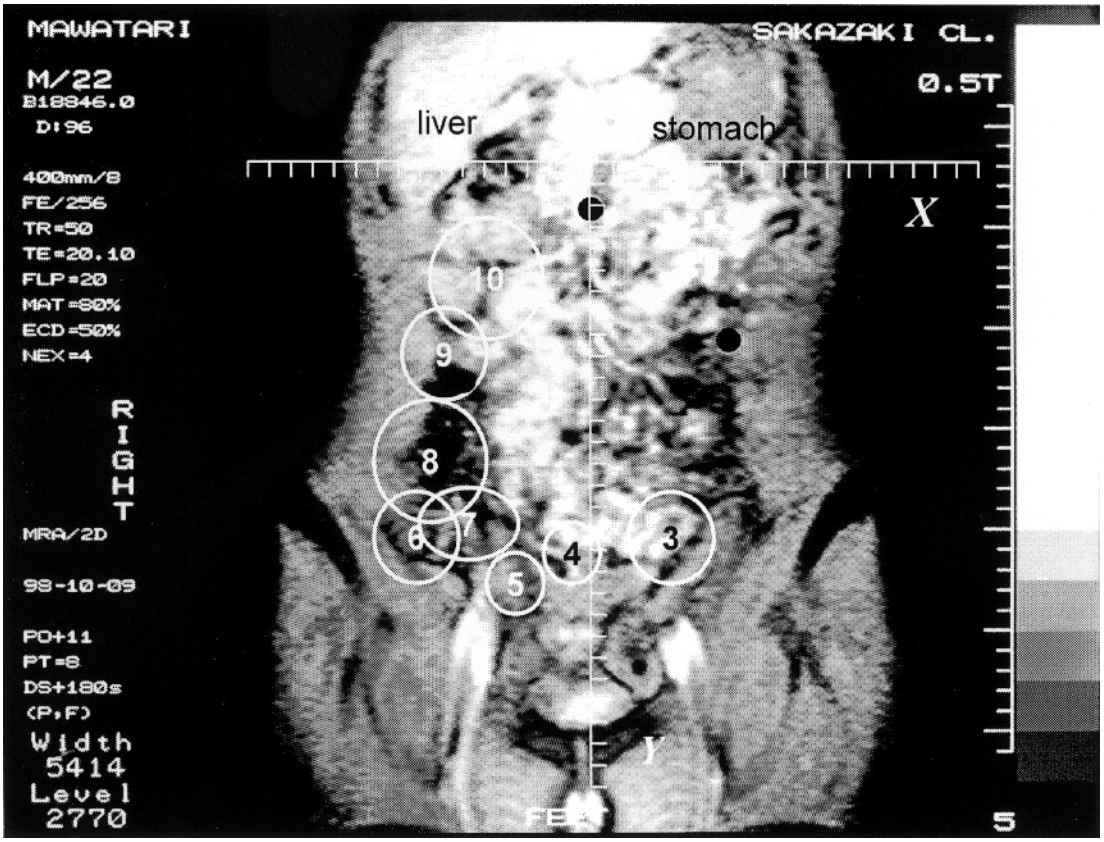

Fig. 4. Serial positions of a magnetic PCDC in the GI tract of human volunteer S. M.'s GI tract. The estimated position of PCDC at each measurement time is shown as a circle. The figure shows the time of measurement. ● shows the positioning of coils.

BMS and its associated software was developed as an advanced instrument that can detect faint magnetic fields of less than 10^{-14} Tesla, such as occur from ionic currents generated by nervous and muscular tissues. The precision of BMS, ie., the range of the estimated position is less than a millimeter when used in the diagnosis of encephalic disease. In our study, rather than monitoring the position of ionic current, we attempted to estimate the location of the magnetic field of PCDCs in the human GI tract. Therefore, we performed a preliminary experiment before *in vivo* human studies were carried out. A magnetized PCDC was transferred 1.0 cm under the SQUID sensor unit and parallel to it. Under these conditions, there were no differences in the obtained contour maps. Next, it was transferred to a distance of 3.0 cm, where we observed the magnetic field was shifted in a plane. Based on this experiment, it was suggested the range of the estimated location of PCDC in the human GI tract by BMS was less than 3.0 cm.

In the first phase of this study using volunteer S. M., we magnetized the ferric oxide cap with strong permanent magnets or an electromagnet and thereafter attached it to the head of the PCDC before scanning the magnetic field with BMS. Although the magnetic strength produced by an electromagnet was stronger than that produced by permanent magnets, the SQUID sensor unit measured no significant differences. When the magnetic PCDC was set at some attitude angle to the detector in the *in vitro* experiment, the pattern of isofield contour map changed, and deviations occurred in estimating the position of the PCDC. As permanent magnets were used in the case of volunteer S. M. to magnetize the PCDC, the estimated positions of PCDC had poor precision, which is shown by the size of circle in Fig. 4. In order to increase the precision of GIMG, the method of magnetization of the PCDCs was altered in the second phase study using volunteer Z. H. Instead of magnetizing the ferric oxide cap before oral administration, the volunteer entered the 0.5 Tesla MRI coil for 1 minute just before each measurement with BMS. The PCDC was magnetized with the MRI system in the volunteer's GI tract, which conformed to the magnetic field in both direction and strength. Therefore, the derivative magnetic field of PCDC that was detected by BMS produced the same pattern of contour maps. As shown in Fig. 5, the deviation was diminished, and the position of the magnetized PCDC was estimated with higher accuracy than in the first phase study.

In the case of volunteer S. M., the PCDC was magnetized before administration and was monitored by BMS. As we described in the *in vitro* experiment section, we could estimate the position of PCDC in the GI tract with high definition from contour maps only in the cases of (a) ~ (f). However, these six cases require special conditions, i e., the longitudinal axis of PCDCs must be parallel with the surface of the sensor unit of BMS. With increasing attitude angle between the longitudinal axis of the PCDC and the detecting surface of the sensor unit, the magnetic dipoles could not divide equally in the isofield contour maps. Thereafter, the deviation in estimated position

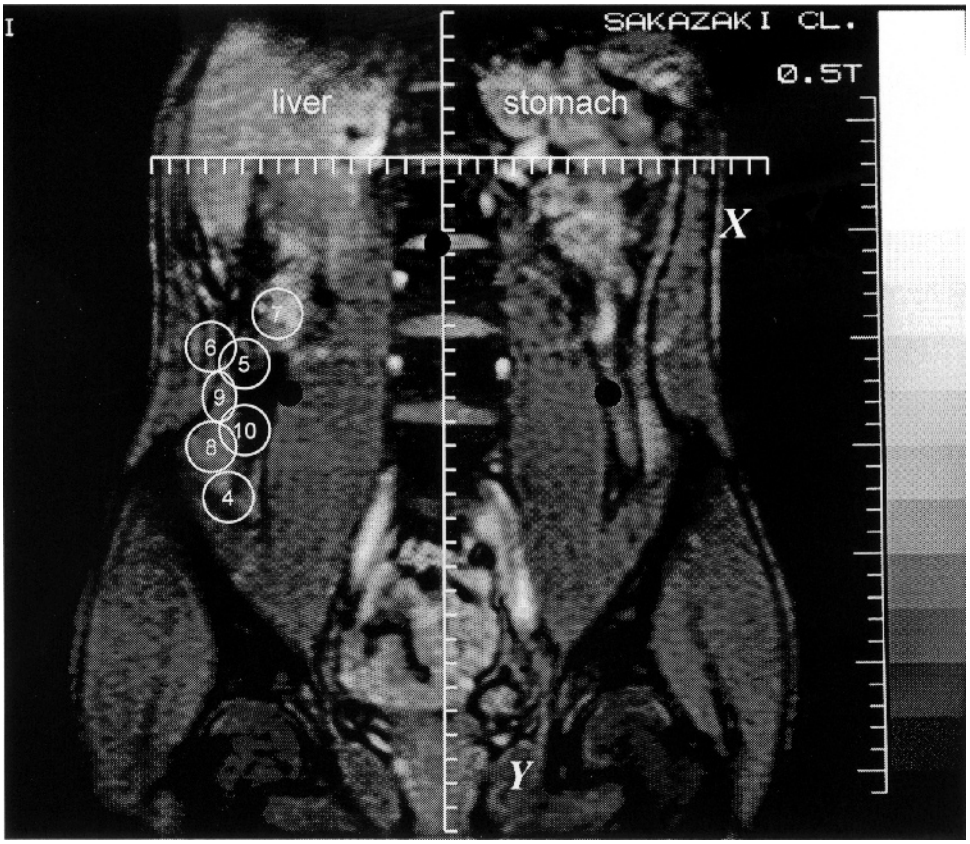

Fig. 5. Serial positions of magnetic PCDC in the GI tract of human volunteer Z. H. The estimated position is shown as a circle. The figure shows the time of measurement. ● shows the positioning of coils.

of PCDC in the GI tract increased. In the human GI tract, the shape of the intestinal tract is not always parallel with the sensor unit surface of the BMS. Therefore, the results obtained with volunteer S. M. had poor precision. In the case of Z. H., the volunteer lay in the coil of the MRI and the PCDC was magnetized with the strong 0.5 Tesla magnetic field, the PCDC had certain strong magnetic dipoles which were paralled with the sensor unit of BMS. Namely, with the sensor unit of BMS the detected magnetic dipole of PCDC in the human GI tract showed the same isofield magnetic pattern as Fig. 3. point (d) or (e) in every measurement. Thereafter, a high definition of estimated PCDC position in GI tract could be obtained.

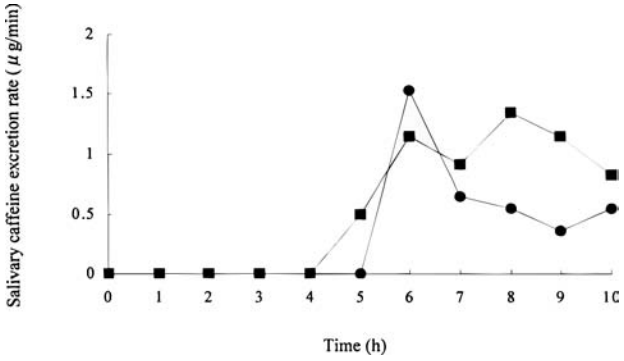

Fig. 6. Salivary caffeine excretion rate-time profile in two human volunteers. (●) volunteer S. M., and (■) volunteer Z. H.

CONCLUSIONS

A 129-channel SQUID sensor unit above the abdomen recorded the magnetic dipole field distributions of a previously or subsequently magnetized PCDC. The corresponding positions of the magnetic PCDC were calculated with a localization algorithm. When the PCDC was treated with permanent magnets or an electromagnet before administration, contour maps were not well resolved. However, when the PCDC was magnetized by a MRI system just before the test with BMS, highly resolved contour maps were obtained and the position of the PCDC in the abdomen of the human volunteer was estimated with high accuracy. After oral administration of a magnetic PCDC, it was delivered to the ascending colon at approximately 5 h after ingestion, a time when caffeine was detected in the saliva. Therefore, it was shown the PCDC was delivered to the human colon and released caffeine there. As compared to γ-scintigraphy, the GIMG method is safer and non-invasive to a volunteer. The GIMG method will be a powerful tool for the study of not only colon delivery efficiencies of PCDCs, but also commonly used oral preparations. Two main advantages of GIMG are its applicability is not restricted by radiation protection requirements, and it offers the chance to obtain even more detailed knowledge of the behavior and fate of solid pharmaceutical formulations during GI passage. In addition, GIMG provides information on the motility of the GI organs by passage of the magnetically marked object. In this study, we used fasted human subjects. In the future, the characteristics

of the delivery of the drug to the colon by PCDCs will be tested with fed subjects

REFERENCES

1. A. B. Hawthorne and C. J. Hawkey. Immunosuppressive drugs in inflammatory bowel disease. A review of their mechanisms of efficacy and place in therapy. *Drugs*. **38**:267–288 (1989).
2. H. B. Stephen. Inflammatory bowel disease. *Drug Ther.* **334**:841–848 (1996).
3. S. S. Davis. Delivery systems for biopharmaceuticals. *J. Pharm. Pharmacol.* **44**:186–190 (1992).
4. M. E. K. Kraeling and W. A. Ritschel. Development of colonic release capsule iosage form and the absorption of insulin. *Meth. Find. Exp. Clin. Pharmacol.* **14**:199–209 (1992).
5. D. T. O'Hagan, K. J. Palin, and S. S. Davis. Intestinal absorption of proteins and macromolecules and the immunological response. *CRC Crit. Rev. Ther. Drug Carrier Sys*. **4**:197–220 (1987).
6. V. H. L. Lee. Enzymatic barriers to peptide and protein absorption. *CRC Crit. Rev. Ther. Drug Carrier Sys.* **5**:69–97 (1988).
7. J. F. Woodley. Enzymatic barriers for FI peptide and protein delivery. *Crit. Rev. Ther. Drug Carrier Sys.* **11**:61–95 (1994).
8. R. J. Mrsny. The colon as a site for drutg delivery. *J. Contr. Rel.* **22**:15–34 (1992).
9. D. R. Friend. Oral colon-specific drug delivery. *CRC Press, Inc., Florida*. (1992).
10. M. Motoki, Z. Hu, T. Shimokawa, S. Sekino, K. Ri-e, Y. Kuoi, Y. Yoshikawa, and K. Takada. Evaluation of intestinal pressure-controlled colon delivery capsule containing caffeine as a model drug in human volunteers. *J. Contr. Rel.* **52**:119–129 (1998).
11. T. Takaya, C. Ikeda, N. Imagawa, K. Niwa, and K. Takada. Development of colon delivery capsule and the pharmacological activity of recombinant human granulocyte colony-stimulating factor (rhG-CFS) in beagle dogs. *J. Pharm. Pharmacol.* **47**:474–478 (1995).
12. A. Kiriyama, T. Nishiura, M. Ishino, Y. Yamamoto, I. Ogita, Y. Kiso, and K. Takada. Binding characteristics of KNI-272 to plasma proteins, a new potent tripeptide HIV protease inhibitor KNI 272 in enteric capsule, *Biopharm. Drug Dispos.* **17**:739–751 (1996).
13. T. Takaya, K. Sawada, H. Suzuki, A. Funaoka, K. Matsuda, and K. Takada. Application of colon delivery capsule to 5-aminosalicylic acid and evaluation of the pharmacokinetic profile after oral administration to beagle dogs, *J. Drug Target*. **4**:271–276 (1997).
14. Z. Hu, G. Kimura, S. Mawatari, T. Shimokawa, Y. Yoshikawa, and K. Takada. New preparation method of intestinal pressure-controlled colon delivery capsules by coating machine and evaluation in beagle dogs. *J. Contr. Rel.* **56**:293–302 (1998).
15. G. A. Digenis, E. P. Sandefer, C. Richard, and D. Waoter. Gamma scintigraphy: an evolving technology in pharmacentical formulation development-part 1. *Rev. Res. Focus*. **1**:100–108 (1998).
16. G. A. Digenis, E. P. Sandefer, C. Richard, and D. Waoter. Gamma scintigraphy: an evolving technology in pharmacentical formulation development-part 2. *Rev. Res. Focus*. **1**:160–166 (1998).
17. T. Ishibashi, G.R. Pitcairn, H. Yoshino, M. Mizobe, and I. R. Wilding. Scintigraphic evaluation of a new capsule-type colon specific drug delivery system in healthy volunteers. *J. Pharm. Sci.* **87**:531–535 (1998).
18. W. Werner, K. Roman, C. Dino, and T. Lutz. High-resolution monitoring of the gastrointestinal transit of a magnetically marked capsule. *J. Pharm. Sci.* **86**:1218–1222 (1997).
19. J. Hughes and J Cohen. Relationship of the magnetoencephalogram to abnormal activity in the electroencephalogram. *J. Neurol*, **217**:79–93 (1977).
20. G. M. Baule and R. McFee, Detection of the magnetic field of the heart. *Am. Heart J.* **66**:95–96 (1963).
21. D. Cohen. Magnetoencephalography: Evidencee of magnetic fields produced by alpha-rhythms currents. *Science.* **161**:784–786 (1968).
22. Y. Yoshida, A. Arakawa, A. Kondo, Y. Kajihara, S. Tomita, and Y. Takanashi. A 129 channel vector meuro-magnetic imaging System. *Adv. Biomagnet. Abs.* 351 (1996).
23. A. Melander. Influence of food on the bioavailability of drugs. *Clin. Pharmacokin.*, **3**:337–351 (1978).