Influence of drug substances with different solubility on hydration processes of prolonged release tablets

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Introduction

Efficient and timely drug delivery requires knowledge of processes occurring inside the tablet during dissolution. In this work MR microscopy was applied for study of water mobility and concentration in tablets, used for drug delivery [1,2]. The tablets made of Hydroxypropylmethylcellulose-HPMC with and without addition of a drug substance of different solubility were tested. Time resolved, quantitative analysis of T_2 spatial distribution, water content, hydration and hydrogel formation are presented.

Materials/Methods

Six formulations, tablets of 9mm diameter were used (Tab.1). 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 at 22.0±0.5°C using a MSME sequence with a FOV=15x15mm, matrix size 256x256, TR/TE=4000/6,5ms, NEX=2, total scan time 30min. T_2 and proton density calculations were carried out using Matlab (The MathWorks, Inc.).

Tab.1. Tablet formulation with abbreviations used in text

HPMC-1	Metolose60SH10000cP (100%)
HPMC-1 + KT	Metolose60SH10000cP + Ketoprofen (50:50%)
HPMC-1 + LD	Metolose60SH10000cP + L-dopa (50:50%)
HPMC-2	Metolose65SH400cP (100%)
HPMC-2 + KT	Metolose65SH400cP + Ketoprofen (50:50%)
HPMC-2 +LD	Metolose65SH400cP + L-dopa (50:50%)

Results/Discussion

Two-dimensional T_2 and proton density (PD) maps were obtained. T_2 maps for HPMC-1, HPMC-1+LD and HPMC-1+KT are shown in Fig.1. Histograms of these maps at 120 minutes of hydration are shown in Fig.2. Three modes corresponding to different physicochemical properties of polymer-water-drug system are observed. First mode, with T_2 up to 20ms (low water mobility) and second mode with T2 between 20ms and 40ms are present in all formulations. For both HPMC+KT formulations, the third mode (T_2's above 40ms) was not observed. It suggests that gel layer (highest water mobility) was not created. Spatial T_2 and PD distributions along a tablet radius were also analyzed. Fig.3-5 show PD distributions at 30, 60, 120 and 180 min of hydration for all formulations containing HPMC-1 (Fig.1.). Additionally, T_2 distribution for HPMC-1 is presented in Fig.6. PD distributions showed differences depending on tablet's composition. PD level at 180 minutes is substantially lower than measured at 120min, while T_2 level remains almost unchanged (Fig.6.) except for formulations with KT. Possible explanations concern structural changes of the polymer-water-drug system [3,4] e.g. the sol-gel transition could result in water incorporation into polymer matrix thus received MRI signal decrease. Alternatively drop of PD value could be induced by syneresis effect, where liquid is extracted from a gel. However syneresis should be visible as gradual change in external region of hydrated tablet and should be correlated with decrease of T_2.

Conclusions

Different mechanisms of tablets hydration were observed due to composition of the formulations. The water penetration was faster in tablets containing drug substances but gel formation was better pronounced in pure HPMC tablets. The penetration of water into the tablet depended on the solubility of drug substance. In case of tablets with L-dopa (solubility – 1.66mg/mL) water penetration and subsequent hydrogel formation was facilitated by dissolving drug which promoted water ingress into the matrix. For formulation with ketoprofen (solubility – 0.24 mg/mL) the hydrogel formation was negligible. The experiment has shown that the phenomena occurring during drug dissolution are closely related to the properties of applied substances. It is especially important for the research and the development studies leading towards more effective drug delivery systems.

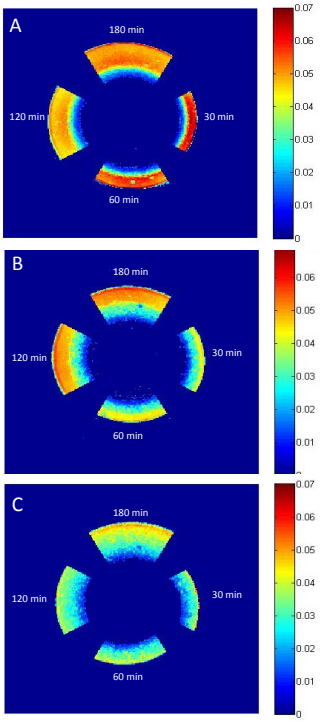

Fig.1. Fragments of T_2 maps at 30, 60, 120, 180 minutes: A) HPMC-1, B) HPMC-1+LD. C) HPMC-1+KT.

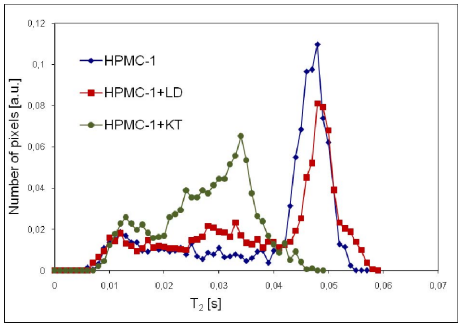

Fig.2. T_2 map histograms at 120 minutes of hydration.

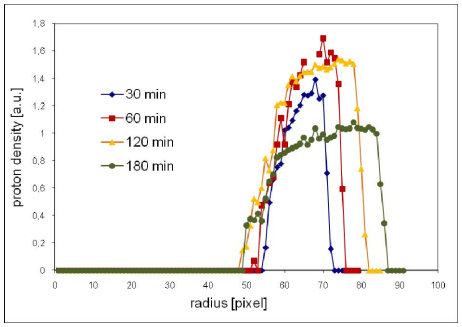

Fig.3. HPMC-1 proton density profiles.

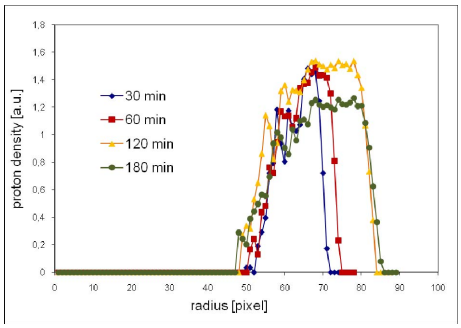

Fig.4. HPMC-1+LD proton density profiles.

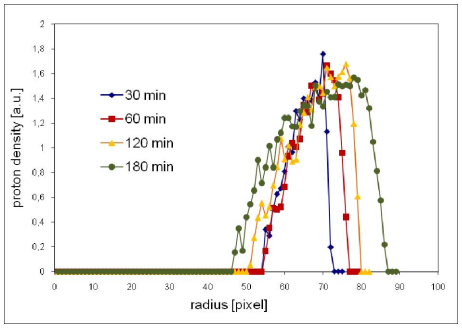

Fig.5. HPMC-1+KT proton density profiles.

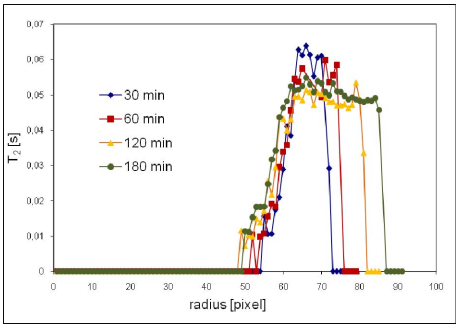

Fig.6. HPMC-1 T_2 profiles.

References

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