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Mechanistic Understanding of Food Effects: Water Diffusivity in Gastrointestinal Tract Is an Important Parameter for the Prediction of Disintegration of Solid Oral Dosage Forms

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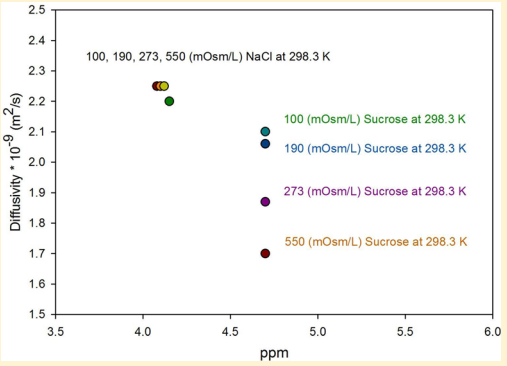
ABSTRACT: Much interest has been expressed in this work on the role of water diffusivity in the release media as a new parameter for predicting drug release. NMR was used to measure water diffusivity in different media varying in their osmolality and viscosity. Water self-diffusion coefficients in sucrose, sodium chloride, and polymeric hydroxypropyl methylcellulose (HPMC) solutions were correlated with water uptake, disintegration, and drug release rates from trospium chloride immediate release tablets. The water diffusivity in sucrose solutions was significantly reduced compared to polymeric HPMC and molecular sodium chloride solutions. Water diffusivity was found to be a function of sucrose concentration in the media. Dosage form disintegration and drug release was to be affected by water diffusivity in these systems. This observation can be explained by hydrogen bonding formation between sugar molecules, an effect which was not expressed in sodium chloride solutions of equal osmolality. Water diffusivity and not media osmolality in general need to be considered to predict the effect of disintegration and dissolution media on drug release. Understanding the relevance of water diffusivity for disintegration and dissolution will lead to better parametrization of dosage form behavior in gastrointestinal (GI) aqueous and semisolid media.



KEYWORDS: *tablets, biopredictive media, dissolution, biopharmaceutic prediction, diffusion coefficient*

INTRODUCTION

Disintegration and dissolution processes represent key steps in the absorption of drugs from solid oral dosage forms. A delay in drug release, for example, in the presence of a homogenized meal may affect bioavailability of drugs, especially for Biopharmaceutics Classification System (BCS) type III compounds with preferential absorption in the upper gastrointestinal (GI) tract.

Viscosity is one of the factors affecting mass transport kinetics. Previous work has shown the significance of media viscosity on retarding drug release, which was explained in part by impaired water ingress into tablets under viscous conditions.[1]

Osmolality has been described as another parameter that may have an impact on drug release. The average gastric osmolality in the fasted state has been reported to be 191 mmol/kg.[2] Gastric osmolality was reported to be elevated following meal ingestion. Postprandial gastric osmolality was reported to be 559 mmol/kg based on human gastric aspirates measurements.[3] Osmolality decreased over time in the fed state due to gastric dilution. In an attempt to simulate fasted conditions of the stomach, Vertzoni et al. have developed fasted state simulated gastric fluid (FaSSGF) using an osmolality value of 120 mmol/kg.[4] Ensure plus, which has been proposed to simulate the fed gastric state, has an osmolality value of 735 mmol/kg. The osmolality effect on release from drug products, however, is variable. Faisant et al. have reported reduced in vitro release rate of 5-FU from PLGA based micro particles with increasing the osmolarity of the release media from 280 to 840 mmol/kg using NaCl.[5] On the other hand, Muschert et al. have shown similarities in the release rate of theophylline, diltiazem HCl, and metoprolol succinate from PVA-PEG graft copolymer coated pellets in media of different osmolalities within the same physiological range but a decrease at higher osmolalities.[6]

Previous work has paid very little attention to the role of water diffusion in dissolution and disintegration media. Instead, the study focus was almost exclusively on the water diffusivity within the tablet;[7] however, the role of water dynamics within the release media on drug release kinetics is still unclear.

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Nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI) have shown to be valuable methods for characterizing water diffusivity in various systems. NMR has been employed to measure water and drug diffusivities in HPMC gels. A dependence of water mobility on HPMC concentration has been shown.[8] Likewise, significantly hindered diffusivity of water molecules in molecular sucrose solutions has been reported.[9] MRI has been proved to be a useful method for following water uptake and tracing dynamic water movement into tablets.[10−15] Brouwers et al. used MRI to follow the swelling and the disintegration behavior of fosamprenavir tablets in simulated gastric fluid and nutritional drink. They have attributed the reduced water ingress and the corresponding delay in disintegration rates in nutritional drink to the formation of a precipitation layer on the HPMC coat of the tablet and reduced water availability[16]

The main objective of this work is to gain further insight on media parameters affecting drug product disintegration and API release and to identify the gaps in the current understanding of these factors relevant to tablet disintegration and dissolution. In this study, particular attention has been paid to water diffusivity within dissolution media as a new parameter. Water diffusivity in various solutions differing in their osmolality and viscosity was examined and correlated with water uptake rates, disintegration times, and drug release.

EXPERIMENTAL SECTION

Dosage Forms and Active Pharmaceutical Ingredient. Trospium chloride as API was kindly donated by Dr. R. Pfleger (Bamberg, Germany). Three marketed trospium chloride tablet dosage forms were investigated: Spasmolyt, 30 mg tablet (Madaus, Germany), Spasmex, 30 mg (Dr. R. Pfleger, Germany) and Trospi, 30 mg (Medac, Germany). Spasmolyt and Spasmex were film-coated tablets, whereas Trospi was a non-coated tablet. The average size of the tablet was 9 mm in diameter and 2 mm in thickness.

Study Media. Sucrose solutions, differing in viscosity and osmolality, were used as disintegration and dissolution media. This difference was achieved by dissolving sucrose in defined proportions in purified water (10, 15, 20, 30, 38, 55, 66.5, 77.2 w/w %) and boiling until complete dissolution followed by rapid cooling.

Comparative studies were performed using sodium chloride aqueous solutions with an osmolality similar to that of sucrose solutions (273, 500, 800, 1780 mmol/kg) by varying the concentration of sodium chloride in SIF. SIF without pancreatin was prepared according to USP by dissolving 6.8 g of monobasic potassium phosphate and 77 mL of 0.2 M sodium hydroxide, adjusting the pH to 6.8 and dilution with distilled water to 1000 mL.

Viscosity Determination. The viscosity of sucrose solutions was determined in triplicate using a capillary viscometer (Schott-Geraete, Germany) at 37 °C.

Solubility Determination. The trospium chloride solubility in different sucrose solutions was characterized by adding excess amount of the drug to 3 mL of the investigated media and keeping them in a shaker incubator at 37 °C. After 24 h, the solutions were filtered and assayed spectrophotometrically at 210 nm. Solubility determinations were performed in triplicate.

Determination of the Osmotic Pressure. Osmolality measurements were performed in duplicate using a Wescor vapor pressure osmometer (MA, USA) calibrated with standard solutions of known osmolality.10 μL aliquots of each sample were used for each determination.

Water Diffusivity. Diffusion ordered NMR spectroscopy (DOSY-NMR) experiments were performed using a 5 mm BBI $^{1}H/X$ z-gradient probe with a gradient strength of 5.350 [G/mm] and a 5 mm $^{1}H^{13}C$ diffusion z-gradient probe with a gradient strength of 128.0 [G/mm] on two Bruker Avance-III 700 NMR spectrometers. The gradient strength of the two different probes was calibrated by analysis of a sample of $^{2}H_2O/^{1}H_2O$ at a defined temperature and compared with the theoretical diffusion coefficient of $^{2}H_2O/^{1}H_2O$ (values taken from Bruker diffusion manual)[17] at 298.3 K.

The temperatures were held constant at 25 and 37 °C and defined with a standard ^{1}H methanol NMR sample. The control of the temperature was realized with a VTU (variable temperature unit) and an accuracy of ±0.1 K, which was checked with the standard Bruker Topspin 2.1 and 3.0 software.

In this work, the diffusion times (d20) were optimized for the BBI probe to 60 ms and for the diffusion probe to 39 ms, while the gradient pulse length was kept at 2.0 ms. The optimization was realized by comparing the remaining intensity of the signals at 2% and 95% gradient strength. The intensity loss of the echo was in the range of 90%. Using longer diffusion times, a loss of signal intensity occurs (from the echo) due to a short spin−lattice relation time (T_1), which was measured with the inversion recovery method[18] before making the diffusion measurements. The diffusion measurements were done with a 2D DOSY sequence[19] by incrementing in 32 linear steps from 2% to 100% with the BBI probe and 16 gradient linear steps with the diffusion probe. The 2D NMR sequences for measuring diffusion coefficients uses echoes for convection compensation and longitudinal eddy current delays to store the magnetization in the z-axis and only be dependent on T_1-relaxation. The self-diffusion coefficient was extracted by least-squares fitting of the monoexponential function to the experimental data:[20]

$$\ln\left(\frac{I(G)}{I(0)}\right) = -\gamma^2\delta^2G^2\left(\Delta - \frac{\delta}{3}\right)D$$

where $I(G)$ and $I(0)$ are the intensities of the signals with and without gradient, γ is the gyromagnetic ratio of the nucleus (^{1}H in this measurements), G is the gradient strength, δ is the duration of the pulse field gradient (PFG), D is the diffusion value in m^2/s, and Δ is the "diffusion time" between the beginning of the two gradient pulses. The relaxation delay between the scans was 2s.

Water Uptake Study. Water penetration into the tablet was studied using two techniques: (1) An Enslin apparatus, which consists of a funnel with a glass filter plate that is connected to a horizontal 1.0 mL volumetric pipet. The liquid uptake rate was measured by placing the tablet on the glass filter and measuring the volume of fluid absorbed from the graduated pipet at defined times. The rate of water uptake was expressed by the volume of fluid taken up by the tablet per unit time (mL/min). Measurements were made in triplicate. (2) Magnetic resonance imaging (MRI): For MR imaging a 4.7 T horizontal, 20 cm bore magnet (Magnex Scientific Ltd., UK) was used. It was equipped with a Maran DRX spectrometer from Oxford Instruments (Oxfordshire, UK) and a SGRAG 195/120/S 12 cm bore gradient system from Magnex Scientific Ltd. (Oxford, UK) with a maximal field gradient strength of 0.2 T/m. All images were acquired with a gradient echo sequence.

The dwell time was 20 μs, the echo time 2 ms, and the repetition delay 500 ms. For all images 16 × 64 points were acquired in x (phase) and y (read) direction respectively, with a FOV of 18 × 18 mm. The short repetition time does not allow to extract quantitative information of the water content inside the tablets, but it allows for visualization of the water uptake with a good temporal resolution (9 s acquisition time per image).

All images were zero filled to four times the number of acquired points. For each experiment between 1000 and 2500 images were recorded in order to obtain a time series. For MRI experiments a Teflon phantom is used, see Figure 1. The phantom contains a reservoir of 0.8 mL volume, with a frit of 2 cm^2 placed on top. Before each experiment the reservoir is completely filled with the fluid used in the respective experiment.

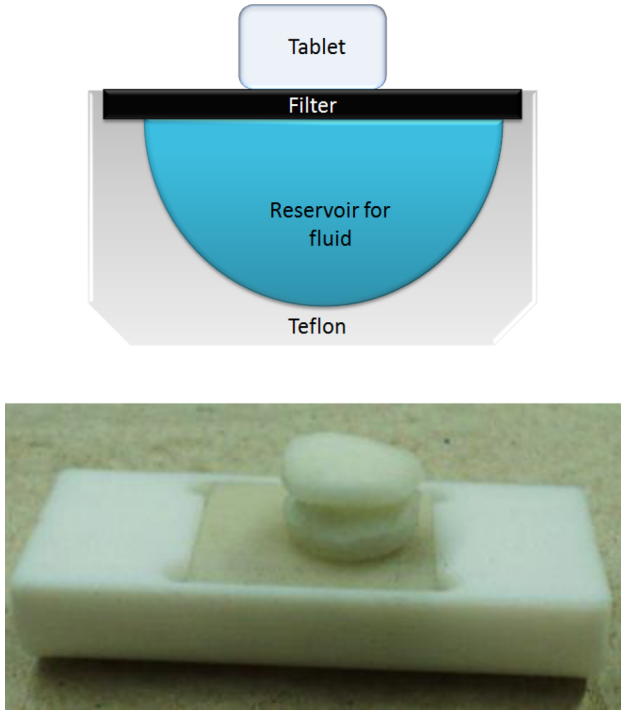

Figure 1. Left: Sketch of the MRI phantom. Right: Photograph of the MRI phantom taken from the side showing a swollen tablet on the frit.

Disintegration Studies. Disintegration times were determined according to European Pharmacopoeia (Ph. Eur.) by using a tablet disintegration tester without disks (PharmaTest, Germany). All tests were carried out in 800 mL of the investigated media at 37 °C using six tablets, one per vessel, for each test.

Drug Release Study. Drug release from the tablets was determined according to Ph. Eur. using a rotating paddle apparatus II (PharmaTest, Germany). All tests were conducted in 900 mL dissolution media at 37 °C with a paddle rotating speed of 50 rpm. Five mL samples were withdrawn at predetermined time intervals, filtered and properly diluted. Trospium concentrations were assayed at 210 nm using UV spectrophotometry (lambda 20 photometer, PerkinElmer, USA). All tests were performed in triplicate. Mean dissolution time (MDT) was calculated to describe drug release kinetics of the different formulations under various conditions.

RESULTS

Physicochemical Characteristics of Trospium Chloride in Disintegration/Dissolution Media. The results of solubility and density determinations of trospium chloride in sucrose media are presented in Table 1. A previous work reported trospium solubility in SIF to be 786 mg/mL at 37 °C.[1] Sugar presence in the media reduced the drug solubility which can be attributed to the interaction between both the hydrophilic sucrose molecules and trospium molecules and the competition between sugar and drug molecules for water. This reduction in the solubility may partly explain reduced release rates in viscous sucrose solutions.

Rheological profiles of sucrose solutions follow Newtonian behavior; that is, the viscosity is independent of shear rate. Viscosity is dependent on the sucrose concentration and increases with increasing sucrose concentration. The mean viscosities of the solutions used in this study are shown in Table 1.

The osmotic pressure of the different dissolution media is also depicted in Table 1. Sucrose solutions showed high osmotic pressures. Media osmolality is a function of sucrose concentration and increases with increasing total sugar content.

Effect of Media Composition on the Diffusivity of Water and Trospium. Self-diffusion coefficients of trospium

Table 1. Physicochemical Characteristics of Trospium Chloride in Sucrose and Sodium Chloride Solutions[a]

media w/w%	viscosity η (mPa·s)	diffusivity H_2O [b] 10^{-6} (cm^2/s)	trospium Cs (g/mL)	density (g/mL)	osmolality (mmol/kg)
0% sucrose (SIF)	0.8	27.5	0.786 ± 0.021	0.997	100
10% sucrose	1.1	26.9	0.714 ± 0.018	1.026	273
15% sucrose	1.4	23.4	0.674 ± 0.011	1.052	550
30% sucrose	2.1	17.8	0.585 ± 0.030	1.117	1400
38% sucrose	2.6	13.8	0.538 ± 0.009	1.144	1780
55% sucrose	22.0	3.47	0.505 ± 0.039	1.250	3670
66.5% sucrose	115	0.74	0.429 ± 0.021	1.315	4450
77.2% sucrose	1300	0.63	[b]	1.359	5350
0.8% NaCl	0.806	25.6	0.691 ± 0.016	0.994	273
1.6% NaCl	0.803	24.5	0.590 ± 0.022	1.003	550
2.3% NaCl	0.811	[b]	0.552 ± 0.036	1.007	800
5.2% NaCl	0.811	[b]	0.480 ± 0.012	1.027	1780

[a]Density and water diffusivity measures were performed once. For solubility (n = 3), osmolality (n = 2) and viscosity (n = 3) the mean values are reported. [b]Not determined.

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and water were determined in different sucrose solutions (Figure 2a). Water diffusivity decreased dramatically in these

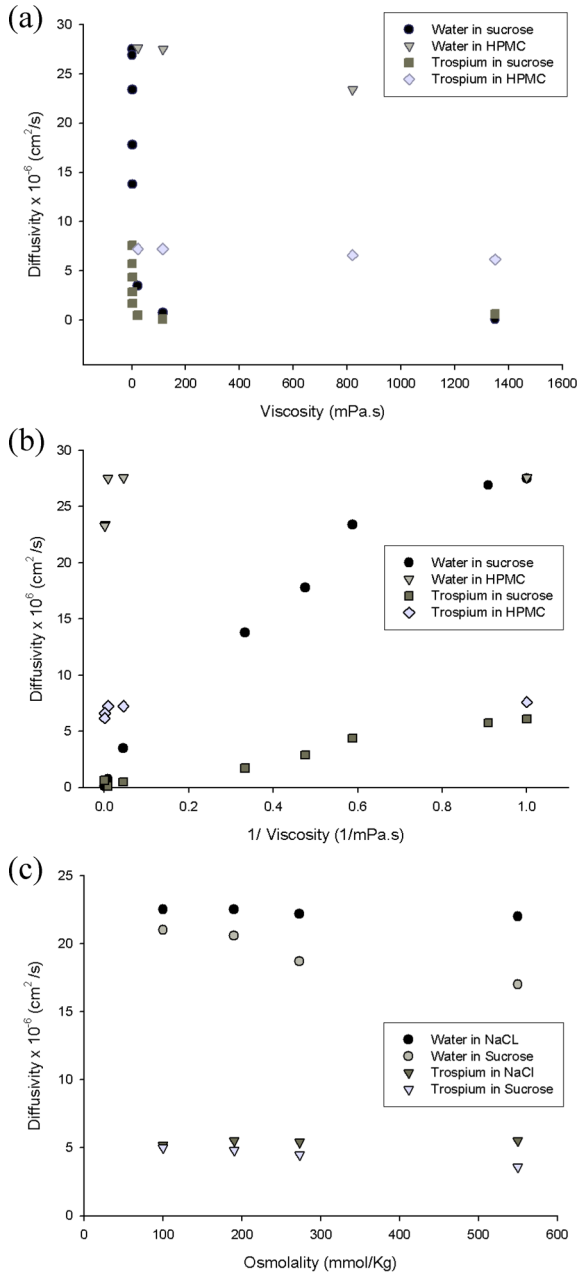

Figure 2. (a) Self-diffusion coefficients of water and trospium molecules in viscous sucrose and HPMC solutions. (b) Diffusivity and 1/viscosity relationship. (c) Self-diffusion coefficients of water and trospium molecules in equal osmolality solutions of sodium chloride and sucrose.

media, and the effect was directly proportional to sucrose concentration. Surprisingly, water diffusivity coefficients in sucrose solutions were much lower than in equal viscosity HPMC solutions, indicating an interaction between the sugar and water which limits the mobility of water in the disintegration/dissolution medium. Measurements of trospium diffusivity reveal a minor influence of HPMC compared to sucrose. Figure 2b shows a linear relationship between diffusivity and inverse viscosity in sucrose solutions, whereas HPMC solutions do not adhere to the same behavior. Self-diffusion coefficients of water in sodium chloride adjusted media are higher compared to sucrose solutions of equal osmolality. The drug molecule mobility is not affected by sodium chloride presence in the media (Figure 2c).

Visualization and Quantification of Water Uptake Kinetics. MRI and Enslin methods were used to follow water uptake into the tablets. The Enslin method provided quantitative information with regard to water uptake (Table 2). Water uptake rates decreased considerably with increasing

Table 2. Water Uptake Rates by Tablet in Different Media Using the Enslin Method (Mean ± SD, n = 3)

media w/w%	Spasmolyt rate $\times 10^{-3}$ (mL/min)	Spasmex rate $\times 10^{-3}$ (mL/min)	Trospi rate $\times 10^{-3}$ (mL/min)
SIF	8.2 ± 0.59	6.4 ± 0.21	8.2 ± 0.58
10% sucrose	7.0 ± 0.51	5.7 ± 0.44	7.1 ± 0.91
15% sucrose	5.5 ± 0.69	4.9 ± 0.18	6.4 ± 0.43
20% sucrose	4.5 ± 0.31	4.0 ± 0.25	4.9 ± 0.75
30% sucrose	3.8 ± 0.42	3.5 ± 0.28	3.2 ± 0.37
38% sucrose	2.5 ± 0.19	2.9 ± 0.04	2.6 ± 0.17
≥55% sucrose	0	0	0
0.8% NaCl	7.0 ± 0.58	6.6 ± 0.46	7.3 ± 0.19
1.6% NaCl	7.2 ± 0.66	6.5 ± 0.48	7.3 ± 0.70
2.3% NaCl	7.1 ± 0.18	5.8 ± 0.23	7.1 ± 0.52
5.2% NaCl	5.8 ± 0.38	5.1 ± 0.37	6.9 ± 0.16

sucrose concentrations. No water uptake has been detected for the three tablets at sucrose concentrations >55%. Differences in the lag times were also obvious. Longer lag times have been shown for film coated tablets (Spasmex and Spasmolyt) compared to uncoated tablets.

Previous work has shown reduced water uptake rates from viscous polymeric HPMC solutions; however, the effect was more pronounced for equal viscosity sucrose solutions. Water uptake rates are in line with the diffusivity data (Figure 3).

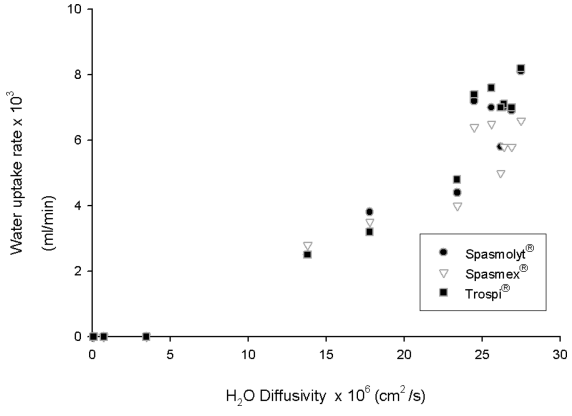

Figure 3. Relationship between water uptake rate into tablets and water diffusivity in the dissolution medium.

When sodium chloride was used for adjusting media osmolality, the rate of water ingress into the tablets was only slightly affected compared to that in equal osmolality sucrose solutions, which is in agreement with the lower effect of sodium chloride on the diffusivity of water molecules.

MRI data underlined qualitatively the results of the Enslin method and provide more information about water distribution inside the tablets.

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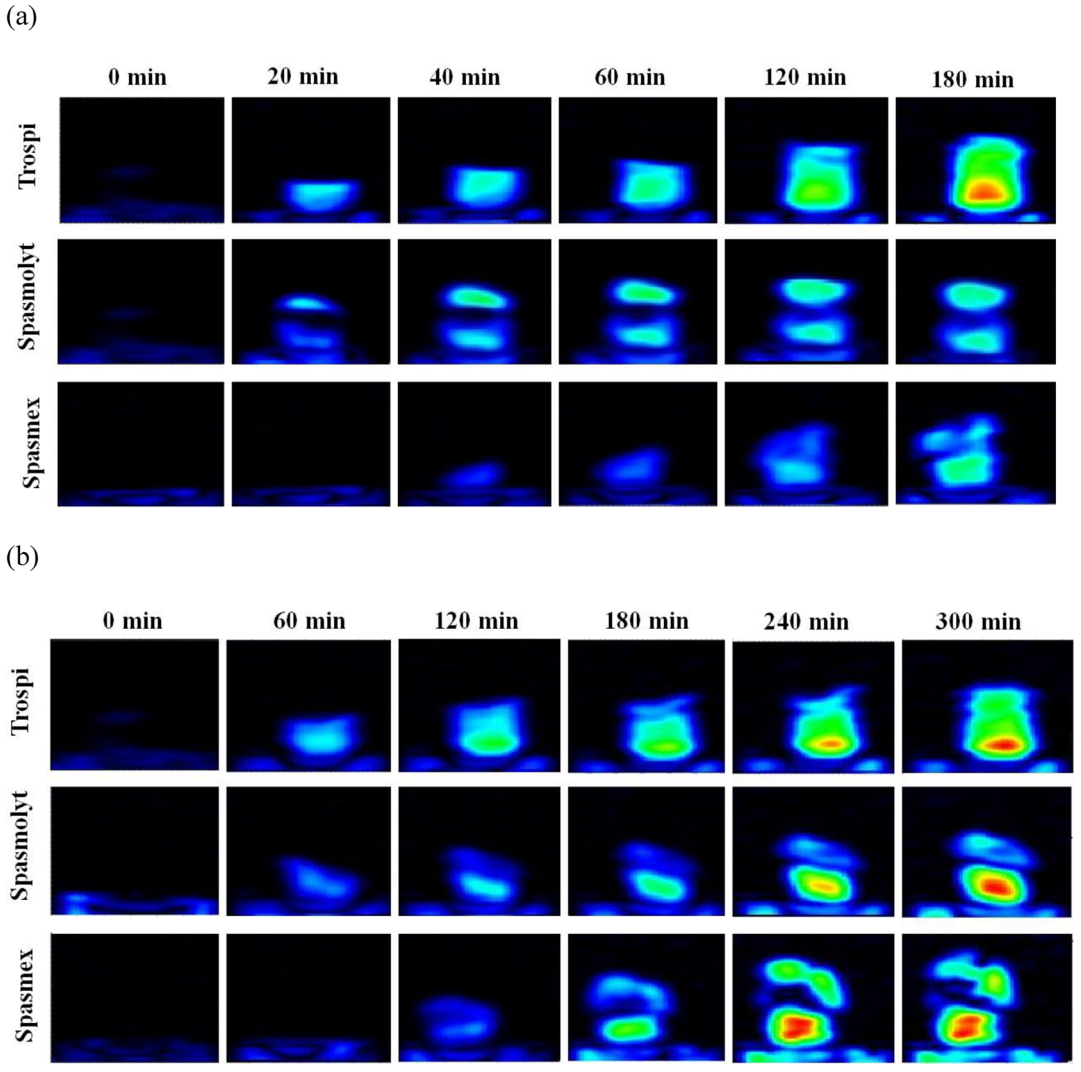

Figure 4. Axial images of the sample tablets as function of time in (a) SIF and (b) 15.8% sucrose solution.

MRI visualized the rate of water entry into the tablet through detecting the change in proton signal intensity. Black areas in MRI images refer to low proton density and represent the dry parts of the tablets. Water concentration is indicated by signal intensity, which increases as the water content increases inside the tablet. The red areas in the MRI images correspond to high water intensity, whereas green areas refer to lower water intensity. Figure 4a and b represents axial images of the sample tablets as function of time in SIF and 15.8% sucrose solutions, respectively. The depicted images represent a zoom to the tablet (18 × 10 mm) and do not show the fluid reservoir to avoid an outshining of the very high signal intensity of the reservoir.

MRI images showed rapid water uptake into the tablets in SIF media compared to sucrose solutions. Distinguished differences in water distribution patterns between the different dosage forms have been observed. For noncoated tablets, water progress was directed into the tablet by one-way direction of water influx, whereas, for film coated tablets, water was shown to distribute in the film coat and then progress into the tablet core. As the water advances toward the center, the dry core gradually diminishes with time. Rates of water uptake continue at a constant rate and slow down thereafter until complete hydration of the tablet. MRI images revealed uneven water distribution through tablets. For noncoated tablets, water accumulates in the center, which is indicated by the reddish signal compared to the periphery. For the coated tablets, a sandwich shape water distribution has been shown, water concentrated near the surface compared to the core.

Effect of Media Composition on Tablet Disintegration. The effect of media osmolality and water diffusivity on disintegration of trospium chloride tablets was investigated using sucrose and sodium chloride at different concentrations. Figure 5 compares the disintegration times of the three formulations obtained in sodium chloride and sucrose adjusted SIF solutions.

Disintegration times were strongly prolonged with increasing sucrose concentration in the media. The three tablets showed no disintegration at sucrose concentrations >55%. Tablet disintegration was significantly delayed in sucrose media compared to equi-viscous HPMC solutions. (Data for the latter have been reported previously.[1])

Increased media osmolality using sodium chloride was not found to significantly affect the disintegration process of the three formulations. On the other hand, in sucrose adjusted media showing identical osmolality to sodium chloride solutions, an increase in the disintegration times for the three products was observed. Clearly, the type of osmotic agent plays

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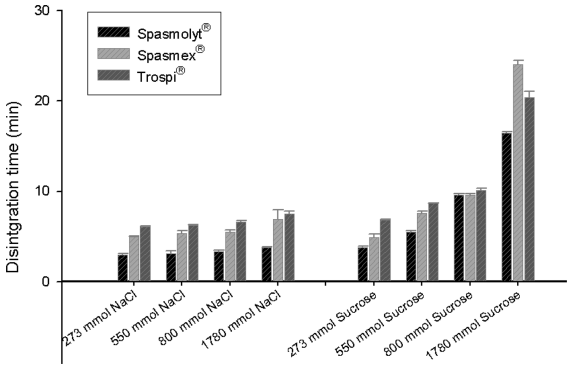

Figure 5. Disintegration times of various trospium chloride products in different osmolality solutions.

a dominating role for the disintegration process and not the osmolality parameter as such.

An inverse relationship exists between water diffusivity in the disintegration medium and the disintegration time which applies for media of different compositions (Figure 6).

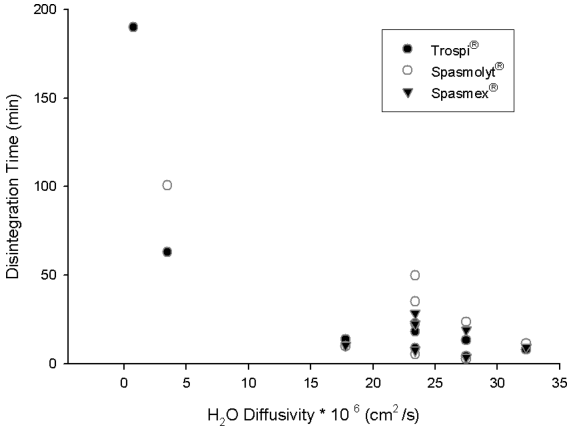

Figure 6. Relationship between water diffusivity and disintegration time for various products of trospium chloride in different media.

Effect of Media Composition on Drug Release. MDTs for the three formulations in various media are given in Table 3. Under standard conditions, trospium chloride tablets undergo rapid dissolution (85% within 30 min; see Figure 7). Increasing sucrose concentration in the medium leads to a pronounced elevation in the MDTs of the three products reflecting the slower disintegration of the tablets and the reduced water diffusivity into them. Drug release for the three products slowed

Table 3. Mean Dissolution Times for the Three Formulations in Different Osmolality Solution

		MDT (min)		
media w/w%	osmolality (mmol/kg)	Spasmolyt	Spasmex	Trospi
10% sucrose	273	9.6	12.5	9.7
15% sucrose	500	12.7	14.4	12.2
20% sucrose	800	12.5	15.3	14.1
38% sucrose	1780	15.1	20.7	17.3
0.8% NaCl	273	7.3	5.7	9.2
1.6% NaCl	500	6.8	8.3	10.9
2.3% NaCl	800	8.3	10.2	13.0
5.2% NaCl	1780	12.3	39	14.0

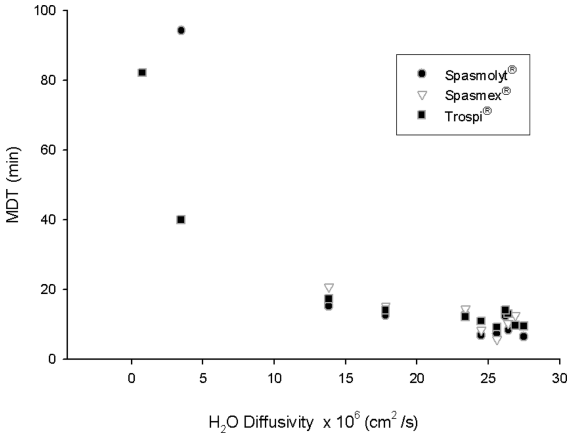

Figure 7. Relationship between mean dissolution times (MDT) for trospium chloride products and water diffusivity in the dissolution media.

down with increasing sucrose solution. In 55% sucrose solutions, Trospi (conventional tablet) was the least affected: 80% of the drug dissolved within 120 min, whereas the Spasmolyt tablet underwent an extensive swelling followed by disintegration after one hour and rapid drug release thereafter. Spasmex showed no dissolution at all in the investigated time frame of 120 min.

In 66.5% sucrose solution, the profile of Trospi showed a marked reduction in the dissolution rate, less than 20% of the drug from formulation dissolved at 120 min. For Spasmolyt and Spasmex no dissolution was observed, and the tablets showed extensive swelling, giving rise to a large swollen mass. Thus, sucrose presence in the media caused a pronounced reduction in the dissolution rate of the three products. The effect was more profound compared to equiviscous solutions of HPMC (data not shown).

MDT for the different products in sodium chloride adjusted SIF solutions, ranging in osmolality from 273 to 1780 mmol/kg, demonstrated that the dissolution in different solutions with identical osmolality is not same. For the sucrose containing solutions, mean dissolution times were always longer when compared to isosmolar solutions which had been adjusted in terms of osmolality using sodium chloride. This is in accordance with our theory.

DISCUSSION

Water diffusivity within gastrointestinal fluids determines the rate of water availability for tablet swelling and disintegration. Maximizing water mobility within the dissolution medium will increase water content inside the tablet and enhance its disintegration and dissolution.

A delay in tablet disintegration and dissolution has been observed under viscous conditions previously.[1] This effect was more pronounced in equi-viscous sucrose solutions compared to HPMC solutions. To explain these differences, water diffusivities in HPMC and sucrose media were measured by NMR. Interestingly, water self-diffusion coefficients in sucrose solutions were greatly lowered as compared to those in equiviscous HPMC solutions. This may be ascribed to the structural differences between the different agents. Sucrose solution is of molecular nature, whereas HPMC forms a polymeric solution.

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The relatively minor reduction in water diffusivity in HPMC solutions can be rationalized on the basis of polymer chains which impose tortuous diffusion paths for water molecules and act as a barrier hindering their mobility. On the other hand, the profound depression of water diffusivity with increasing sucrose concentration in solutions can be explained by molecular interactions between water and sucrose molecules through hydrogen bonding and also by means of physical steric hindrance. These findings are in agreement with previous reports, which ascribed the slow water dynamics in sugar solutions to the hydrogen bonding between sugar molecules and water.[21,22]

Reduced drug diffusivity in viscous sucrose media is another factor accounting for slowed drug release. Drug molecule movement is hindered by similar small size sucrose molecules. Moreover, sucrose solution was used at high concentration to produce similar viscosity solutions of HPMC; therefore, based on the free volume theory, the solvent volume available for drug diffusion is limited. Sucrose molecules have been reported to form clusters in concentrated solutions, thus reducing the free volume available for drug diffusion and restricting drug mobility to the voids between these clusters.[23]

The Einstein−Stokes equation describes a reciprocal relationship between the diffusion coefficient and viscosity. Accordingly, the diffusivity of the molecules will decrease as the viscosity of the media increase. The Einstein−Stokes equation is shown to be applicable for molecular sucrose solutions, whereas it does not hold for HPMC polymeric solutions. Deviation from Einstein Stokes behavior has been reported for hydroxypropylcellulose (HPC) solutions.[24] Diffusivity in aqueous polymeric solution is not affected by the macroscopic viscosity of the media, since the movement of solute and solvent molecules is not significantly hindered by polymer macromolecules. Nelson and Shah reported decreased diffusivity of p-aminobenzoate in sucrose solution under constant flow condition, whereas the diffusivity of the compound in HPC polymer is found to be negligibly affected.[25]

Reduced water availability may also explain the reduced solubility of trospium in sucrose systems and may contribute for the delayed disintegration and dissolution profiles.

Reduced water diffusivity in sucrose media compared to equal osmolality sodium chloride adjusted solutions could explain the observed differences in the disintegration and dissolution of the formulation in these media. Media osmolality as such showed an insignificant effect on drug release when maintained within the physiological range.

Future studies should demonstrate the effect of other food media composites such as peptides, amino acids, and other sugars such as lactose, glucose, and so forth, on water diffusivity. Due to their structural similarities, we expect similar tendencies as described here for sucrose.

An impact of nonfunctional film coating on tablet disintegration and dissolution has been demonstrated in this investigation. The observed differences between the formulations may be attributed to the presence of the film coat. For Spasmex and Spasmolyt the HPMC thin coat may undergo swelling forming a thick gel layer acting as a barrier for the diffusion of both the solvent and the drug molecules in and out of the tablet, respectively. Williams et al. have reported retarded drug release from HPMC matrixes in low concentration of sugar solutions due to formation of a gel layer and increased diffusion pathway for dissolved drug molecules.[26] An effect on nonfunctional film coats however has not been reported.

■ CONCLUSION

Water diffusivity in disintegration and dissolution media appears to be an ignored physiochemical parameter with relevance for predicting and controlling drug release. Water diffusivity affects solvent intrusion and is directly related to the drug release behavior and may be used for prediction purposes. The new insight on the role of water diffusivity may help in better understanding and predicting disintegration and dissolution process in media with nonpharmacopeial composition such as gastrointestinal fluid following ingestion of a meal.

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Notes

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