Simultaneous *In Vivo* Visualization and Localization of Solid Oral Dosage Forms in the Rat Gastrointestinal Tract by Magnetic Resonance Imaging (MRI)

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Purpose. Bioavailability of orally administered drugs is much influenced by the behavior, performance and fate of the dosage form within the gastrointestinal (GI) tract. Therefore, MRI in vivo methods that allow for the simultaneous visualization of solid oral dosage forms and anatomical structures of the GI tract have been investigated.

Methods. Oral contrast agents containing Gd-DTPA were used to depict the lumen of the digestive organs. Solid oral dosage forms were visualized in a rat model by a ^{1}H-MRI double contrast technique (magnetite-labelled microtablets) and a combination of ^{1}H- and ^{19}F-MRI (fluorine-labelled minicapsules).

Results. Simultaneous visualization of solid oral dosage forms and the GI environment in the rat was possible using MRI. Microtablets could reproducibly be monitored in the rat stomach and in the intestines using a ^{1}H-MRI double contrast technique. Fluorine-labelled minicapsules were detectable in the rat stomach by a combination of ^{1}H- and ^{19}F-MRI in vivo.

Conclusions. The in vivo ^{1}H-MRI double contrast technique described allows solid oral dosage forms in the rat GI tract to be depicted. Solid dosage forms can easily be labelled by incorporating trace amounts of non-toxic iron oxide (magnetite) particles. ^{1}H-MRI is a promising tool for observing such pharmaceutical dosage forms in humans. Combined ^{1}H- and ^{19}F-MRI offer a means of unambiguously localizing solid oral dosage forms in more distal parts of the GI tract. Studies correlating MRI examinations with drug plasma levels could provide valuable information for the development of pharmaceutical dosage forms.

KEY WORDS: gastrointestinal transit; magnetic resonance imaging; nuclear magnetic resonance; oral drug delivery; solid oral dosage forms.

INTRODUCTION

The bioavailability of drugs from solid oral dosage forms is influenced by the performance and fate of the pharmaceutical formulation in the gastrointestinal tract. Physiological factors like peristalsis, stomach residence time and intestinal transit can have an important influence on processes such as swelling, erosion, disintegration and possible bioadhesion of the dosage form in vivo. These processes have an impact on drug release, absorption and bioavailability. Therefore, in vivo methods that allow for the direct visualization of such processes in the digestive tract are being sought (1).

Over the past years much progress has been made in the evaluation of pharmaceutical formulations by non-invasive γ-scintigraphy which has been the subject of numerous studies (2,3,4). Monitoring of the gastrointestinal transit of pharmaceutical dosage forms is possible with γ-scintigraphic methods (5,6). Compared to MRI, another imaging modality, γ-scintigraphy, has a limited spatial resolution and the display of distinct organs is more accurate with MRI. Furthermore, the accurate determination of a dosage form in the gastrointestinal tract by scintigraphic analysis requires an experienced analyst in order to assign the regions of the gastrointestinal tract including the stomach, duodenum, jejunum, ileum and colon. The anatomical region passed by a dosage form during gastrointestinal transit is assigned with respect to defined "landmarks" (anatomical markers containing γ-scintillators). Simultaneous visualization of both the dosage form and the gastrointestinal environment is not possible. The improved outline of the anatomical feature of the gastrointestinal tract is described in a study using water containing ^{99}Tc-labelled DTPA (7). The gastric emptying, intestinal transit and caecum arrival times of different multiple-unit (pellet) dosage forms (8) as well as the differential transit behavior of single-unit and multiple-unit dosage forms (9,10,11) have been investigated under fed and fasted conditions by means of γ-scintigraphy. Furthermore, in vitro release kinetics and absorption data were correlated with drug release in vivo and gastrointestinal transit times obtained by γ-scintigraphy to perform in vitro-/in vivo-correlations (7,10,12).

In γ-scintigraphic studies radiolabelled dosage forms are used. The labelling techniques used for these dosage forms, e.g. the incorporation of gamma emitting nuclides, are specific and well-known, whereas appropriate dosage form labelling techniques for MRI applications have hardly been investigated. MRI, as a non-invasive and non-radioactive technique, allows the observation of anatomical structures in detail. The major advantage of MRI versus other imaging techniques is its superb contrast resolution (13). Visualization of the digestive tract may be improved by the application of oral contrast media. To our knowledge, only a few MRI studies on in vivo localization of dosage forms have been carried out in humans and animals. When appropriate techniques for dosage form labelling become available, MRI in vivo visualization of solid oral dosage forms will add to the information obtained by established techniques such as γ-scintigraphy. In this project, we have investigated MRI as an experimental approach to visualize the in vivo behavior of pharmaceutical dosage forms. For this purpose, some basic investigations on the labelling of solid oral dosage forms and the evaluation of different MRI techniques in an animal model were necessary.

MATERIALS AND METHODS

Oral Contrast Agents

To depict the lumen of the digestive organs, an oral contrast emulsion was developed. Gd-DTPA (Magnevist®, Schering) and ferric ammonium citrate (Aldrich) were mixed with different lipid formulations and investigated by MRI in vitro (details of the development of such a formulation will be reported separately). The contrast emulsion with the best MRI in vitro signal enhancement was later investigated by MRI in vivo.

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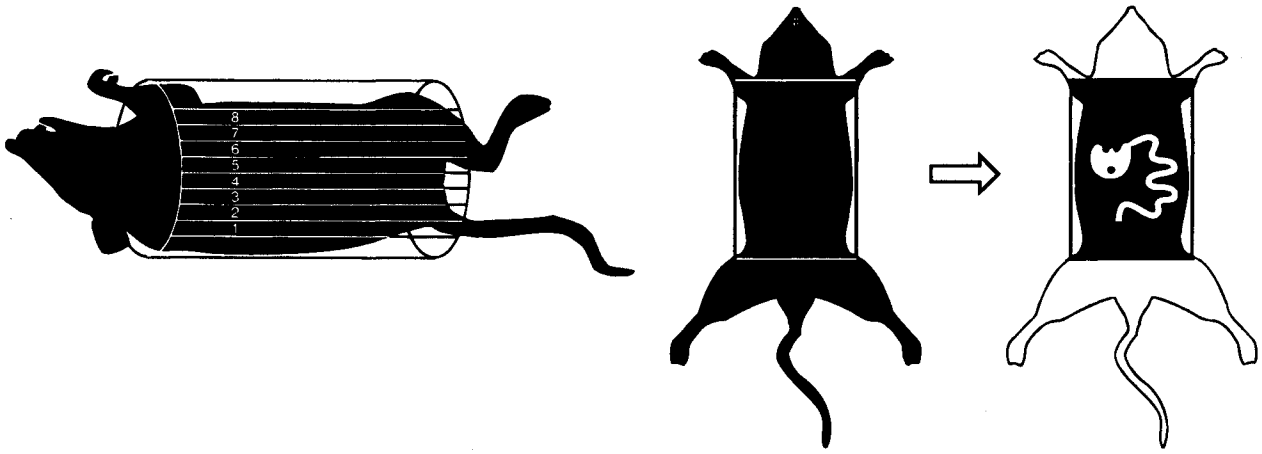

Fig. 1. *Position of the rat in the receiver coil with image slice definitions.* Anaesthetized animals were positioned in a birdcage-type resonator (length: 90 mm, diameter: 60 mm). T1-weighted spin-echo images of the rat abdomen were obtained in eight contiguous coronal ^{1}H-MRI slices (slice thickness: 2 mm) and one corresponding central coronal ^{19}F-MRI slice (slice thickness: 10 mm).

During this investigation, an aqueous oral contrast agent (Magnevist® enteral-concentrate, Schering) became available and was also used, mainly to avoid interactions due to fat content of the "contrast emulsion". Magnevist® enteral-concentrate contains Gd-DTPA, buffer and mannitol (14). These two oral contrast agents both containing Gd-DTPA in a final concentration of 1 mmol/l and referred to as "oral contrast emulsion" or "aqueous oral contrast agent" respectively, were routinely used for in vivo MRI.

Oral contrast emulsion: 20 µl of an aqueous solution containing 500 mmol/l Gd-DTPA (Magnevist®, Schering) were mixed with 9.98 ml of an oil emulsion with a high fat content for parenteral nutrition (Lipofundin® MCT 20%, Braun Melsungen).

Aqueous oral contrast agent: a 1:10 dilution of Magnevist® enteral-concentrate (Schering) with purified water.

Solid Oral Dosage Forms

Tablets

Different types of *s*uper*p*aramagnetic *i*ron *o*xide particles (SPIO) were inorporated in swelling tablet formulations and first investigated by ^{1}H-MRI in vitro to test the suitability of SPIO as tablet marker agents in general. In order to optimize further the SPIO content in pharmaceutical tablet formulations, a series of SPIO-labelled tablets of varying concentrations was investigated and compared to unlabelled tablets in vitro. For this purpose, SPIO were incorporated in a sodium alginate formulation (commercial product, Knoll) at concentrations ranging from 0.01–1.0% [w/w]. Biplanar tablets of 13 mm i. d. and weighing 700 mg were compressed (compression: 100 kN) on a manually operated hydraulic press type "Specac" (Specac, Orpington, Kent, England). The tablets were perforated in the center with a small hole of 2.7 mm i. d. allowing them to be fixed in a tablet holder and to be immersed in distilled water or contrast medium. ^{1}H-MR images of the swelling tablets were taken at defined time points.

Following the in vitro determination of the optimum SPIO contents in tablets a respective swelling tablet formulation was investigated in comparison to an unlabelled tablet by ^{1}H-MRI in vitro. Results were compared with photographs of the same tablets taken at the same times.

Microtablets

Microtablets, 4 mm in length and 2 mm i. d., were prepared by incorporating 0.025% [w/w] SPIO (15 nm i. d., provided by BASF) into a 50:50 mixture of a sodium alginate formulation (commercial product, Knoll) and hydroxypropyl methylcellulose (Methocel® K100M, Colorcon). The microtablets were compressed (compression: 1 kN) on a tablet excenter press type "Korsch EK0" (Korsch, Berlin) equipped with five punches.

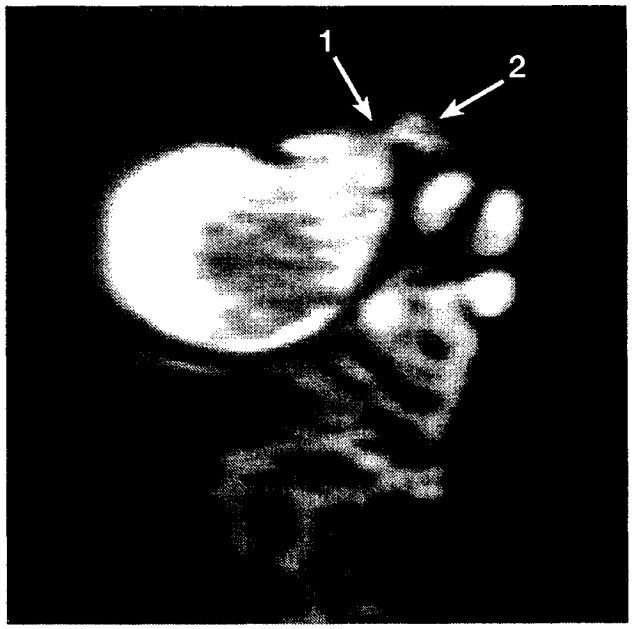

Fig. 2. ^{1}*H-MRI* in vivo: *signal enhancement of the rat stomach by oral contrast emulsion.*
1: Sphincter Pylori
2: Duodenum

Coated Microtablets

Some batches of microtablets were coated with copolymers based on methacrylic acid and methyl methacrylate to prevent them from swelling in the rat stomach. The microtablets were dip-coated in solutions of 12.5% [w/w] dry substance in aqueous isopropyl alcohol (Eudragit® L 12.5 P or Eudragit® S 12.5 P, Röhm).

Microtablets Made of Polytetrafluoroethylene

Polytetrafluoroethylene microtablets (PTFE-powder, Aldrich) served as a model for solid oral dosage forms for the investigation of whether single unit dosage forms pass the sphincter pylori in the rat model. These PTFE-microtablets (length: 4 mm, diameter: 2 mm) were compressed on a tablet excenter press type "Korsch EK0."

Minicapsules

Capsule-shaped, sealed minitubes made of I) polyethylene (KRONLAB Labortechnik, Sinsheim) and II) polytetrafluoroethylene (Reichelt Chemietechnik, Heidelberg) were used as surrogates for pharmaceutical capsules. These "minicapsules" with an inner diameter of I) 1.4 and II) 1.7 mm, and an outer diameter of I) 1.9 and II) 2.08 mm and a length of 6 and 8 mm respectively, were filled with hexafluorobenzene (Aldrich) and sealed with plasticine and tissue adhesive based on enbucrilate (Histoacryl®, Braun Melsungen).

MRI Experiments

MRI experiments were performed at 2.0 Tesla on a General Electric CSI II animal scanner equipped with Acustar® shielded gradients (maximum gradient strength: ±200 mT/m, bore: 15 cm in diameter). The anaesthetized animals were positioned in a home-built birdcage-type resonator (90 mm in length and 60 mm diameter, Fig. 1) tuned to 85.54 MHz (^{1}H-MRI) or 80.47 MHz (^{19}F-MRI). T1-weighted spin-echo images (TR = 400 ms, TE = 25 ms) of the rat abdomen were obtained in eight contiguous coronal ^{1}H-MRI slices of 2 mm slice thickness and one corresponding central coronal ^{19}F-MRI slice of 10 mm slice thickness. The field of view was 70 mm, resulting in a pixel resolution of 270 μm.

For the detection of magnetite-labelled microtablets ^{1}H-MRI was applied after administration of the contrast agent used for the enhancement of the GI lumen. The combination of ^{1}H- and ^{19}F-MRI was used to localize fluorine-labelled minicapsules.

Animal Model

The animal studies met the requirements of the "German Animal Protection Law" and were conducted according to the guideline "Principles of Laboratory Animal Care" (NIH publication #85-23, revised 1985).

The oral administration of microtablets and minicapsules to rats required the development of a suitable instrument. Therefore appropriate devices for the administration of solid oral dosage forms to rats were developed and constructed in-house. A patent application covering these instruments has been filed (details will be reported separately).

24 h fasted, male Sprague Dawley rats (250–300 g) received oral contrast agent and a solid oral dosage form simultaneously. The rats were anaesthetized immediately after this treatment with 2 mg/kg azaperone and 90 mg/kg metomidate hydrochloride (Stresnil®/Hypnodil®, both Janssen) and placed into the MRI resonator.

At the end of the experiments and prior to laparotomy, the rats were killed by an overdose of pentobarbital sodium (Narcoren®, Rhone Merieux).

Group 1

Group 1 received *I*) 10, *II*) 15 or, *III*) 19 ml/kg oral contrast emulsion or aqueous oral contrast agent and a microtablet, coated microtablet or minicapsule orally.

Group 2

Group 2 received 10 ml/kg oral contrast emulsion or aqueous oral contrast agent and a microtablet, coated microtablet or minicapsule orally. After defined transit times the rats were

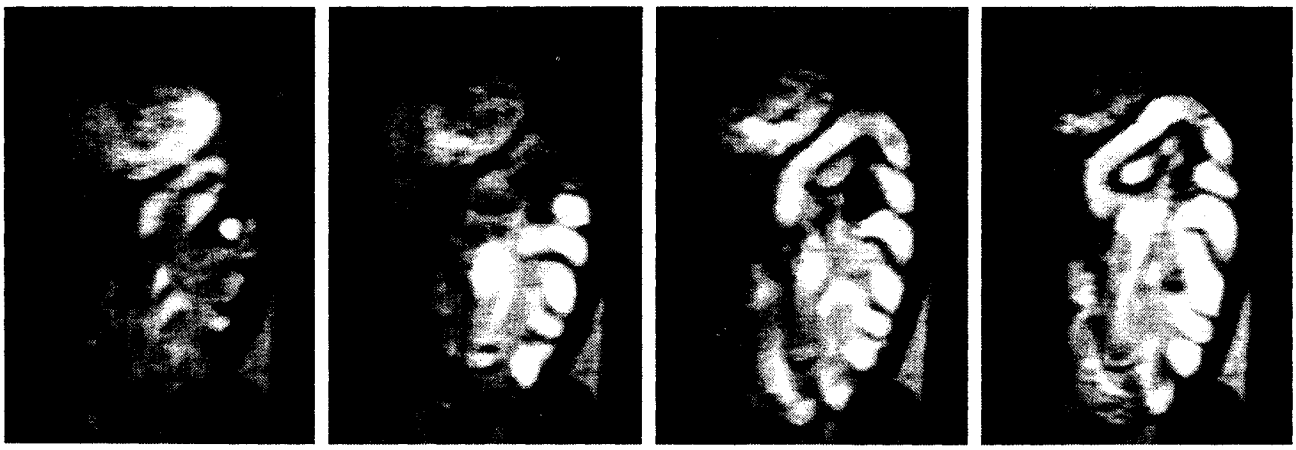

Fig. 3. ^{1}*H-MRI* in vivo: *signal enhancement of the rat gastrointestinal tract by oral contrast emulsion.* Time dependent degree of filling of the intestinal loops with contrast medium from 10 to 85 minutes post dose.

Dosage form	GI tract	MRI technique	Symbol
^{1}H-MRI double contrast technique			
Dark	Bright	^{1}H-MRI	
Combined ^{1}H- and ^{19}F-MRI			
Dark	Bright	^{1}H-MRI	
Bright	Dark	^{19}F-MRI	

Fig. 4. *Visualization of solid oral dosage forms* in vivo *in the gastrointestinal tract by MRI techniques (Overview).*

gavaged a second time, receiving only 10 ml/kg oral contrast emulsion or aqueous oral contrast agent.

Group 3

Group 3 (control group) received a coated microtablet or a microtablet made of polytetrafluoroethylene with 10 ml/kg water or high fat containing oil emulsion (Lipofundin® MCT 20%, Braun Melsungen). After defined transit times the distance which the coated microtablet or the PTFE-microtablet had travelled was ascertained by visual inspection of the gastrointestinal tract.

RESULTS

Signal Enhancement of the Rat Gastrointestinal Tract

Both contrast agents, the contrast emulsion and the aqueous oral contrast agent, produced excellent signal enhancement in the rat stomach (Fig. 2) and the rat intestinal loops (Fig. 3). The signal enhancement of the contrast emulsion in the rat abdomen was slightly better compared to the aqueous contrast agent. Furthermore, the distribution of the oral contrast emulsion in the rat intestinal loops was found to be more homogeneous.

However, we focussed our studies on the aqueous oral contrast agent Magnevist® enteral to avoid aggravating interactions due to fat burden and also to shorten the stomach residence time.

^{1}H-MRI Double Contrast Technique

In our first studies, a ^{1}H-MRI double contrast technique was developed to display tablet formulations in vivo in the rat gastrointestinal tract (Fig. 4): in the ^{1}H-MRI double contrast technique, tablets appear as "dark spots" within a brightly enhanced gastrointestinal lumen.

Longitudinal (T1) and spin-lattice (T2) relaxation times are important parameters that affect the differential display of

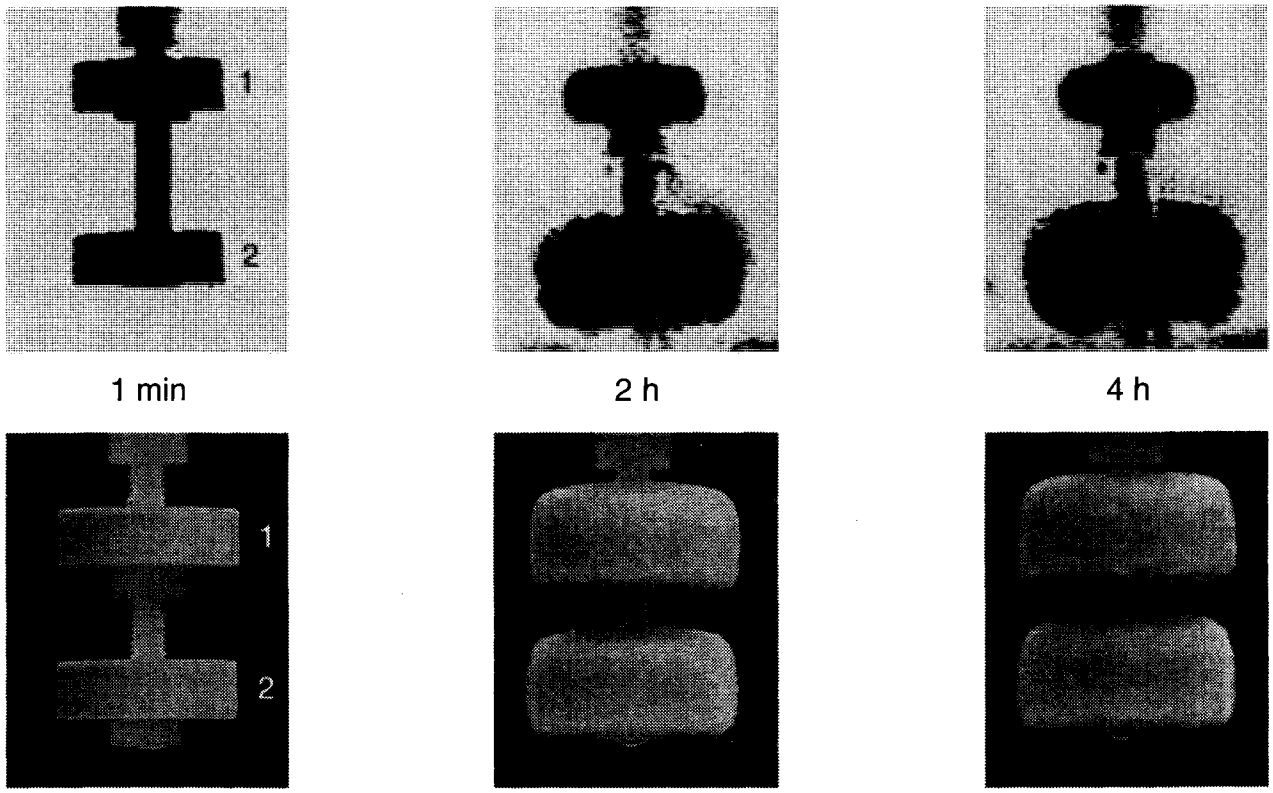

Fig. 5. *Investigation of swelling tablet formulations* in vitro: *^{1}H-MRI versus photography*
Swelling tablet formulations containing 0.025% of magnetite (SPIO) were investigated versus unlabelled tablets in vitro by ^{1}H-MRI (top) for comparison with photographs (bottom).
1: Unlabelled tablet
2: Tablet containing 0.025% of magnetite particles
Outer medium: purified water.

tissues. In T1-weighted MRI experiments superparamagnetic iron oxide particles (SPIO) locally attenuate signal intensity; such particles are commonly used as "negative contrast agents" (15,16). For our studies tablets containing trace amounts of SPIO were prepared.

Gadolinium chelates and ferric ammonium citrate shorten the T1 of freely moving water; such paramagnetic agents are commonly used as "positive contrast agents" (15,16,17). Oil emulsions with a high fat content typically have short T1's (16). Based on results of previous studies (18), the combination of paramagnetic agents and oil emulsions was presumed to result in a good oral contrast agent. Therefore, an oral contrast emulsion was developed. For comparison, aqueous oral contrast agents were also investigated. Comparison of the images of swelling tablet formulations in vitro obtained by ^{1}H-MRI with photographs (Fig. 5) proved the suitability of SPIO as ^{1}H-MRI tablet markers. In ^{1}H-MR images the size of the unlabelled tablet appears to decrease whereas the SPIO-labelled tablet seems to increase in size. However photographic images revealed that both tablets swelled to a similar extent. The reason for this phenomenon is that only the inner, dry tablet core but not the outer gel layer of the swelling unlabelled tablet formulation can be visualized by ^{1}H-MRI.

With the MR parameters used, the swollen gel layer could not be differentiated from the outer medium (purified water) when the tablet was immersed in liquid, which would be the case under in vivo conditions. These results demonstrate that it is necessary to incorporate SPIOs to ensure the correct visualization of the real extent of swollen tablet formulations in ^{1}H-MR images. Furthermore, the photographic images prove that incorporation of SPIOs in solid oral dosage forms is feasible without hampering processes such as swelling, erosion and disintegration.

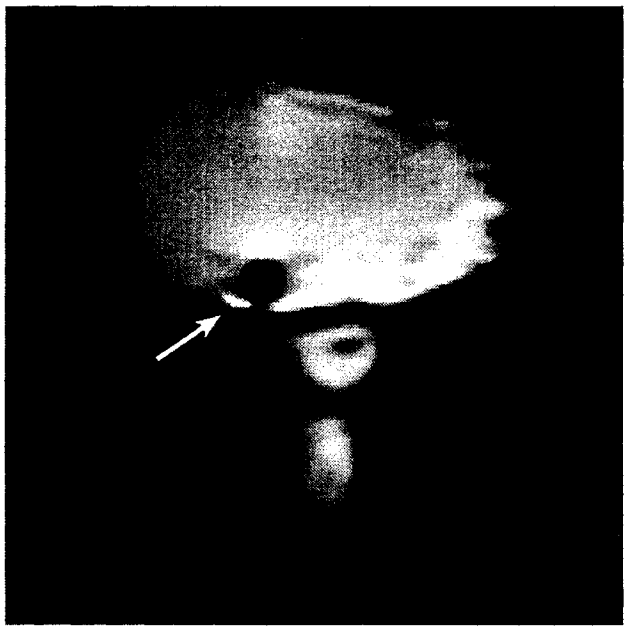

Fig. 6. ^{1}*H-MRI* in vivo: *magnetite-labelled microtablet* in vivo *in the rat stomach.*
Simultaneous visualization of a solid oral dosage form (microtablet) and the gastrointestinal surroundings in the rat by ^{1}H-MRI double contrast technique (signal enhancement by oral contrast emulsion). Magnetite-labelled microtablets could reproducibly be monitored in the rat stomach.

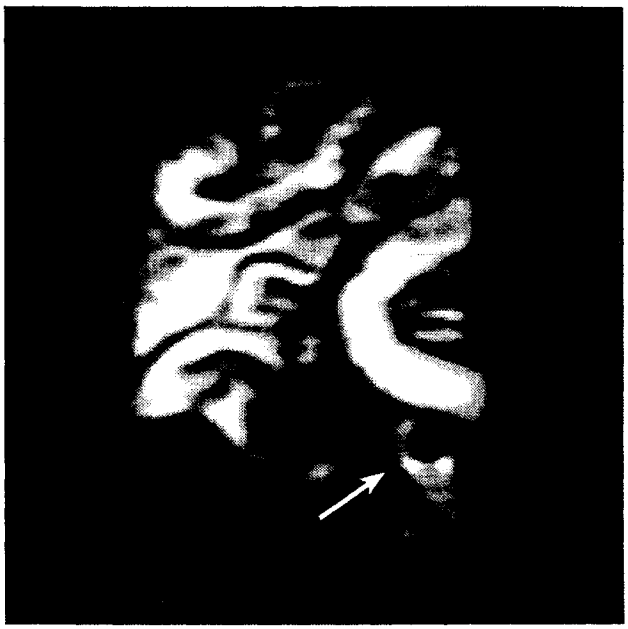

Fig. 7. ^{1}*H-MRI* in vivo: *magnetite-labelled microtablet* in vivo *in the rat small intestine.*
In the rat intestines, visualization of coated, magnetite-labelled microtablets was possible using ^{1}H-MRI double contrast technique (gastrointestinal signal enhancement by aqueous oral contrast agent). Susceptibility effects manifest themselves by signal intensity enhancements (bright spots) close to the microtablet and were used as an additional indicator for the localization of the dosage form within the gastrointestinal tract.

Coated and uncoated microtablets were monitored in the rat stomach (Fig. 6). In the rat intestines, however, uncoated microtablets were invisible, as were tablets with a relatively thin (2.6 % [w/w]) coating. However, after increasing the thickness of the coating to 7.4 % [w/w], coated microtablets were also detected in the rat small intestine (Fig. 7).

Combined ^{1}H- and ^{19}F-MRI

Combined ^{1}H- and ^{19}F-MRI (Fig. 4) was adopted as a second approach for the visualization of solid oral dosage forms (capsules) in vivo.

Normally, fluorine is not present in the gastrointestinal tract. The high MR sensitivity of the 100% natural abundant isotope (19) makes the ^{19}F nucleus suitable as a label for solid oral dosage forms. Most of the fluorinated compounds used in ^{19}F-MRI contain non-equivalent fluorine atoms. This leads to a multiplicity of resonances and insufficient signal intensity. To evaluate the visualization of fluorinated compounds, experiments were performed with perfluorinated agents. Although known to be toxic, the ^{19}F-MR spectroscopy reference compound hexafluorobenzene (20,21) was used in sealed minicapsules for the investigation in a rat model. Hexafluorobenzene is characterized by six chemically and magnetically equivalent atoms, resulting in a single ^{19}F resonance frequency. In ^{1}H-MRI, fluorine labelled capsules appear as "dark spots" within a brightly enhanced gastrointestinal lumen. ^{19}F-MRI only displays the inner lumen of the fluorine filled capsule as a bright

spot. Finally, the ^{1}H- and ^{19}F-MR images can be superimposed to identify the dosage form unambiguously.

Analogous results were obtained using minicapsules filled with hexafluorobenzene in the rat stomach (Fig. 8).

DISCUSSION

In previous studies ^{19}F-NMR was used for the detection of nylon capsules filled with a fluorinated agent in vivo (22). We focussed on the in vivo visualization by ^{1}H-MRI of disintegrating pharmaceutical tablet formulations in the rat gastrointestinal tract. Suitable labelling techniques for dosage forms are not described for ^{1}H-MRI applications and had to be developed for our studies. Our approach of labelling tablets with magnetite particles which do not bias the disintegration processes was reproducible. To display such tablet formulations and their gastrointestinal surroundings simultaneously in vivo in a rat model, special contrast combinations were needed. In the ^{1}H-MRI double contrast technique we developed, the microtablets appeared as "dark spots" within a brightly enhanced digestive lumen and were successfully monitored in the rat stomach. The signal enhancement of the digestive lumen was provided by the orally administered contrast agents "oral contrast emulsion" or "aqueous oral contrast agent".

Due to the incorporated superparamagnetic magnetite particles, susceptibility effects were observed around the microtablets. These susceptibility effects are due to a local perturbation of the homogeneity of the magnetic field and appear as increased signal intensities (23,24). Susceptibility effects manifest themselves as enhanced boundaries or bright spots (24). Therefore, these susceptibility effects were used as an additional indicator for the depiction of the dosage forms within the gastrointestinal tract.

In the rat intestines, however, visualization of the microtablets proved to be more difficult: although laparotomy revealed that the coated microtablets had passed the sphincter pylori, no tablets could be detected at first in the MR images regardless of the contrast agent used. To avoid interactions due to fat burden with respect to expected effects on normal gastrointestinal physiology, such as prolonged stomach residence time, the aqueous oral contrast agent Magnevist® enteral was used routinely. Magnevist® enteral-concentrate contains Gd-DTPA, mannitol and buffer and may still have some side effects due to mannitol, like possible diarrhea, vomiting, nausea and flatulence (14,16). Apart from increased bowel movements, such side effects were not observed in the animals in our studies. For the evaluation of solid oral dosage forms under normal conditions in vivo by such an approach, the use of contrast agents interfering with the GI physiology must be avoided. From pilot experiments with a more powerful scanner, however, we have preliminary evidence that oral contrast agents might not be necessary at all.

After thickening the coating to reduce swelling in the rat stomach, visualization of the microtablets in the rat small intestine was also successful. Potential reasons for the difficulties of visualizing the microtablets in the rat intestines might be, I) a too fast disintegration of the microtablets after stomach passage, II) the irregular distribution and signal of the contrast media in the rat intestines or, III) intestinal contents interfering with the signal of the (disintegrated) tablets. However, the experiments using fluorine-labelled minicapsules indicated that the interference problem can be solved with combined ^{1}H- and ^{19}F-MRI. Although known to be toxic, we used hexafluorobenzene in sealed minitubes as a proof of principle for the in vivo localization in the rat GI tract, anticipating that safe polyfluorinated labelling compounds might become available for such purposes in the future.

In conclusion, the findings show that the simultaneous visualization of solid oral dosage forms and their gastrointestinal environment in a rat model can be achieved by MRI. A ^{1}H-MRI double contrast technique allowed us to depict and observe pharmaceutical dosage forms in the rat stomach in vivo reproducibly. Provided they were prevented from disintegration by an appropriate coating, the visualization of tablets in the rat intestines was also possible. ^{1}H-MRI might serve as a promising tool to observe pharmaceutical dosage forms in the gastrointestinal tract not only in the rat but also in human beings. The excipients are pharmaceutically approved and labelling agents on magnetite basis are available for MR examinations in man. A pilot project to investigate this possibility is contemplated.

Our studies proved that superparamagnetic iron oxide particles (SPIO) are suitable marker agents for solid oral dosage forms in ^{1}H-MRI. Since only trace amounts (less than 0.1% [w/w]) have to be added to utilise their labelling properties, SPIO may be incorporated in various types of pharmaceutical

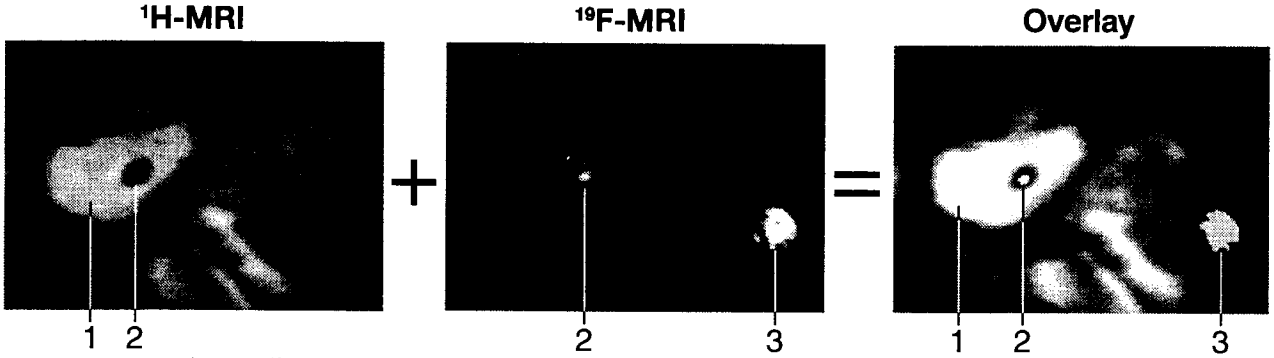

Fig. 8. *Combined ^{1}H- and ^{19}F-MRI* in vivo: *fluorine-labelled minicapsule* in vivo *in the rat stomach.*
Fluorine-labelled minicapsules were visualized in the rat stomach by combined ^{1}H- and ^{19}F-MRI in vivo.
1: Signal enhanced rat stomach (aqueous oral contrast agent)
2: Minicapsule, content: hexafluorobenzene (model substance)
3: Reference (hexafluorobenzene)

dosage forms without disturbing any in vitro or in vivo behavior. In consequence, the investigation of the in vivo behavior of a wide range of pharmaceutical formulations will be practicable by ^{1}H-MRI.

Combined ^{1}H- and ^{19}F-MRI may offer a means to visualize and unambiguously localize solid oral dosage forms in more distal regions of the rat gastrointestinal tract. To perform such studies in man, however, it would be necessary to identify suitable non-toxic fluorine compounds.

Studies correlating MRI examinations with drug plasma levels could provide valuable information about the in vivo behavior of single unit dosage forms. This information, especially on the main sites of in vivo processes such as swelling, disintegration, possible bioadhesion, drug release and absorption, would be useful for the targeting of solid oral dosage forms to different parts of the gastrointestinal tract. The correlation of MRI data with drug plasma levels and in vitro dissolution profiles would give complementary information for the development of solid oral dosage form design.

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