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Spatially resolved studies of hydrating polymeric matrices – true medium penetration and polymer mobilization

Introduction

The development of drug delivery systems with specific properties, e.g. specific drug dissolution profiles, is of fundamental importance for the pharmaceutical technologists both from the industry and academia. The drug dissolution process is a result of complex interactions of multiple factors. The most important are:

- drug properties: solubility, crystalline structure, particle size, polymorphic forms etc.,
- characteristics of excipients: type, solubility, viscosity, particle size etc.,
- structural characteristics of dosage form: porosity, geometry, physical properties (hardness, tensile strength) etc.

All these factors influence the mechanisms of water transport inside the matrix and drug dissolution and transport outside. Therefore, it is, in general, difficult to predict the dissolution behaviour of solid matrices. The studies of mechanisms of drug dissolution were carried out for more than five decades. However, introduction of Magnetic Resonance Imaging techniques in 1990s. brought real insight into the processes occurring within the dosage forms during hydration in a non-invasive way [1, 2]. The review of various MRI techniques that were applied for characterization of drug delivery systems including Single Point Imaging (SPI) method can be found in review articles by Mantle [3] and Dorożyński et al. [1]. These review articles can also serve as an introduction to Magnetic Resonance Imaging – they cover many topics, including relaxation times. Moreover, excellent introduction to T_2 and T_2^* relaxation times in the context of samples characterized by existence of short and very short T_2 and T_2^* components can be found in the article by Robson et al. [4].

Due to the physical requirements of Nuclear Magnetic Resonance signal acquisition, the main area of interest for the application of this technique is monitoring the water (protons) distribution and mobility within the pharmaceutical matrix systems. However, in some specific conditions, the protons with very short relaxation times, even from un-hydrated polymeric matrix, can be recorded. There are two

main reasons for the application of methods allowing for the acquisition of a signal originating from regions characterized by very short T_2/T_2^* relaxation times:
– assessment of true solvent (water) penetration,
– assessment of polymer distribution and mobilization.

The aim of this work is to present an overview of methods that can be used for these purposes together with a short discussion of the results and future perspectives of their application.

Review of the application of short echo time sequences

Assessment of polymer distribution within the hydrated matrix can be achieved by separating the signal from polymer chains and the medium. One possible solution is the immersion in deuterated medium (D_2O). The approach was used for obtaining water and polymer concentration profiles of hydrating poly(ethylene oxide; PEO) with T_1 preconditioned spin-echo imaging sequence (echo time of 5.65 ms) by Hyde and Gladden in 1998 [5]. Because ^2H nuclei have different resonance frequency than ^1H, ^1H imaging allows direct observation of polymer protons. In this study, polymer concentration profiles were obtained twice independently: (1) directly in D_2O and (2) in H_2O by T_1 fitting assuming two T_1 components. Both methods gave similar results, however T_1 measurement in H_2O gave higher local variations in assessed profiles. The authors suggest that the local variations arise exclusively from the presence of air bubbles in the swollen matrix.

The example of spin-echo based studies was combined Broad Line Imaging Package (BLIP) and Multi Slice-Multi Echo (MSME) study by Kulinowski et al. [6, 7] at 11.7 T (echo times started from 3 ms, repetition time TR=500 ms for BLIP and 4s for MSME, in-plane spatial resolution of 59 μm). One of the goals was to obtain a signal from minimally hydrated part of the matrix. 2D images of hydrating model matrices containing pure hydroxypropylmethyl cellulose (HPMC) and HPMC with drug substances of different solubility were obtained. The shortest available echo time was of 3 ms and it allowed registering sharp hydration front (high proton density gradient) as well as detection of minimal hydration of the matrix core. But the echo time used did not allow direct polymer imaging – it requires starting signal acquisition as soon as possible after excitation (in the order of tens of microseconds). In this study, T_2 mapping revealed two components in the analyzed signal – a situation similar to that described in the study by Hyde and Gladden [5]. The shorter component was probably somehow related to mobilized polymer and originating from water in close vicinity to polymeric chains.

By using spin-echo techniques, the authors of the works described shortly above could not obtain signal from the whole matrix, including un-hydrated part of the matrix. The regions of the matrix having T_2s in the order of milliseconds denote plastic (swollen) phase. To be able to acquire signal from solids (T_2s in the order of tens of microseconds – lower than ~50 μs), SPI pulse sequence can be used [3].

T_2 mapping with 1D Single Point Imaging sequence was applied for studies of xanthan matrices loaded with pentoxifylline (highly water-soluble drug) by Mikac et al. [8] at 2.35 T (encoding time t_p=0.17 ms, rf pulse angle α=20°, repetition time TR=200 ms, inter echo time varied between 0.3 and 10 ms, spatial resolution of 350 μm). The xanthan matrices were hydrated in six media differing in pH and ionic strength. The SPI sequence was used as one of the imaging methods to fill the gap in signal acquisition from regions characterized by very short T_2^*/T_2 relaxation times (for regions with T_2 values shorter than 5 ms). The sequence was used for determining the border between dry and hydrated glassy xanthan. In this study, only true solvent penetration could be assessed, polymer concentration was out of the scope of the study.

Application of D_2O as a dissolution medium was used in a set of papers utilizing SPI technique at 4.7 T published by Dahlberg et al. [9-11]. In the first work, the authors assessed the polymer mobilization (^{1}H 1D SPI with encoding time t_p=40 μs, rf pulse flip angle α≈10°, spatial resolution of 59 μm, acquisition time of 7 min.) of tablets containing solid dispersion of antipirine, highly water-soluble substance, and HPMC (13 wt. % of drug) [9]. Using SPI, it was possible to obtain images of tablets starting from unhydrated tablets. To allow 1D imaging, matrix hydration was allowed only from one side – the matrix tablet was placed in a test-tube and sealed. Similar approach enabled assessment of local hydration level (^{2}H 1D SPI with encoding time t_p=36 μs, rf pulse flip angle α=5.5°, repetition time TR=100 ms, spatial resolution of 117 μm, acquisition time of 8 min.) and local mobility of the polymer matrix (^{1}H 1D SPI with encoding time t_p=150 μs, rf pulse flip angle α=22.6°, repetition time TR=400 ms, spatial resolution of 78 μm, acquisition time of 14 min.) [11]. In this case the subject were HPMC based solid dispersion matrix tablets containing flutamide (a substance poorly soluble in water) and matrix tablets containing physical mixture of HPMC and drug. The authors strongly emphasized that polymer mobility profiles obtained by 1D SPI imaging cannot be interpreted in quantitative manner. It is due to the complicated signal dependency on sequence parameters (TR and t_p) and on sample properties (T_2 and T_1 relaxation times). Interesting feature observed for matrices with antipyrine, which is a very water-soluble drug substance, was a dent in the polymer concentration profile at the position of initial tablets border starting from 5 h of hydration (Dahlberg et al. [9]). It was identified by authors as a potential artefact caused by the holder, but other explanation should be taken into account, i.e. damping of polymer signal due to highest local porosity of the hydrated matrix. The effect was not reported for matrices containing flutamide, which is practically insoluble in water.

Another interesting approach is the work by Knöös et al. [12], where drug-loaded (with griseofulvin – a substance practically insoluble in water) Hydrophobically Modified Poly (acrylic acid) (HMPAA) tablets were studied by 1D Chemical Shift Imaging (spectral width SW=20 ppm, echo time TE=0.5 ms, repetition time RD=5 s, 64 gradient steps giving spatial resolution of 317.8 μm, acquisition time 20 min.).

In the CSI method Magnetic Resonance, the whole spectrum is assigned to each spatial location (not single image intensity as in the case of simple imaging). Therefore, it is possible to construct spatial images from components present in the MR spectrum by fitting or integration of separate spectral lines. In this particular case the surfactant, protons of ethanol (EtOH), polymer and semiheavy water (HDO) can be distinguished in the spectrum.

In all presented studies, with the exception of works by Kulinowski et al. [6, 7], matrix swelling was considerably restricted – matrix swelling was allowed in one direction only. On the one side it simplifies the experimental setup but on the other side it is a highly unrealistic situation. Polymeric matrices loaded with drug used as an oral, modified release dosage forms swell freely in all directions. SPI method used in most of these studies acquires one data point per gradient step – it makes the acquisition slow and in consequence impractical for in vivo studies as well as for studies of dynamically changing objects as in the case of hydrating polymeric matrices [3, 13]. From the point of view of pharmaceutical technologist, the ability to image hydrated matrices swelling without restriction is crucial. Ultra Short Echo Time sequence (UTE) allows 2D or 3D image registration, while it relies on slice-selective radio frequency pulses and typically radial sampling of k-space. It makes possible to obtain very short echo times – typically 100–250 μs. The technique was used, for example, for imaging of the enamel, dentine, bones, tendons or knee menisci, where T_2 relaxation times ranged from 70 ms to 10 ms [4, 13]. Moreover, UTE also allow a reasonable acquisition times for 2D images, which should be less than 15 min for HPMC matrices under hydration. Therefore, it can be concluded that UTE techniques can be successfully applied to studies of polymer matrix hydration.

Conclusion

Despite its advantages, the SPI method allows mainly 1D imaging at reasonable acquisition time. Alternatively, UTE sequences can be used to obtain 2D images from a selected slice which is a significant advantage over previously used 1D methods.

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Abstract

The article gives an overview of application of Magnetic Resonance Imaging methods for characterization of hydrating polymeric matrices loaded with drug substances used as modified release oral dosage forms with emphasis on regions/materials having very short T_2^*/T_2 relaxation times. These methods allow for detection and imaging of low mobility water inside the matrix as well as gradually mobilizing polymeric chains.

Key words: Matrix tablets, Magnetic Resonance Imaging methods, Single Point Imaging, Ultra Short Echo Time Imaging, Chemical Shift Imaging

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