Biexponential T_2 approach to investigate water organization and molecular mobility of hydrated HPMC dosage forms. Influence of drug substances with different water solubility.

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Introduction

The growing interest in research on the dosage form dissolution process leads to application of appropriate MRI methods in order to quantify the phenomena occurring during this process. Knowledge of pharmaceutical formulation structure and hydration dynamics is necessary to create efficient and timely drug delivery systems. In this study, an MRI time-resolved approach was used to measure the spatial distribution of T_2 and Proton Density (PD) of hydroxypropylmethylcellulose (HPMC)-based tablets during hydration. As a result of the monoexponential T_2 data analysis in the previous MRI studies [1,2], usually two regions were identified: a dry polymer, and a gel layer. The structure of the hydrating polymer presented in the previous studies [3,4] suggests that it should be possible to distinguish more than only these two areas.

Materials/Methods

Influence of two active substances, that are freely and poorly soluble, on matrix structure during hydration was tested. The substances were L-dopa (LD) and Ketoprofen (KT) respectively. Three formulations, that is pure HPMC polymer (*Metolose 65SH400cP*), HPMC+LD (50:50) and HPMC+KT (50:50) were used; all tablets had a 9mm diameter. MR experiments were performed on a 11.7T vertical bore magnet (Oxford Instruments, U.K.) equipped with a 72mm ID gradient set (Magnex, UK) and an Avance console (Bruker,Germany). MR images were acquired using two sequences: MSME (Multi Slice Multi Echo) and BLIP (Broad Line Imaging Package Modes), in order to properly cover the timescales of T_2 decay during data acquisition and reveal two T_2 decay components within the tablet. Temperature was measured throughout the imaging via a thermocouple (22.0±0.5°C). The following MSME parameters were used: TE/TR = 6,5/4000ms, NEX = 2, number of echoes = 32, matrix size = 256x256x1, slice thickness = 1mm, FOV = 15x15 mm. TR was set to 4000ms to eliminate influence of T_1 on image intensity (longest T_1 was ~700ms). BLIP sequence parameters were: TE/TR = 3/500ms. NEX = 2, number of echoes = 10, matrix size = 256x256x1, slice thickness = 1mm and FOV = 15x15 mm. The first echo image was acquired after 3ms while the next 9 images were acquired with 1ms interleave. T_2 and proton density calculations were carried out using Matlab 2008a (The MathWorks, Inc.). Quantitative data analysis in terms of biexponential T_2 fitting was applied in order to distinguish regions with different hydration levels and water mobility.

Results/Discussion

In all three cases, two components (i.e., short and long) of T_2 decay were observed. Coexistence of two components along almost the entire hydrated area radius suggests a non-homogenous nature of the hydrated matrix. Ueberreiter [3] lists the following areas within the hydrating tablet: pure polymer, infiltration layer, solid swollen layer, gel layer, liquid layer and pure solvent. In our experiments solvent (dissolution medium) was removed prior to the MR experiments and thus only the first four layers were present. According to this classification the hydrated matrix can be divided into three radial regions, starting at the center of the tablet: 1) *infiltration layer* – an interface sublayer where only a short T_2 component exists with an amplitude which increases with the radius of the matrix (high total PD gradient in this region exists); 2) *solid swollen layer* - an interface sublayer, where the amplitude of the short T_2 component decreases and the long T_2 component appears ("amplitude crossing" pattern); and 3) *gel layer* – a semi-external layer, where both T_2 components coexist with almost constant amplitudes (while the T_2 value of both components increases slightly). In case of tablets with L-dopa (solubility – 1.66mg/mL) water penetration and subsequent hydrogel formation was facilitated by the dissolving drug which promoted water ingression into the matrix (Fig.1.). For formulation with ketoprofen (solubility – 0.24 mg/mL) the hydrogel formation was negligible (Fig.2.).

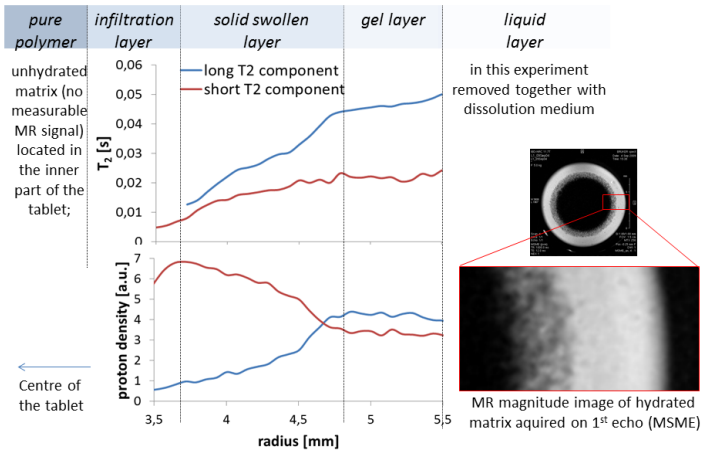

Fig.1. T_2 components for pure HPMC+LD after 2h of hydration with region segmentation.

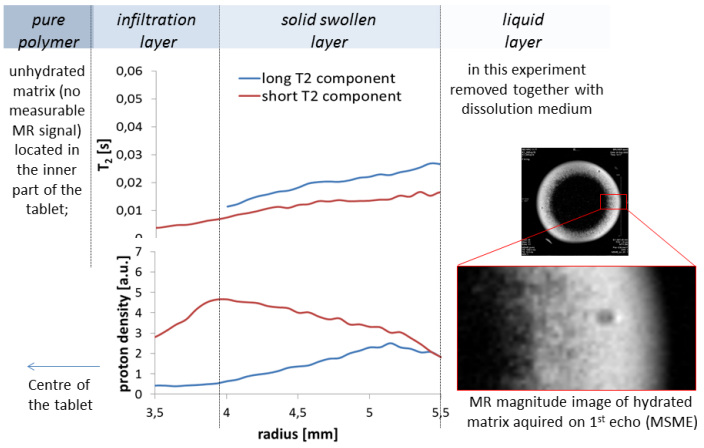

Fig.2. T_2 components for pure HPMC+KT after 2h of hydration with region segmentation.

Conclusions

In this study, an biexponential T_2 approach was used to distinguish regions with different water organization and molecular mobility. Subpixel-level heterogeneity during hydration was clearly visible, allowing a more accurate estimation of the hydration process dynamics. In all cases, the hydrated area consists of several separated sub-areas (layers) with well-defined properties. Differences between formulations with KT and LD were found. In case of the formulation with LD the solid swollen layer is thicker comparing to pure HPMC while gel layer is accordingly thinner due to smaller polymer concentration. In the case of KT formulation, the gel layer area is not present which has great influence on drug dissolution during hydration.
Combined with other pharmaceutical testing methods, the obtained results may provide useful information for the preparation of a dosage form with certain properties.

References

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