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Review

Benchtop-NMR and MRI—A new analytical tool in drug delivery research

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ABSTRACT

During the last years, NMR spectroscopy and NMR imaging (magnetic resonance imaging, MRI) have been increasingly used to monitor drug delivery systems in vitro and in vivo. However, high installation and running costs of the commonly used superconducting magnet technology limits the application range and prevents the further spread of this non-invasive technology. Benchtop-NMR (BT-NMR) relaxometry uses permanent magnets and is much less cost intensive. BT-NMR relaxometry is commonly used in the food and chemical industry, but so far scarcely used in the pharmaceutical field. The paper shows on several examples that the application field of BT-NMR relaxometry can be extended into the field of drug delivery, including the characterisation of emulsions and lipid ingredients (e.g. the amount and physicochemical state of the lipid) and the monitoring of adsorption characteristics (e.g. oil binding of porous ingredients).

The most exciting possibilities of BT-NMR technology are linked with the new development of BT-instruments with imaging capability. BT-MRI examples on the monitoring of hydration and swelling of HPMC-based monolayer and double-layer tablets are shown. BT-MRI opens new MRI opportunities for the non-invasive monitoring of drug delivery processes.

Contents

1. Introduction

During the last years, NMR spectroscopy and NMR Imaging (magnetic resonance imaging, MRI) have been increasingly used to monitor drug delivery systems in vitro and in vivo. The majority of the in vitro applications of MRI are linked to the monitoring of the hydration, swelling and erosion of matrix tablets (Baumgartner et al., 2005; Fyfe and Blazek-Welsh, 2000; Kojima and Nakagami, 2002; Tritt-Goc et al., 2005). Preclinical in vivo applications of MRI on mice and rats include studies of the fate of biodegradable polymers, liposomes, mucoadhesive polymers and cells (Albrecht et al., 2006; Arbab et al., 2004; Beckmann et al., 2007; Kremser et al., 2008; Mäder et al., 1996; Torchilin, 2002). In addition to drug delivery, MRI has also unique preclinical applications in monitoring the efficiency of drug candidates (Beckmann et al., 2007; Rudin et al., 1999). Furthermore, MRI has also been used to follow the fate of oral dosage forms in man in relation to ingested food (Steingoetter et al., 2003). An overview on drug delivery-related MRI applications has been published by Richardson et al. (2005). The usefulness and capabilities of MRI are generally well appreciated in the drug delivery community. However, very high installation and running costs of the commonly superconducting magnet technology limit the application range and prevent the further spread of MRI.

Commercial low cost Benchtop-NMR (BT-NMR) systems with permanent magnet technology have been used in the food and chemical industry since many years. They are much cheaper compared to high field superconducting NMR machines, but they were not capable to acquire NMR spectra or images. Instead, BT-NMR machines were mainly used to detect the total amount of protons and their relaxation times T1 (spin lattice) or T2 (spin–spin). The relaxation times correspond to different materials (e.g. oil and water; water and polymer) and/or to different states of the same

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material (molten or solid, free or adsorbed). Also the BT-NMR-based measurement of diffusion coefficients is common.

Chemistry-related applications include the monitoring of crystallisation processes in polymers (Hertlein et al., 2006). As an example, one of the investigated polymers was polycaprolactone, which demonstrates the potential of BT-NMR in polymeric drug delivery (e.g. characterisation of polymers after melt extrusion or spray drying under different storage conditions). BT-NMR is also useful to monitor cross-linking of polymers. Chinn et al. suggested recently the implementation of an automated low-field NMR relaxometer for quality control of polymers in a production setting (Chinn et al., 2007). BT-NMR has also been used in the petrol industry to investigate the porosity distributions of rocks (Mai and Kantzas, 2007).

Guichet et al. describe the characterisation of clay suspensions by BT-NMR (Guichet et al., 2008). They measured the diffusion coefficients and the relaxation times under the influence of salts and related the NMR data to inter- and intra-particle distances and aggregation phenomena.

The majority of the BT-NMR relaxometry applications have been developed and implied in the food industry (see review by Hills, 2006). Examples include the measurement of water content and mobility in cookies and the interactions between milk and cereals (Cornillon and Salim, 2000), the direct measurement of phase transitions in milk fat during cooling of cream (Bertram et al., 2005). Other authors used BT-NMR relaxometry to investigate the effects of salt on the water mobility in potato tissue (Straadt et al., 2008). Several studies focus on the oil and water content and status in fish (Veliyulin et al., 2005; Aursand et al., 2008).

Assifaoui et al. used BT-NMR relaxometry to characterize biscuit, which is a complex system composed of many components, including starch, gluten, lipids (flour constituents), sugars, fats and water (Assifaoui et al., 2006). They observed different population which were assigned to intra- and extra-granular hydrophilic protons and lipid protons.

Other studies describe the BT-NMR measurement of droplet sizes in o/w emulsions (Denkova et al., 2004; Gabriele et al., 2009) and in butter (Van lent et al., 2008) and the ageing of proteins (Kemps et al., 2007). Using NMR self diffusion and relaxation parameters, the influence of fat globule membrane composition on water holding capacity and water mobility in casein rennet gel was studied by BT-NMR (Metais et al., 2006). BT-NMR has also been used for the assessment of oil quality (Prestes et al., 2007). Stangierski and Baranowska used BT-NMR to study the dynamics of water binding in enzymatically modified poultry meat (Stangierski and Baranowska, 2008). Transglutaminase treatment caused a crosslinking of the meat proteins, which increased the texture and water binding capacity. Because these effects have been shown to be time dependent, BT-MRI could be useful to optimize the enzymatic process by the measurement of the T2 relaxation times.

Many food systems are very similar to drug delivery systems with respect to their general composition (e.g. starches, celluloses, lipids, water) and their physicochemical properties (not regarding their regulatory aspects). Therefore, BT-NMR relaxometry should have a high potential in the field of drug delivery. This statement is supported by a recent publication of Kuentz et al., which used BT-NMR to monitor the status of water in gelatine and HPMC capsule shells (Kuentz et al., 2006).

NMR relaxometry and the measurement of diffusion coefficient give important information, but in many cases, a spatial resolution by MRI would be desirable. Many papers exist on MRI in drug delivery, but these were mainly acquired with high field superconducting MRI machines. The general trend in MRI was to move to very high fields, to achieve a better resolution and higher sensitivity. In this aspect, BT-MRI appears like a ghost driver on the highway. On the other hand, increasing installation and running costs limit the spread of MRI. In addition, small and portable MRI equipment would be desirable and open new opportunities.

There are indeed, to best of our knowledge, only a very small number of publications which describe the use of BT-MRI. The reasons are probably the following: (i) commercial equipment was established only recently and not well known to the scientific community, (ii) BT-MRI has intrinsic limitations due to the low field (causing lower sensitivity) and less homogeneity of the magnetic field (leading to less resolution and faster T2*relaxation). However, the low installation and running costs are very attractive. So the key question is, whether or not sufficient resolution can be obtained by BT-MRI.

Blümichs group in Aachen developed the so-called "NMR-mouse", which overcomes the object size restrictions of NMR. Such "single sided NMR" systems have a small size and can be placed even on large objects (even studies on castles have been done). They permit mobile NMR-measurements and have therefore a high degree of flexibility. The history, obstacles and the fascinating progress of this technology have been reviewed very recently (Blümich et al., 2008). This mobile NMR technology can also be used for spectroscopy and Imaging experiments (Perlo et al., 2005a,b). Mainly 1D-profiles have been published, from a very broad range of objects and subjects including polymers, food, tendon, skin, soil, wood stones, old master paintings and even mummies (!) (Blümich et al., 2008). The resolution has been increased with time and the possibility of 1D-skin profiling certainly demonstrates: (1) the resolution of this method and (2) the potential for dermopharmaceutics. The system has now been commercialized and further progress can be expected.

Within the food area, BT-MRI has been used to monitor the heterogeneity of soft caramel candy filled with a chocolate creme (Cornillon and Salim, 2000).

BT-MRI has been used for drug delivery processes only very recently. It has been shown that the resolution of BT-MRI is high enough to resolve the hydration and swelling of floating noneroding, poly-(vinylacetate)-based matrix tablets (Strübing et al., 2008b) and to characterize the polymer hydration and CO_2 formation inside coated floating tablets (Strübing et al., 2008a). In a further study, BT-MRI has been applied to characterize commercial and lab-made osmotic controlled release tablets (Malaterre et al., in press). A detailed monitoring of the hydration of both the push and drug layer was achieved. Furthermore, it could be shown that unbalanced composition of both layers may lead to bypassing of the push layer and incomplete release (Malaterre et al., in press).

In the following section, several examples for pharmaceutical applications of BT-NMR/BT-MRI will be presented. It should be underlined that the main focus is to show the principal suitability of BT-NMR and BT-MRI in drug delivery. It was not the intention to cover all applications. Instead, we would like to stimulate the use of this new technology.

2. Examples for pharmaceutical applications of BT-NMR/BT-MRI

The BT-NMR/MRI instrument is shown in Fig. 1. It is temperature-controlled and permits both relaxometry measurements and Imaging. A typical example of BT-NMR relaxometry is shown in Fig. 2. The T2 relaxation decay of parenteral o/w- emulsions consists of two main contributions which can be assigned to the lipid (faster decay) and water (very slow decay). The higher oil content of the parenteral emulsion with a lipid content of 20% leads to a more pronounced decay during the first 400 ms compared to the 10% emulsion. A change of the lipid or lecithin content and/or composition would affect the relaxation curve. In general, the relax-

Fig. 1. (Left) NMR-MRI-Benchtop system consisting of the (1) temperature controlled permanent magnet with resonator, (2) power supply and electronic accessoires and (3) computer and (Right) permanent magnet with resonator.

ation curves can be fitted by mono-, bi- or multi-exponential decay, reflecting the existing of a homogenous or multicomponent species.

Furthermore, a more detailed data analysis of the relaxation data can be achieved using the inverse Laplace transformation. It results in a plot of the distribution of the relaxation times as shown in Fig. 3. The water protons have a long T2 relaxation time (>1 s). The lipid protons relax faster and show a multimodal distribution of relaxation times.

The relaxation times of ingredients and formulations depend on the material and the processing as shown in Fig. 4. The middle chain partial glycerides Capmul MCM have, compared to middle chain triglycerides (Capmul MCM) shorter relaxation times (maxima around 85 ms compared to 240 ms). The encapsulation of MCT within a starch or starch/caseinate matrix leads to a solid product and induces a drop of the MCT relaxation times (see Captex CA and Captex MCT 70). A stronger interaction between the liquid MCT and the solid encapsulating material is seen for the lower lipid load (25% in Captex CA compared to 70% in Captex MCT 70%). The MCT oil in the Captex CA shows clearly a maximum around 90 ms (compared to 240 ms of bulk MCT) and a shoulder around 15 ms, which indicates the existence of different MCT populations (strong and less tightly bound oil).

The adsorption on porous carriers is an alternative to encapsulation to transform liquid lipid formulations into an oral solid dosage form. MCT was adsorbed on Neusilin®, an amorphous magnesium aluminium metasilicate (Al_2O_3–MgO–1.7SiO_2–xH_2O). Fig. 5 shows the distribution of T2 relaxation data of pure MCT and different

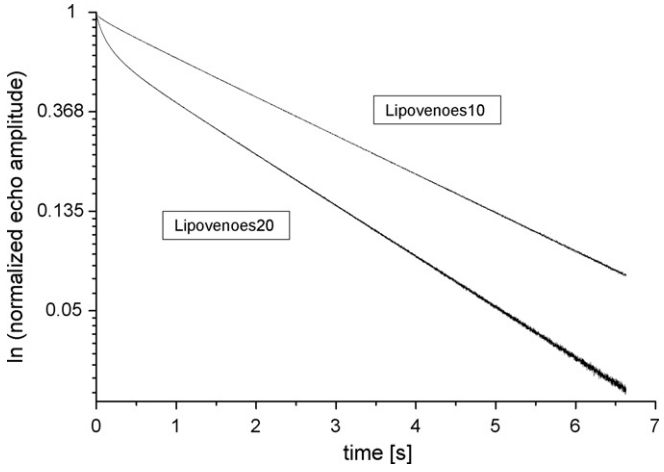

Fig. 2. T2 relaxation decay of parenteral fat emulsions. The two phase decay caused by a fast relaxation of oil and a slow relaxation of water is clearly visible in the sample with a lipid load of 20%.

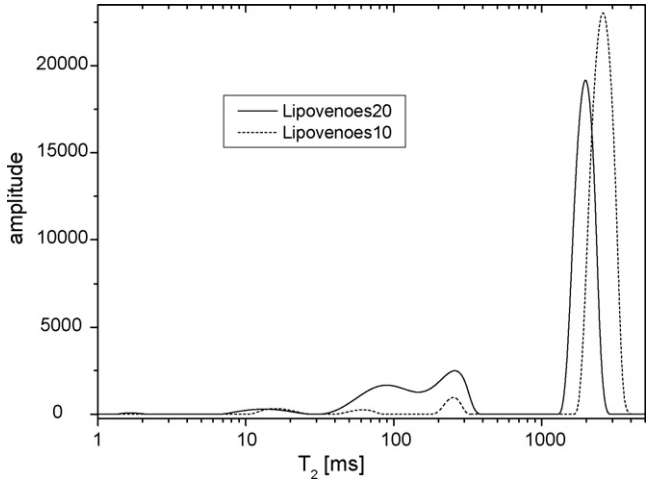

Fig. 3. Distribution of T2-relaxation times within parenteral fat emulsions. Water has a long relaxation time (>1000 ms), the relaxation times of the oil and the lecithin show a multimodal distribution of shorter relaxation times with maxima around 15, 70 and 270 ms. Increasing oil loads lead to a higher intensity of the oils signals and a slight decrease of the water relaxation time due to the increased relaxation at the lecithin stabilised oil–water interface.

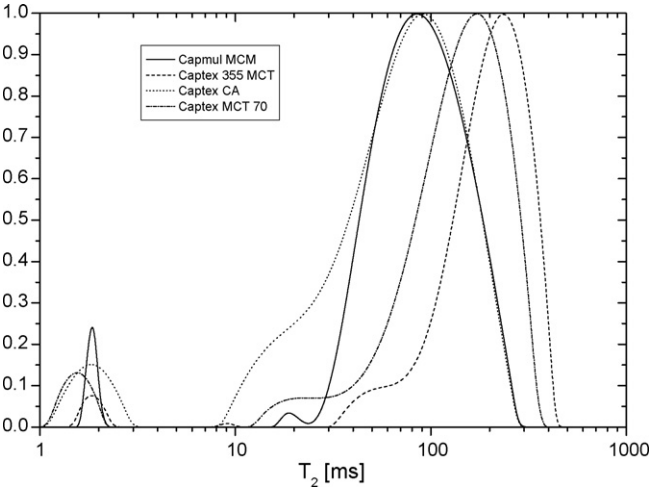

Fig. 4. Distribution of T2 relaxation times for different lipid ingredients. Captex 355 MCT is a liquid mixture of MCT (glycerol mainly esterified with capyrlic and capric acid); Captex CA is a dry powder consisting of MCT and food starch (lipid content around 25%), MCT 70 is a starch caseinate powder with a MCT content of 70%. Capmul MCM consists mainly of middle chain mono and diglycerides. Note that encapsulation of MCT leads to a drop of the T2 relaxation times due to the interaction of the liquid oil with the encapsulating solid material. The signal amplitudes were adjusted to equal height.

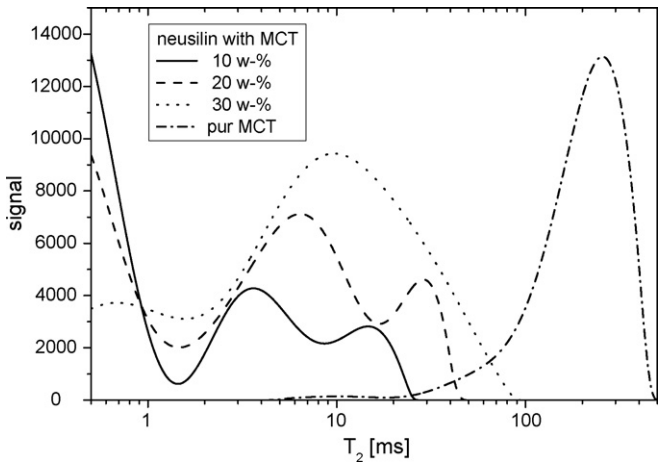

Fig. 5. Distribution of relaxation times of MCT oil adsorbed on Neusilin. The T2 relaxation time of the oil is considerable decreased due to the adsorption on the solid Neusilin matrix.

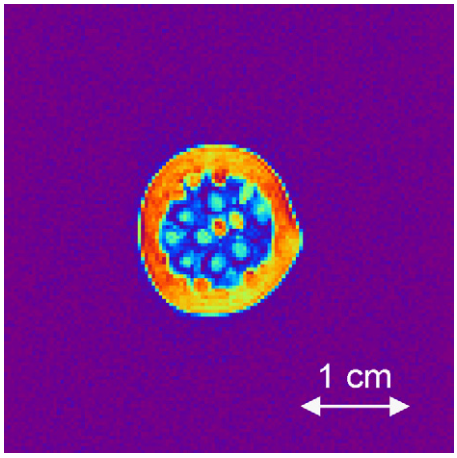

Fig. 6. Benchtop MRI of a rosehip of a dog rose. The outer layers give a bright contrast, the core has low signal intensity due the low water content. The single seeds within the core are clearly visible: 40 mm × 40 mm, 128 × 128.

MCT/Neusilin mixtures. The pure MCT has a distribution of relaxation times with a small part in the range between 20 and 100 ms and the main part in the 100–500 ms range. Adsorption on the solid carrier lead to a dramatic decrease of the relaxation times. For the lowest oil load of 10%, the majority of the MCT is very strongly bound with T2 relaxation times of less than 1 ms. In addition to the very strongly bound part of MCT molecules, two other MCT populations exist which are less bound. Their relaxation maxima

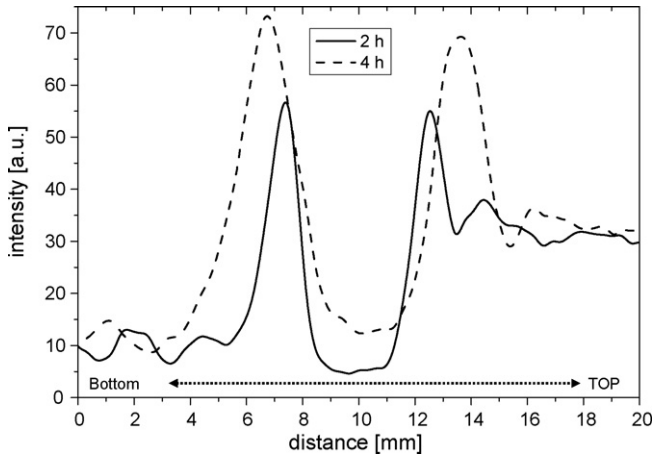

Fig. 8. MRI signal intensity profiles of HPMC tablets (see Fig. 7) after 2 and 4 h. The signal intensity is high in the hydrated polymer layers and low in the dry tablet core.

are around 4–5 ms and 10–20 ms. All MCT molecules relax within 30 ms which indicates a strong binding. The increase of the oil load from 10 to 20% and 30% leads to an increase of the overall proportion of the moderately bound MCT molecules and their relaxation times. The experimental data indicate that Neusilin binds few percentages of MCT very strongly and thereafter, a still strong, but decreased interaction is observed. Within the observed MCT load (10–30%), the existence of MCT with bulk properties can be excluded due to the lack of a relaxation maximum around 240 ms. Ongoing BT-NMR relaxation studies with different ingredients indicate that the solid–liquid interaction depends on the origin of the characteristics of the solid and liquid material (kind of material, supplier, batch) and the processing. In addition to oily liquids, BT-NMR relaxometry can also be applied to monitor the interaction of water with solids (e.g. water binding by MCC, starch; granulation and extrusion processes, etc.). The results of ongoing studies in our laboratory indicate that BT-NMR is useful tool to characterize solid–liquid interactions in a quantitative manner.

The application of BT-NMR relaxometry mainly presents an adoption of methods from the food and chemical industry to the pharmaceutical field. BT-MRI is, however, a new possibility. The 20 MHz BT-MRI instrument shown in Fig. 1 is dedicated to the characterisation of monolithic oral dosage forms. BT-MRI clearly has, compared to standard superconducting MRI instruments, advantages with respect to installation and running costs. It has, however, to demonstrate that useful MRI images can be obtained. An illustration of the resolution capacity is shown in Fig. 6. The image of a rosehip of a dog rose clearly provides the inner structure and single seeds are visible. In the following, BT-MRI was applied to monitor the hydration and swelling of a HPMC tablet. The images displayed

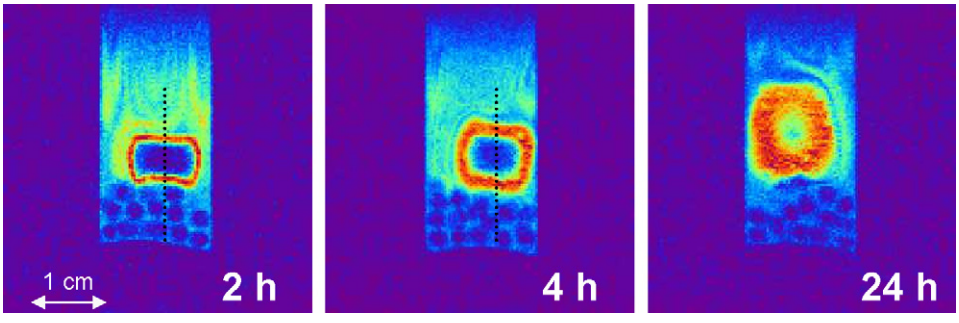

Fig. 7. BT-MRI monitoring the hydration and swelling of a 6cp HPMC tablet. The dotted lines show the position of the intensity profile displayed in Fig. 8. The bottom of the vial was filled with glass spheres.

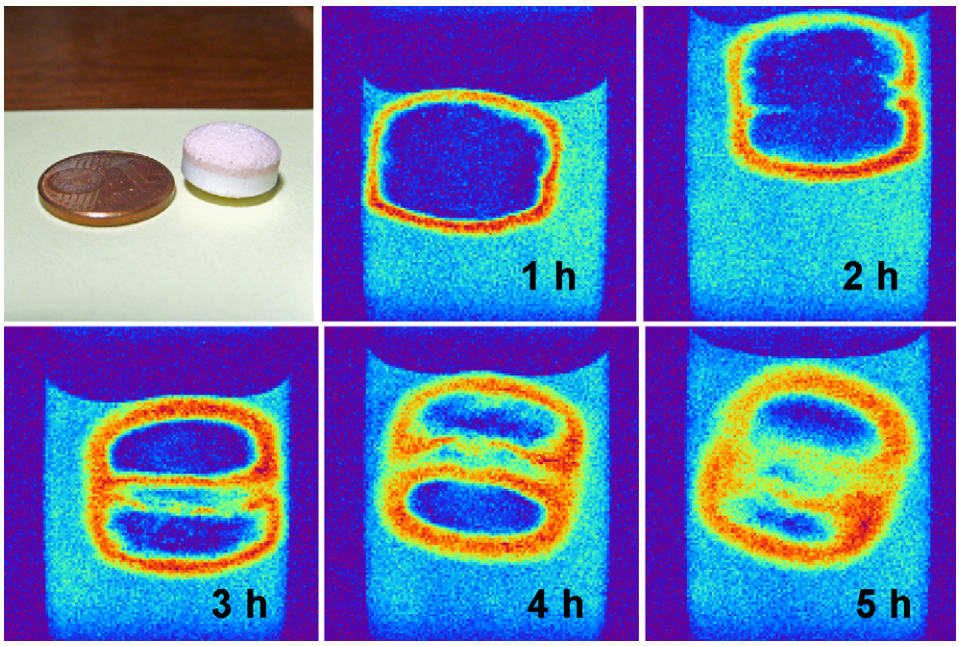

Fig. 9. Photograph (double-layer tablet and 1 eurocent) and BT-MRI images of HPMC-based double-layer tablets "formulation A" after different exposure times to buffer. The images show clearly the water penetration between the lower and upper layer.

in Fig. 7 show clearly the water penetration and swelling of the tablet. After 24 h, the water has reached the tablet core, although the hydration is still stronger in the outer layers. The intensity profiles are shown in Fig. 8. The swelling is clearly visible by the shift of the signal maxima. The distance between the maxima is increasing from 5.2 to 7 mm. The higher signal intensity on the top of the tablet is caused by the increased polymer concentration of eroded HPMC.

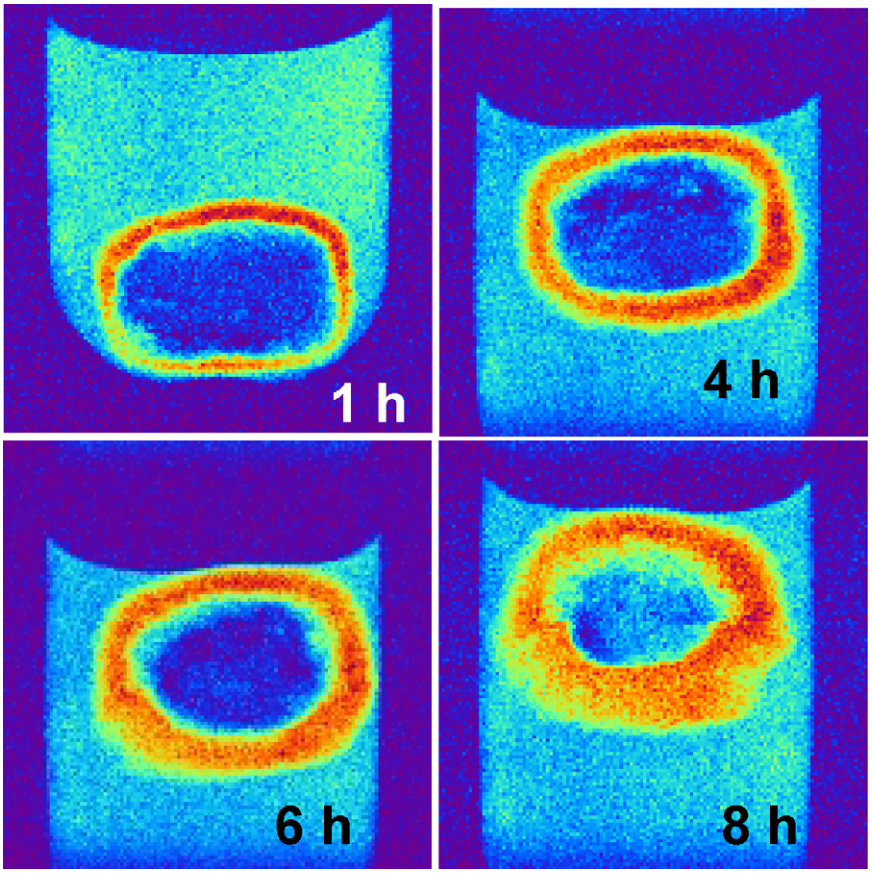

Fig. 10. BT-MRI images of the double-layer tablet "formulation B" after different exposure times to buffer. Water penetration between the layers does not occur, indicating the high quality of the layer interface.

In further experiments, BT-MRI was used to investigate double-layer tablets. Double-layer tablets are used to separate incompatible drugs or to obtain different release rates. They are also used for floating systems because to achieve an optimization of the floating and drug layer. An example of an experimental formulation of a double-layer floating tablet is shown in Fig. 9. The BT-MRI images clearly show that water penetrates into the layer interface of tablet formulation A. This observation indicates that the layer interface is not tight and the connection between the layers is not as strong as it should be. Water penetration could potentially lead to a separation of the drug and the floating layer. Tablet formulation B has a different composition and does not show any water penetration into the layer interface as shown in Fig. 10.

3. Summary and outlook

In summary, BT-NMR relaxometry and BT-MRI are useful techniques to characterize non-invasively drug delivery systems in vitro. Applications of BT-NMR relaxometry include, but are not limited to the measurement of the lipid and water content, the characterisation of adsorbed liquids, the monitoring of crystallisation processes, the measurement of the solid fat index. BT-MRI is a new technique which provides, despite the lower frequency compared to superconducting magnets, sufficient and often comparable resolution to monitor tablet hydration and swelling. Further developments are ongoing and a new generation of BT-MRI instruments with improved resolution and a USP flow have now entered the market. Furthermore, first pilot studies indicate the possibility of in vivo BT-MRI on mice, which would ease the preclinical use of MRI to a large extent. We strongly believe that BT-NMR relaxometry and BT-MRI will spread into many drug delivery research laboratories in academia and industry.

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