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Expert Opinion

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Using quantitative magnetic resonance methods to understand better the gel-layer formation on polymer-matrix tablets

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Introduction: Magnetic resonance imaging is a powerful, non-invasive technique that can help improve our understanding of the hydrogel layer formed on swellable, polymer-matrix tablets, as well as the layer's properties and its influence on drug release.

Areas covered: In this paper, the authors review the NMR and MRI investigations of hydrophilic, swellable polymers published since 1994. The review covers NMR studies on the properties of water and drugs within hydrated polymers. In addition, MRI studies using techniques for determining the different moving-front positions within the swollen tablets, the polymer concentration profiles across them, the influence of the incorporated drug, and so on, are presented. Some complementary methods are also briefly presented and discussed.

Expert opinion: Using MRI, the formation of a hydrogel along with simultaneous determination of the drug's position within it can be observed non-invasively. However, the MRI parameters can influence the signal's intensity and therefore they need to be considered carefully in order to prevent any misinterpretation of the results. MRI makes possible an *in situ* investigation of swollen-matrix tablets and provides valuable information that can lead, when combined with other techniques, to a better understanding of polymeric systems and a more effective development of optimal dosage forms.

Keywords: drug release, hydrogel, hydrophilic polymer, magnetic resonance imaging, matrix tablet, nuclear magnetic resonance, swelling

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1. Introduction

Modified-release matrix tablets have been used extensively by the pharmaceutical industry as one of the most successful oral drug-delivery systems. The dominant matrix excipients for most modified-release formulations are hydrophilic polymers, which hydrate when in contact with the release medium. After the concentration of the medium is high enough, the glassy polymer transforms into a rubbery state and the polymeric molecules become flexible (i.e., the glass transition temperature T_g of the polymer reduces to the system temperature T), forming a hydrogel layer that regulates the penetration of the medium into the matrix and the dissolution of the incorporated active ingredient. At the surface of the hydrogel layer some erosion may occur due to polymer dissolution through the chain disentanglements. As a result of all these processes running at the same time, different moving fronts have been postulated. The boundary between the hydrogel layer and the medium is called the erosion front. The diffusion front is an interface between the undissolved and the dissolved drug within the hydrogel layer. The boundary where

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Article highlights.

- Drug release from hydrophilic matrix tablets is regulated by the hydrogel's formation around the dry matrix core. The hydrogel regulates the drug-release kinetics and the mechanism, therefore its thickness and properties should be known so as to be able to anticipate the drug-release dynamics.
- Nuclear magnetic resonance can provide useful information about the hydrogel's properties at different polymer concentrations in different conditions (medium's properties, at different temperatures, etc.).
- Magnetic resonance imaging is capable of providing, in a non-invasive way, internal images of the investigated materials and can therefore give information about moving-fronts' (penetration, swelling and erosion fronts) positions and the hydrogel's properties *in situ*. By combining the NMR parameters obtained from hydrogels at different polymer concentrations, the polymer concentration profiles across the formed hydrogel can be determined for different swelling times.
- The combination of MRI and USP-4 apparatus can simultaneously measure the polymer-swelling kinetics and the drug release, and can thus link together the hydrogel properties with the drug release.
- The combination of the data obtained with different methods can provide the information needed to design hydrophilic matrix tablets with the desired drug-release kinetics.

This box summarizes key points contained in the article.

the glassy polymer transforms into the rubbery polymer is called the swelling front. Furthermore, there is an extra front that is frequently overlooked, referred to as the penetration front, which is the border between the dry glassy polymer and the hydrated glassy polymer, that is, the position of medium's penetration into the dry glassy polymer [1-3].

The hydrogel layer formed on polymer-matrix tablet is important for regulating the drug-release mechanism and kinetics from them. For this reason, numerous parameters have been investigated: the hydrogel layer's thickness and the position of the different fronts within the hydrogel [4,5], the presence of different excipients [6,7], the properties of the selected polymer and the investigated drug substance [8-10], the polymer concentration across the hydrogel, the mesh size of the polymeric network [11], and so on. A large spectrum of mathematical models describing the drug release from the hydrophilic matrix tablets has been developed, and these try to include many of these important parameters. However, in many cases the use of simple empirical or semiempirical models is sufficient; but, when reliable, detailed information is required, more complex, mechanistic theories must be applied [12].

Magnetic resonance imaging (MRI) is a non-invasive method that has the ability to provide internal images of soft materials such as hydrophilic matrix tablets. In addition, it can provide sufficiently high spatial (50 μm) and time resolution to monitor the swelling processes *in situ*. The purpose of this article is to review the current state-of-the-art for magnetic resonance measurements that are relevant to the swelling behavior of hydrophilic matrix tablets and to show the suitability of the technique for following the swelling kinetics and the release of the drug.

2. Brief summary of the techniques used for investigating the swelling process of polymer-matrix tablets

2.1 Studies using optical imaging

The swelling process of polymers has been studied using a variety of techniques. Optical imaging is perhaps the most well established of these. Studies of hydrogel-layer formation have been conducted using a variety of optical imaging methods, which cover techniques ranging from simple pictures of the matrix tablets' cross-sections to advanced video imaging with computer analyses.

Colombo and co-workers [4,13] and Bettini *et al.* [14] have identified the movement of the swelling, diffusion and erosion fronts in the established hydrating-gel layer using colored visual aids. In their method the tablet was placed between two transparent Plexiglas® sheets and the hydrogel formation was monitored from the axial direction of the sample. Simple video optical microscopy was introduced by Papadimitriou *et al.* to follow the swelling of hydroxypropyl methylcellulose (HPMC) *in situ* [15]. They found that the swelling is faster in the axial than in the radial direction as a consequence of the tableting process and relaxation. Gao and Meury introduced another optical-imaging method to determine the HPMC concentration profile across a swollen tablet *in situ*. On the basis of the empirical relationship between the scattered light intensity and the HPMC concentration for equilibrium swollen hydrogels, the polymer concentration profile of the gelled region was estimated. Using the postulated model they determined the position of the apparent hydrogel front, and in this way the hydrogel thickness [16]. Adler *et al.* [17] used fluorescence imaging, such as confocal laser scanning microscopy (CLSM), to monitor the swelling of internal domains within the hydrogel layer by tracking the embedded fluorescent particles, and a soluble fluorophore has been used to monitor liquid ingress into the HPMC matrices [18]. This technique offers good spatial resolution and sensitivity, with an optical sectioning capability and the time resolution necessary to monitor rapid changes. These are important in the early stages of swelling, where the rapid development of a coherent hydrogel diffusion barrier is a critical stage in the establishment of the extended release properties in hydrophilic matrices. The early stages of hydrogel-layer formation *in situ* were thus investigated by CLSM imaging using a cellulose-activated fluorophore, that is, Congo Red. Using this fluorophore, the mapping of the hydrated polymer regions during the development of the early hydrogel layer was possible. Their results revealed a temporal sequence in which the capillary uptake of the hydration medium into the tablet pores is followed

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by a changing morphology of the surface of the HPMC particles, as they swell in a columnar manner to form the nascent gel barrier [19]. The same authors also investigated the increase in ionic strength on HPMC swelling and found that increasing the salt concentration in the hydration medium suppressed the hydrogel layer's growth. The method they proposed provides possible evidence in the form of images for mechanisms that may contribute to salt acceleration of drug release in HPMC matrices [19]. The CLSM technique was also used to investigate the influence of different sugars on early gel-layer formation and on accelerated drug release from HPMC matrices. It was shown that the presence of sugar has a different effect on HPMC particle hydration and swelling with regard to viscosity type. The authors found that the selection of diluents such as microcrystalline cellulose, fine particle size fraction of HPMC and its highest viscosity grade are key parameters for designing HPMC matrices with reduced sensitivity to high concentrations of dissolved sucrose [20-22]. Further, the effects of incorporated alkalizing buffers such as sodium citrate and tris(hydroxymethyl) aminomethane (THAM) on release of the weak acid drug from HPMC matrices were studied by CLSM imaging. The inclusion of each buffering system in HPMC tablets improved the release of drug in alkaline and acidic media. However, the inclusion of THAM was shown to maintain the pH elevation for a greater period and was found to have minimal effect on HPMC particle swelling and gel-layer formation [23,24].

There are also other potent imaging methods for investigating the mechanisms regulating drug release from the dosage forms. One of these is Fourier transform infrared (FTIR) spectroscopic imaging in attenuated total reflection (ATR). The ability to record spatially resolved chemical images as a function of time allowed the dynamic process to be viewed via simultaneous measurement of the distribution of the polymer, drug and water within the pharmaceutical formulations. However, a more detailed description of this method can be found in the cited literature and is out of the scope of this paper [25-27].

2.2 Studies using ultrasound

The formation of a hydrogel layer around the swellable tablets can be followed by a promising non-destructive method using ultrasound [28]. Luprano *et al.* used an ultrasound pulse-echo technique to measure the hydrogel water sorption and monitored the advancement of the swollen–unswollen fronts of polymer films [29]. A further step was made by Leskinen *et al.*, who monitored the erosion and swelling front movements during the tablet-dissolution process simultaneously, using an ultrasound window technique. It was noted that the sensitivity for following the hydrogel formation and thickening by ultrasound monitoring varied depending on the polymer under investigation. The polymers to be studied by ultrasound must possess certain acoustic properties in order to make the medium–polymer interface detectable. These properties also depend on the ultrasound frequency being used. The authors found that multi-front detection is challenging because the hydrogels formed by different polymers may have totally different acoustic properties. Furthermore, owing to limited spatial resolution of these methods, observation of the early stages of polymer swelling can be problematic. In spite of these challenges, the ultrasound window technique introduced in their study has proved to be a promising method for simultaneous multi-front detection [30].

2.3 Studies using texture analyzer

An important characteristic of the formed hydrogel layer is its texture. This can be examined with texture analysis, a penetrometry technique where the material is subjected to a controlled force. From the resulting force–displacement plot, several parameters of the material can be derived that are directly related to the performance of the sample [31]. Although the texture analyzer technique is destructive and does not allow measurements *in situ*, the pharmaceutical applications for quality-control purposes have increased significantly during the past few years, as it is relatively simple, versatile and cost-effective; it is possible to use the same instrument for multiple measurements by changing either the testing probes or the measurement parameters [32]. Jamzad and co-workers studied the influence of water-soluble and insoluble excipients on the dynamics of hydration, front movement, erosion and drug release from HPMC matrix tablets containing a water-soluble drug. They determined the swelling front's position as well as the hydrogel layer's thicknesses. They found that within the context of hydrophilic polymeric matrices containing a water-soluble drug, excipients should not be regarded as neutral or simple additives because they are certainly capable of altering the water penetration, erosion, and hence the mechanism of drug release [6,33]. In addition to HPMC and PEO [6,33-34], xanthan-based tablets were also investigated using texture analysis [7,35]. It was found that the firmer matrix structure does not necessarily lead to a slower drug release because the hydrogel-layer thickness, polymer-network mesh size and the water distribution within the hydrogel are also important. It was concluded that only combinations of different techniques reveal the detailed structure of swollen matrix tablets that is necessary to understand the release of the active substance from them.

3. Short theory and principles of NMR and MRI

Nuclear magnetic resonance (NMR) is based on the phenomenon that nuclei possessing a magnetic moment (e.g., ^{1}H, ^{19}F, ^{31}P, ^{13}C, ^{2}H, etc.), after being placed in an external magnetic field, tend to align with the magnetic field, causing a weak net magnetization along the applied magnetic field. The application of a radiofrequency (rf) magnetic field alters the spin population distribution and consequently induces a small voltage in the surrounding rf coil by a process of electromagnetic induction

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that generates the NMR signal. Unfortunately, the NMR signal is intrinsically weak, but it increases with increasing gyromagnetic ratio γ (i.e., a property that varies for different nuclei, and is largest for the hydrogen nucleus) and increasing magnetic field strength. As the rf pulse is turned off, the spins relax back to the equilibrium position owing to spin-lattice (T_1) and spin-spin (T_2) relaxation processes (**Figure 1**). The NMR signal intensity thus depends on the concentration of the observed nuclei in the sample, on their relaxation times T_1 and T_2, and on their self-diffusion coefficient (D) [36,37]. Using special NMR pulse sequences, the relaxation times T_1 and T_2 [38,39] and the self-diffusion coefficient [40,41] of different materials can be measured. Those parameters can give valuable information about the local molecular environment and are thus implemented in research conducted on the different properties of matrix tablets, that is, information about the mobility of the water and polymer molecules and about water–polymer interactions in the swollen hydrogel can be obtained from the T_1, T_2 and D measurements. With the application of more complex NMR pulse sequences, a better insight into water–polymer interactions can be provided [42-44].

Magnetic resonance imaging utilizes magnetic field gradients that are applied across the static magnetic field in order to obtain spatial information about the system. In the case of MRI, only the NMR signal from a small part of the sample (one pixel) is collected. To reach an adequate signal-to-noise ratio for each pixel in acceptable times, a relatively high NMR signal is needed. Therefore, in most applications high magnetic fields are used and ^{1}H MRI is applied to samples containing ^{1}H nuclei in high concentrations and used to measure the distribution of the water within the investigated samples.

To observe the signal of all the protons in the sample, the *TE* (the time between the signal's excitation and detection) should be much shorter than their T_2 and the repetition time (*TR*) should be long compared with their T_1. As the swelling of the polymer-matrix tablets is a dynamic process and the measuring time is limited to a couple of minutes, usually one-dimensional (1D) or two-dimensional (2D) experiments are performed, depending on the system symmetry. To increase the contrast between the media, hydrogel and dry polymer in the sample, T_1- or T_2-weighted magnetic resonance images, by changing *TE* and *TR*, respectively, or diffusion-weighted magnetic resonance images, by using a pulsed field gradient spin-echo (PGSE) technique, are applied [38]. Moreover, the relaxation times and self-diffusion maps can be used to obtain the spatial distribution of T_1, T_2 and D [38,45]. To improve the time resolution, it is also possible to use faster imaging methods, such as rapid acquisition with relaxation enhancement (RARE) [46-49].

Owing to the limited strength of the magnetic field gradients and their rising time and the use of shape pulses in 2D experiments, *TE* is in the range of a couple of milliseconds. In this time the NMR signal of the solid polymer has already decayed to zero and, by using standard spin-echo MRI pulse sequences, only water protons with a long enough T_2 can be spatially detected. For polymer and water protons with short T_2 values (water in a hydrated glassy polymer and water in a hydrogel with a high polymer concentration), a special magnetic resonance sequence, the single-point-imaging (SPI) pulse sequence, which enables the imaging of protons with short T_2 values and their modifications for spatial encoding of the relaxation times, can be used [50,51]. As the SPI sequence uses phase encoding in all the imaging directions it is time consuming, and, owing to the limited available measuring time during swelling, usually only a 1D SPI sequence can be applied. By combining different magnetic resonance techniques, the quantification of spatial properties during swelling, that is, the penetration, swelling and erosion front positions, and thus the hydrogel thickness together with the polymer concentration across the formed hydrogel can be determined.

In addition to the proton NMR signal, other nuclei can also be detected. If the drug substance incorporated into the matrix tablet contains one of those nuclei, the spatial distribution of the drug and thus the drug release during the polymer swelling can be concomitantly measured using MRI.

4. NMR spectroscopy as an analytical tool for the investigation of swollen polymer-matrix tablets

NMR can give valuable information about polymer properties in the rubbery state that can help in the search for an optimal polymer that will fulfil the specific needs of drug delivery from hydrophilic matrix tablets. The hydrogel's properties and their dependence on temperature changes, polymer concentrations, pH of the medium, drug incorporation, and so on, were studied using relaxation times and the self-diffusion coefficient.

The relaxation times T_1 and T_2 of the water protons are determined by the modulation of the intra- and intermolecular dipolar interactions, the magnetization transfer and the chemical exchange processes between the water and the polymer molecules. Therefore, the measurements of T_1 and T_2 allow a study of the physical and chemical properties of hydrogels [52]. The diffusion coefficient of the incorporated drug can give valuable information about the drug release, while the diffusion of the water is a measure of the water-penetration rate, which determines the kinetics of the hydrogel's formation. In the hydrogels, both drug and water diffusivity can be measured, as the water and drug protons have slightly different NMR signals owing to a chemical shift. This makes it possible to distinguish the spectral lines of the water and the drug.

4.1 Polymer and drug self-diffusion coefficient

It was found that the drug (D_D) and water diffusivity (D_W) decrease exponentially with increasing polymer concentration in the hydrogel, indicating an entangled

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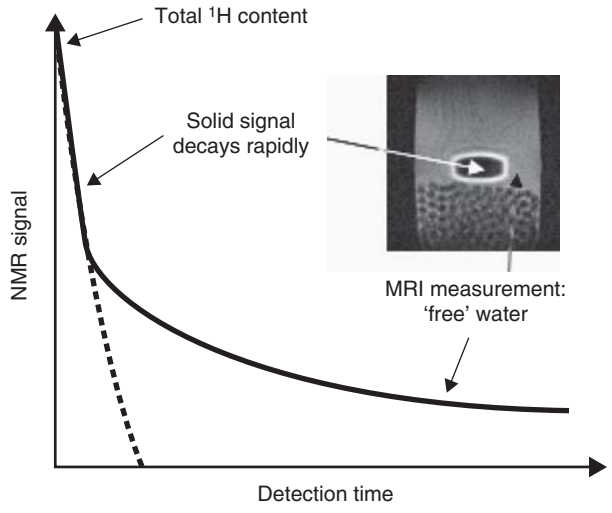

Figure 1. Schematic of basic NMR signal, the free induction decay after a radiofrequency pulse together with an example of a magnetic resonance image of a matrix tablet during swelling.
Adapted with permission from [74].

three-dimensional network structure [53-57] – except for egg albumin, where the relationship is linear and a diluted network structure was proposed [57]. The degree of D_D decrease with polymer concentration depends on the degree of polymerization of the polymer, and is smallest for glucose (a monomer unit of HPMC) and largest for HMPC. Water diffusion, on the other hand, is independent of polymer chain length [53]. D_D is also exponentially dependent on the drug concentration [53,56]. It was also observed that D_D and D_W do not vary significantly with molecular mass of the polymer [53-56]. The temperature dependence of D_D and D_W showed an Arrhenius-type behavior, with similar activation energies for the drug and water, comparable to the hydrogen-bonding energy. Based on these results, the authors concluded that the diffusion barrier for the drug and water is determined solely by the interactions between the water molecules [53]. It was also shown that the smaller drug is more mobile owing to the smaller size and fewer interactions with the polymer [58]. Study of D_D dependence on the drug's molecular mass showed that D_D strongly decreases with increasing molecular mass of the drug [59]. The results for the multicomponent gels (a mixture of HPMC, lactose and drug) showed that D_D is affected by all the existing components, resulting in an additive retarding effect from all the components [53].

From the NMR measurements of D_D and D_W in the presence of various polymers and drugs, it was concluded that medium diffusion depends on the interaction between the medium and the matrix polymer [54], and that the D_D is dictated by the microviscosity of the system and by the steric obstruction mechanism [53,55]. Based on a comparison of the measured data with the theoretical approach, agreement with the free-volume theory [60,61], predicting that drug diffusion is the consequence of jumps in voids, which are created by correlated motions between the water and the surrounding polymer molecules, was confirmed [53,55]. Some deviation from the free-volume theory was observed for the diffusion of larger molecules at higher polymer volume fractions, where other models were proposed instead [54]. A comparison between experimental values with theoretical models gives information about the hydrogel's microstructure connected with the drug's mobility in the hydrogel and thus the drug-release mechanism.

4.2 NMR relaxation times

The temperature dependences of the proton-relaxation times T_1 and T_2 in the hydrogels were used to determine the transition temperature from the glassy to the rubbery state, T_g. The spin-spin relaxation time T_2 is almost constant below T_g and increases significantly with temperature above T_g. The spin-lattice relaxation time T_1 has a minimum at T_g. The T_g values that were determined were verified by the values obtained from a differential scanning calorimetry (DSC) experiment [62-64].

The relaxation times were also used to investigate the water mobility within the hydrogels, to obtain information about the hydrogel's structure (the homogeneity of the hydrogel) and to measure the average number of water molecules bound per polymer repeating unit. In the hydrogel's measured relaxation times there are two exponentials, indicating two types of proton: a 'polymer' pool, comprising non-exchangeable polymer protons ($T_1 \sim 250$ ms and T_2 in the order of hundreds of microseconds); and a 'water' pool, comprising protons of bound and free water and exchangeable polymer protons. The latter are in a fast exchange relative to the NMR timescale, having a single component of T_1 and T_2 (T_1 from hundreds of milliseconds to seconds and T_2 in the range from some to hundreds of milliseconds). The relaxation times of the water pool decrease with increasing polymer concentration [49,65-71], reflecting the increase of interactions between the water and the polymer molecules with increasing polymer concentration. The relaxation times of the polymer pool are, on the other hand, independent of the polymer concentration in the hydrogels of poly(amidoamine)s, suggesting that the mobility of the polymer is relatively constant once the polymer is in contact with the water [65]. By contrast, in the HPMC hydrogels, significant changes in the mobility of the polymer were observed when changing the polymer concentration [69,72]. T_1 and T_2 were found to be independent of the polymer's molecular mass, but T_1 was sensitive to the polymer substitution type in different cellulose ethers [66,67]. From T_1 and T_2 data it is also possible to calculate the average number of water molecules bound per polymer repeating unit. It was found that this is independent of the molecular mass within a given polymer type, but increases with the

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degree of hydrophilic substitution of the polymer chains [66]. The T_1 and T_2 parameters are influenced by polymer crosslinking as well. Calucci *et al.* observed a decrease of both relaxation times with decreasing degree of crosslinking of the hydrogel, indicating that higher crosslinking leads to a more rigid heterogeneous polymer structure [65]. A study of the impact of the medium's pH and ionic strength on the hydrogels made of xanthan, which is an anionic polymer and thus its properties are strongly affected by pH and ionic strength, on the relaxation times and on the mobility of the protons within the hydrogel, showed that T_1 is mostly independent with respect to different media, whereas T_2 relaxation times are significantly lower using pH 1.2 media than for media with higher pH values. This was interpreted as a more restricted mobility of the polymer chains in low-pH media, as the spin-spin relaxation time is strongly correlated with the rigidity of the hydrogel – a slower T_2 decrease, showing a more rigid hydrogel, which was confirmed by the rheological studies [68]. The results obtained by NMR for different hydrogels are summarized in **Table 1**.

5. What can be seen within swollen-matrix tablets using MRI?

To obtain spatial information about the tablet's swelling and erosion, magnetic resonance imaging has been used extensively [73-75]. The technique is non-invasive, fast enough to be able to follow changes during the swelling processes and can give reliable information about the medium's penetration into the matrix tablet and hydrogel formation.

5.1 MRI methods and equipment

Different approaches have been applied to determine the erosion, swelling and penetration fronts and thus the hydrogel thickness during swelling of the matrix tablet. One of the most frequently used approaches is that of T_1-weighted images. In the hydrogel-forming systems the magnetic resonance signal of the hydrogel is higher than the signal of the medium on the T_1-weighted images owing to the longer T_1 of the medium. Furthermore, the MRI signal increases when the polymer transforms from the glassy (the T_2 of which is too short to be observed by a spin-echo MRI sequence) to the rubbery state owing to the longer T_2 of the hydrogel [67,68,76-86]. Therefore, the position of the swelling front is usually determined by the appearance of the MRI signal inside the tablet and the position of the erosion front is determined at the position where the signal decreases to the value of the magnetic resonance signal of the bulk medium (**Figure 2A**). The difference between the swelling front and erosion front position represents the thickness of the hydrogel, which is an important parameter influencing drug release from the hydrophilic matrix tablets.

Another approach to determining the hydrogel thickness is to measure the spatial variation of the spin-spin relaxation time, that is, the T_2 map [49,58,68-70,79,87-94]. Combining the MRI technique with a Carr-Purcell-Meiboom-Gill (CPMG) sequence does not significantly increase the measurement time compared with the standard spin-echo technique. T_2 was found to be changed through the hydrogel, from very short values at the interface between the glassy and rubbery regions to much longer values at the interface between the rubbery hydrogel and the bulk region (**Figure 2B**). As T_2 reflects the rotational and translational freedom of the water molecules, the changes in T_2 over the hydrogel regions indicate that the hydrated polymer in the hydrogel layer close to the glassy state possesses a greater proportion of more tightly bound water and that a strong interaction occurs between the adsorbed water and the polymer [88,91-93]. By using spin-echo-based MRI pulse sequences only protons with long enough T_2 values compared with TE can be observed. To overcome the problem of the short T_2 values of the hydrogels with high polymer concentrations, the SPI technique that enables samples with short T_2 values to be imaged was used [68,72]. As the SPI technique is time-consuming, only 1D imaging can be performed in order to obtain a sufficiently high time resolution. It was shown that with a combination of the T_1-weighted spin-echo MRI technique, the SPI technique and T_2 mapping measured with the SPI technique, an accurate determination of the medium-penetration position, the position of hydrogel formation, that is, the swelling front and the erosion front, can be achieved for polymers, even though the T_2 values for hydrogels at high polymer concentrations are short (**Figure 3**) [68]. To study directly the polymer response during the medium penetration and swelling, D_2O was used as the penetration medium. With this approach only the polymer protons contribute to the ^1H signal, and thus direct measurements of the molecular processes of the polymer carriers during swelling can be imaged [72,95].

MRI measurements of water self-diffusion coefficient maps during swelling are also a very useful technique for obtaining the properties of the hydrogel with different polymer concentrations formed during swelling [49,76,77,81,87-89,91-93,96-97]. For different polymers it was shown that the water diffusivity is restricted in the polymer matrix owing to the limited mobility of the polymer chains, and that the diffusion coefficient changes with distance from the dry polymer through the hydrogel towards the medium region as the polymer concentration changes through the hydrogel layer. The water self-diffusion coefficient was found to have a constant value near the polymer–water interface and was similar to the diffusion coefficient of free water, indicating that in this region a dilute solution of polymer chains exists for all the swelling times. Water self-diffusion is much slower inside the tablet during the early stages of swelling, where the diffusion coefficient changes with the swelling time as the water penetrates the tablet and causes an increase in mobility of the polymer chains [76,77,88].

The intensity of the MRI signal increases with magnetic field strength, and therefore in most cases high fields were used in order to achieve better resolution and a higher

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Table 1. Summary of the NMR results obtained from measuring the spin-lattice T_1, spin-spin T_2 relaxation times, water and drug self-diffusion coefficients of the hydrogels made from different polymers and drugs forming the matrix tablets.

NMR parameter	Polymer	Drug	Observations and conclusions	Ref.
D_W	HPMC		Polymer concentration: exponential	[53,56-57]
	PVA, HPMC, PNNDEA, PNIPA		dependence	[54]
	EA		Polymer concentration: linear dependence	[57]
	HPMC		Polymer weight: no significant changes	[53,54,56]
	HEC, HPC			[55]
	HPMC, glucose, lactose		Polymer chain length: not dependent	[53]
	HPMC		Temperature: Arrhenius-type behavior	[53]
D_D	HPMC	Adinazolam	Polymer concentration: exponential	[53]
	HPMC, HEC, HPC	Sodium salicylate	dependence	[55]
	HPMC	Naproxen sodium		[56]
	HPMC	Adinazolam	Drug concentration: exponential dependence	[53]
	HPMC	Naproxen sodium		[56]
	HPMC	Adinazolam	Polymer molecular mass: no significant changes	[53]
	HPMC	Naproxen sodium		[56]
	HPMC, HEC, HPC	Sodium salicylate		[55]
	HPMC	Adinazolam	Polymer chain length: longer chains ⇒ smaller D_D	[53]
	HPMC	Adinazolam	Temperature: Arrhenius-type behavior	[53]
	PEG	FITC-dextrans	Drug molecular mass: higher-molecular-mass ⇒ more restricted mobility	[59]
	HPMC	5-Fluorouracil or triflupromazine-HCl	Drug size: smaller drug is more mobile	[58]
T_1 and T_2	PAAHn		Polymer concentration: higher polymer	[65]
	HPMC, HEC, HPC		concentration ⇒ shorter T_1 and T_2	[66,67]
	HPMC			[49,58,69-70]
	XAN			[68]
	XAN + locust bean gum			[71]
	HPMC		Polymer molecular mass: no influence	[66,67]
	HPMC, HEC, HPC		Polymer substitution: T_1 sensitive, T_2 no influence	[66,67]
	PAAHn		Polymer crosslinking degree: lower crosslinking degree ⇒ shorter T_1 and T_2	[65]
	XAN + locust bean gum	Mannitol as model drug	Incorporated drug and its solubility: T_1 no influence, T_2 slightly increases	[71]
	XAN		Medium pH: T_1 not dependent, lower pH ⇒ shorter T_2	[68]

DCP: Dicalcium phosphate; EA: Egg albumin; FITC-dextrans: Fluoresceine isothiocynate-labeled dextrans; HEC: Hydrohyethylcellulose; HPC: Hydroxypropylcellulose; HPMC: Hydroxypropyl methylcellulose; MCC: Microcrystalline cellulose; PAAH: Poly(amidoamine); PEG: Poly(ethylene glycol); PEO: Polyethylene oxide; PNIPA: Poly (*N*-isopropylacrylamide); PNNDEA: Poly(*N*,*N*-diethylacrylamide); PVA: Poly(vinyl alcohol); PVP: Poly(vinylpyrrolidone); XAN: Xanthan.

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sensitivity. However, as high-field MRI systems are very expensive, their use is limited. To expand the use of MRI in pharmaceutical research, a low-field, bench-top MRI system that is accessible for standard laboratory environment was developed. It proved to have sufficient resolution to monitor tablet hydration and swelling [98-101].

As one of the most important properties of tablets with controlled drug release is time dependence of the drug delivery itself, instantaneous measurement of the formed hydrogel's properties and drug release would provide very useful information. For that reason, a combination of MRI and the USP-4 apparatus was developed (**Figure 4**) [78,79,86,102]. The other approach to concomitantly measuring the released drug was to measure the ^{1}H spectrum of the medium. Owing to the chemical shift, the drug's signal can be distinguished from the medium's signal [72]. The third option is to measure the drug's signal directly; for example, by measuring the ^{19}F MRI signal [58].

5.2 Results and findings obtained by MRI

The dependences of the relaxation times and the diffusion coefficient on the polymer's concentration in the hydrogel were used to determine the polymer's concentration profile in the hydrogel during swelling, which directly shows the

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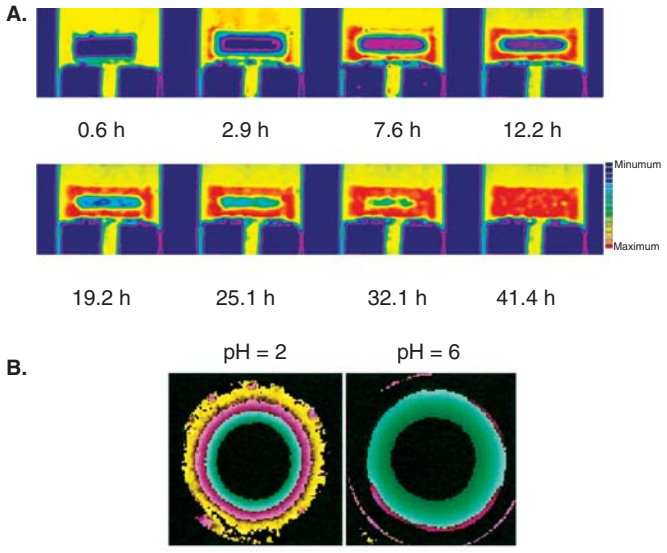

Figure 2. Representative examples of the ^{1}H magnetic resonance images. A. T_1-weighted magnetic resonance images of a Contramid-I tablet at different swelling times with an in-plane resolution of 78 μm and a slice thickness of 0.5 mm. **B.** Effective T_2 maps of HPMC tablets at 190 min after immersion in a medium of pH 2 and a medium of pH 6 with an in-plane resolution of 117 μm and a slice thickness of 2 mm. The effective T_2s range from 440 ms (yellow color) to 0 ms (black).
Adapted with permission from [79] **A.** [84].

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rate of water penetration into the polymer matrix and thus the swelling kinetics. By knowing the dependence of the polymer hydrogel's concentration on the relaxation times and by using a phantom sample with known relaxation times to calibrate the signal, the polymer concentration across the formed hydrogel can be determined from the signal intensity for each pixel in the image [49,67]. Another method to determine the polymer-concentration profiles as functions of the distance and the swelling time is to measure T_1 [95], T_2 [49,58,69,70,89] or the diffusion maps [85,103]. However, the polymer concentration within the hydrogel cannot be determined in a straightforward way from the MRI data and special care should be taken in the evaluation of the data. Namely, the presence of trapped air in the tablet can lead to an overestimation of the polymer concentration as a result of the volume occupied by the air and because of shortening of water T_2 in the vicinity of the air resulting from the susceptibility effects [89]. Further, using the spin-echo method it is not possible to determine small water concentrations in the hydrogel because of the effect of T_2 and diffusion losses [70].

From the different MRI methods, various findings for polymer-matrix tablets were observed that can lead to a better understanding of the swelling process and drug release. Based on these fundamental results, optimum polymer selection for the required performance of the drug-delivery system is possible. One interesting study involved NMR measurements of water ingress into polymer powders with different levels of compaction and, therefore, with different levels of porosity. On the basis of the NMR results the authors proposed a mechanism of water penetration into the solid polymer matrix. It was shown that at the interface between the water and the polymer, first the vapor diffuses into the polymer, followed by liquid water diffusion, and that the liquid-water transport rate is controlled by the water-vapor diffusion between the powder particles [96,104]. This was supported by other measurements where the core expansion of HPMC matrix tablets was observed before hydrogel formation [49,70,88,89,94]. MRI showed that the tablets' properties during swelling are different in the axial direction from in the radial direction [49,81,84,85,88,89,91,94,100]. This was explained by release of the compression stress from the granules or powder particles as the water penetrates the matrix, or with a smaller amount of bound water in the radial direction leading to different hydrogel properties [88,91,94].

It is not only the thickness, but also the hydrogel's properties that have an important role in the control of drug release. Using MRI, it was shown that the polymer's characteristics (different substitution type, molecular mass, hydrophilicity, polymer–water and polymer–polymer interactions) influence the hydrogel's thickness, on the one hand, and the amount of absorbed medium, on the other, leading to different hydrogel properties and a different drug release rate [56,57,67,76-78,92-93]. Furthermore, the influence of different polymer crosslinking of high amylose starch on the swelling was investigated, showing that higher crosslinking leads to higher swelling [82].

Usually, polymer-matrix tablets are investigated by MRI without any incorporated drug because of the complexity of the experiments. However, some valuable results were

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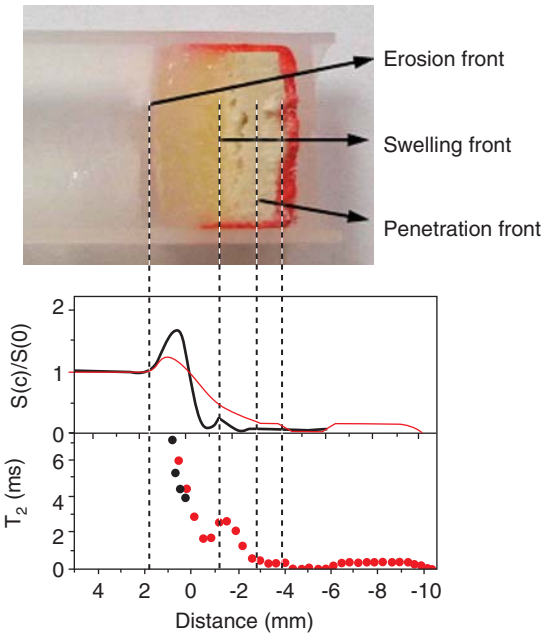

Figure 3. Photographs of a hydrated xanthan tablet after 3 h of swelling in a pH 1.2 medium, together with 2D spin-echo MRI (black line) and 1D SPI (red line) normalized signal intensities and T_2 profiles (T_2 values were determined from 2D T_2 maps for T_2 longer than 5 ms (black circles) and from 1D SPI measurements for shorter T_2 values (red circles)). The penetration front was determined from the increase of the normalized single-point-imaging signal intensity above the signal intensity of the dry tablet, the swelling front from the T_2 value of the maximally hydrated glassy polymer (2.6 ms in the xanthan tablet) and the erosion front from the decrease of the 2D spin-echo MRI signal.
Adapted with permission from [68].

obtained from studying the influence of an incorporated drug on the swelling behavior of polymer-matrix tablets. It was shown that the presence of the drug increases the hydrogel's thickness at drug concentrations that are high enough and that highly soluble drugs have a greater impact than a drug with a lower solubility [93,94]. The presence of the drug also increases the medium penetration rate; however, this is more in the case of a more highly soluble drug than a lower solubility drug [81,94]. The rate of erosion was also found to depend on the drug's solubility. It is much slower for a low-solubility drug [94]. As mentioned already, direct measurement of the drug's position in the hydrogel during swelling is possible when the drug molecule possesses other MRI-seen nuclei, such as ^{19}F. It was shown that the drug self-diffusion coefficient should be higher than the expansion rate of the matrix tablet in order to enable the release of the drug from the polymer tablet [58]. MRI was also used to examine the floating properties of different matrix tablets in the presence of gas-generating substances or substances with a low density [99,100].

The influence of external parameters, such as the temperature, the medium's pH, the presence of air bubbles, stirring of the medium and the tablet size, on the swelling behavior was also studied extensively using MRI. It was found that a higher temperature increases the water-penetration rate and can change the water diffusion from case II to Fickian behavior [79,82,105]. The temperature dependence of the swelling rate can be described by the Arrhenius law with an activation energy similar to the potential energy of the H-bonds, indicating that the swelling is a consequence of the breaking up of the H-bonds [83]. The medium's pH also causes different swelling or water-penetration mechanisms with respect to the polymer matrix. For HPMC polymers, it was found that the diffusion changes from Fickian at pH 6 to case II in the presence of a medium with a pH equal to 2 [79]. In xanthan the medium's pH does not influence the penetration and swelling front positions, but it lowers the erosion rate at low pH and therefore influences the resulting thickness of the hydrogel [68]. The tablet size was shown to influence the swelling behavior, that is, in the case of smaller tablets an increased swelling rate and water uptake were observed [84]. It was shown that a higher stirring rate causes a more rapid medium penetration and faster polymer erosion [85]. Furthermore, the flow of the medium through the cell containing the tablet was studied, leading to a thinner hydrogel due to mechanical perturbation of the hydrogel that strips away the outermost, highly hydrated, polymer chains [86]. The observed influences of the polymer type, incorporated active ingredients and external parameters on the swelling kinetics are summarized in **Table 2**. From a comparison of the hydrogel thickness and drug release, the MRI measurements show that the hydrogel thickness regulates the drug release, that is, drug release is faster in the case of a thinner hydrogel layer [68,78,88]. However, as the hydrogel-layer thickness is a consequence of different polymer conformations, the hydrogel's microstructure is also equally important. MRI measurements were also used to verify mathematical models describing the swelling and drug release from polymer-matrix tablets and to determine the critical parameters that can sometimes be the key to a successful design of matrix tablets for a particular application [76,77,96,103,106-107].

6. Expert opinion

Drug release from hydrophilic polymer-matrix tablets is a very complex process that is mainly influenced by the structure of the hydrogel layer [1]. Magnetic resonance is a very useful technique for the study of the hydrogel's properties and its thickness because it is non-invasive, sufficiently fast to be able to follow the changes during the swelling processes, and can give reliable information about the medium's penetration into the matrix tablet and the hydrogel's formation. In addition, it has the advantage of not requiring any contrast agents to obtain the system properties. Other methods are also used in the pharmaceutical research of the swelling of polymer

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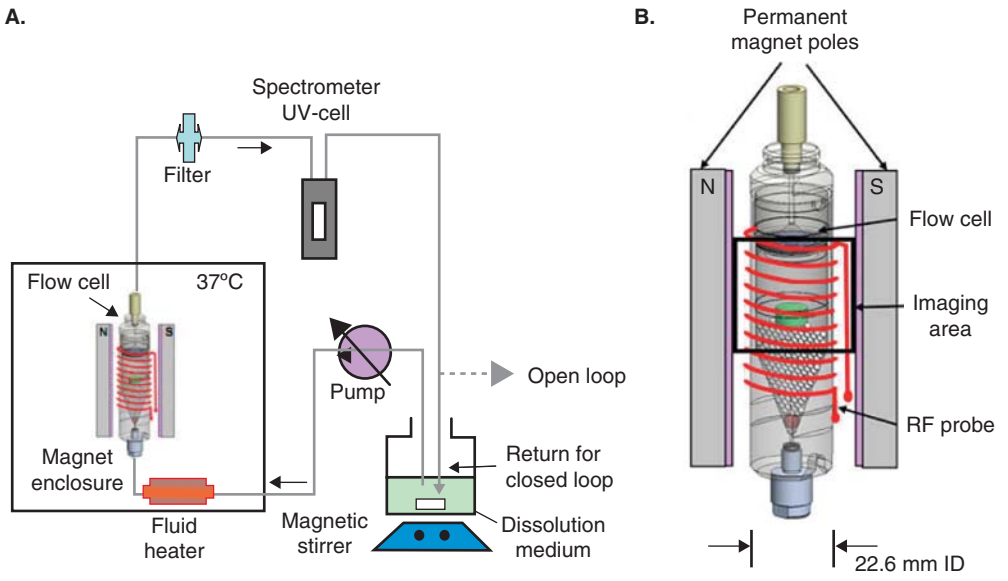

Figure 4. Schematic diagram of (A) a low-field magnetic resonance imager with an integrated USP-4 dissolution circuit (MARAN-iP) and (B) an enlarged picture of the MRI-compatible flow cell.
Adapted with permission from [74].

Table 2. Summary of the results obtained from *in situ* MRI measurements of the matrix tablets made from different polymers and drugs swelling in media with various pH values and temperatures.

Processes and parameters during polymer swelling	Polymer type/drug or additive	Observations and conclusions	Ref.
Medium penetration	HPMC, PVA	Depends on the polymer molecular masses:	[76,91]
	PEO	higher molecular mass ⇒ slower medium penetration rate	[85]
	High-amylose starch	Tablet size: smaller size ⇒ faster penetration and larger water uptake	[84]
	High-amylose starch	Temperature: Arrhenius-type behavior	[82,83]
	PMMA		[105]
	HPMC	Medium pH: lower pH ⇒ faster penetration	[79]
	XAN	No influence	[68]
	High-amylose starch/ciprofloxacin or acetaminophen	Drug increases the penetration rate: higher drug molecular mass ⇒ faster penetration	[81]
	HPMC/mannitol or DCP	higher soluble drug ⇒ faster penetration	[94]
	PEO	Stirring rate: higher stirring rate ⇒ faster penetration	[85]
Erosion	XAN	Medium pH: lower pH ⇒ slower erosion	[68]
	HPMC/mannitol or DCP	Drug: higher soluble drug ⇒ faster erosion	[94]
	PEO	Stirring rate: higher stirring rate ⇒ faster erosion	[85]
Gel thickness	HPMC, HEC, HPC	Polymer substitution: higher hydrophilicity ⇒ thicker gel	[67]
	High-amylose starch	Crosslinking: higher crosslinking ⇒ higher swelling	[82]
	PEO	Stirring rate: higher stirring rate ⇒ thinner hydrogel	[85]
	HPMC	Flow-through: causes thinner hydrogel	[86]

DCP: Dicalcium phosphate; HEC: Hydrohyethylcellulose; HPC: Hydroxypropylcellulose; HPMC: Hydroxypropyl methylcellulose; PEO: Polyethylene oxide; PVA: Poly (vinyl alcohol); XAN: Xanthan.

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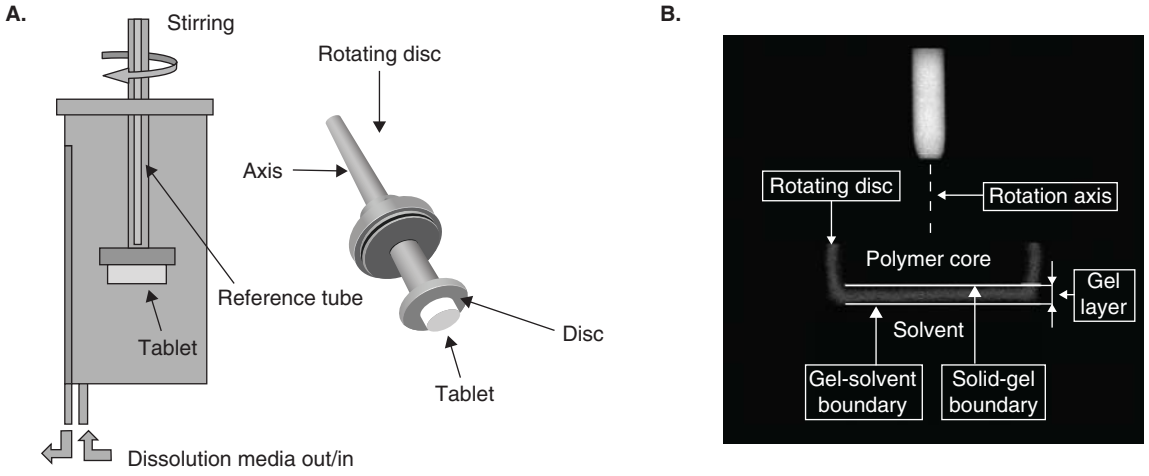

Figure 5. Combination of a rotating disc dissolution and MRI experiment. A. Schematic drawing of the MRI stirring release cell. **B.** The magnetic image obtained from a rotating disc dissolution experiment, showing the gel-solvent, the solid-gel boundary and gel layer.
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tablets, but these methods can be destructive and do not allow the *in situ* measurements (texture analyzer), need the addition of different markers that can influence the properties of the hydrogel layer (optical imaging), or cannot accurately distinguish between different moving-front positions (ultrasound, X-ray microtomography). Nevertheless, some of these are more accessible, cheaper and easier to use, and it is important to stress that they provide complementary information about the properties of the matrix tablets.

The applicability of MRI in pharmaceutical research has been known for a long time [73], but the optimal procedure for time and spatial resolution for observing processes occurring during swelling and drug release is still under investigation. One of the main obstacles in MRI studies is that a quantitative characterization of the MRI results of a particular polymer system is not straightforward, because the NMR parameters for hydrogels with different polymer concentrations should be determined first – a very labor-intensive part of the research. Another problem is also the short T_2 of the polymer and hydrogel with a high polymer concentration, which cannot be observed using the standard spin-echo MRI technique. This can lead to imprecise determination of the swelling front and consequently an underestimation of the hydrogel layer's thickness – a weaknesses that many researchers are unaware of. A possible solution was shown to be the use of the SPI sequence [68,72], but it is time-consuming and, owing to unacceptable time resolution, only 1D images can be determined, which requires the use of a special sample geometry. The other possibility would be to use the Sweep Imaging with Fourier transform (SWIFT) technique, which is sensitive to nuclei with short T_2 values and is significantly faster than the SPI technique [108]. With these methods it is possible to determine precisely the penetration front, but the problem remains: how does one detect the position of the hydrogel formation, meaning the true swelling front's position, where the polymer transforms from the glassy to the rubbery state? However, it was proposed that a combination of the SPI signal intensity and the T_2 measurements could overcome this problem [68]. Another obstacle to the MRI measurements is the diffusion losses causing a loss of the MRI signal and, therefore, an underestimation of the T_2 values, which leads to an overestimation of the polymer concentration across the hydrogel layer. These effects should be considered when the polymer concentration profiles during tablet swelling are determined. The magnetic resonance images are strongly affected by selected imaging parameters and pulse sequences, and because the hydrated polymeric systems are very complex, interpretation of the magnetic resonance images can sometimes be misleading if the magnetic resonance parameters of the investigated systems are not considered properly.

A further step in the MRI implementation of research on the polymer-matrix tablets is simultaneous measurements of the behavior of the hydrogel layer's formation and the drug's position within it. This can be achieved by observing other nuclei (such as ^{19}F) that are part of the drug molecule, but are not present in the composition of the polymer or the medium [58]. The drawback is that the NMR sensitivity of such a nucleus is much lower than for the protons, which require a high magnetic field and a high ratio of the observed nuclei in the drug molecule. Drug release can also be monitored simultaneously with the MRI measurements using flow-through systems, where only the released drug can be detected using standard UV-VIS spectroscopy [74]. Although this method does not allow any observation of the drug's position within the hydrogel, it can give useful information about the hydrogel's impact on the drug release.

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One of the reasons for the scarce use of MRI in pharmaceutical research is the high investment and running costs of superconducting MRI systems. Therefore, low-field MRI, bench-top instruments were developed recently. Their lower price and running costs make their widespread use possible in analytical laboratories. The use of these systems is partially limited by the lack of sensitivity for detailed investigations of the hydrogel's properties and the drug's position. However, on the other hand a bench-top MRI system is still very useful in the optimization process for matrix-tablet formulation and is expected to be developed further.

Most of the MRI research on swelling tablets was performed using *in vitro* methods, with the intention to predict the behavior of the systems *in vivo*. However, a major concern with *in vitro* experiments is the lack of a direct correlation between the *in vitro* and *in vivo* conditions. In some cases attempts to simulate the *in vivo* conditions were made by changing the medium's pH and ionic strength [68,79], fixing the temperature during swelling to 37°C [78,81-84,87,94,102], implementing the USP-4 flow-through cell [78,86,102], or introducing a specially designed stirring cell (**Figure 5**) [85] to simulate the mechanical stress in the gastrointestinal tract. However, the simulated conditions are never exactly the same as the physiological ones, and some improvements should be made in the direction of simulating the influence of food, gender, age and disease conditions [109]. *In vivo* monitoring of the tablet's position can be achieved by the incorporation of MRI contrast agents into the delivery system. Some attempts have already been made *in vivo* to follow the position of a floating tablet in the stomach [110].

It can be concluded that the MRI technique is a complementary method for other methods commonly used in pharmaceutical research. It can provide extra information that can lead, together with the results of other techniques, to a better understanding of polymeric systems and, therefore, to the design of systems with the desired properties for a particular need. The technique is still developing and some further improvements are expected to make MRI even more accurate and also more accessible for a wider range of applications in pharmaceutical research and analytics.

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Declaration of interest

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