

Polymer mobilization and drug release during tablet swelling

A ^1H NMR and NMR microimaging study



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Introduction

Pharmaceutical tablets have been investigated to obtain information about the molecular processes during release. Nuclear magnetic resonance (NMR) imaging revealed *in situ* the swelling behavior of tablets when exposed to water. By using deuterated water, the spatial distribution and

molecular dynamics of the polymer carrier hydroxypropyl methylcellulose (HPMC) and its kinetics during swelling could be observed selectively. In parallel, NMR spectroscopy provided the concentration of the drug released into the aqueous phase.

1D Constant time imaging

For both our imaging and release experiments two flat-faced tablets with the hydrophilic drug antipyrine incorporated in a HPMC matrix (Fig. 1) were fixed onto a support, see Fig. 2. The tablet swelling and the drug release were restricted to one dimension.

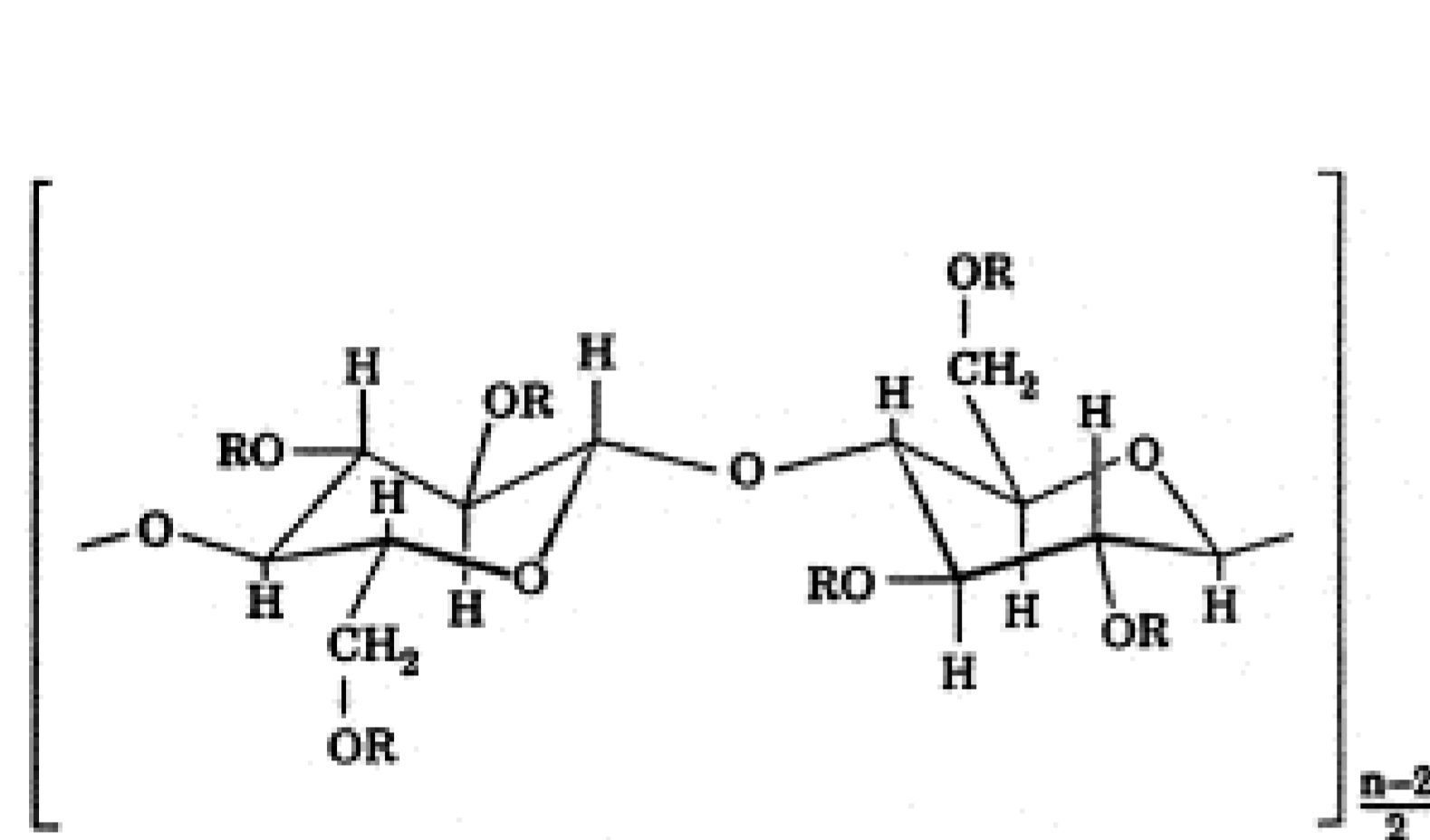


Fig. 1. Chemical structure of HPMC. The substituent R represents either a $-\text{CH}_3$, or a $-\text{CH}_2\text{CH}(\text{CH}_3)\text{OH}$ group, or a hydrogen atom.

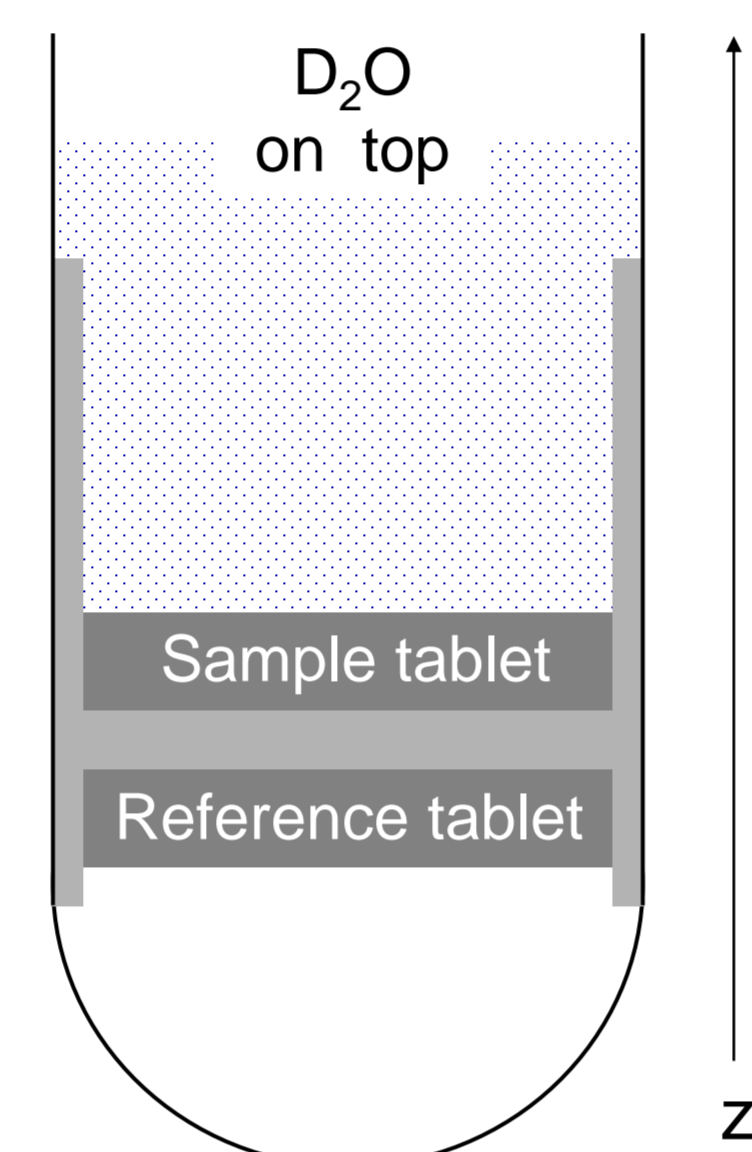


Fig. 2. Schematic image of the sample setup.

Generation of NMR images of rigid and semi-rigid polymers is hampered by their short transverse relaxation time, T_2 . By using a one-dimensional constant time imaging (CTI) sequence [1] the entire swelling process could be followed, starting with the dry tablet. This pure phase encoding method provides high-resolution images for materials with short T_2 and allows investigation of the polymer properties directly.

Polymer swelling and drug release

A possible indicator of polymer swelling is the rate by which the swelling front moves, see Fig. 4. To connect our results to release characteristics, we also used spectral integrals obtained by ^1H NMR spectroscopy to measure the concentration of the drug in the water above the tablet, see Fig. 5.

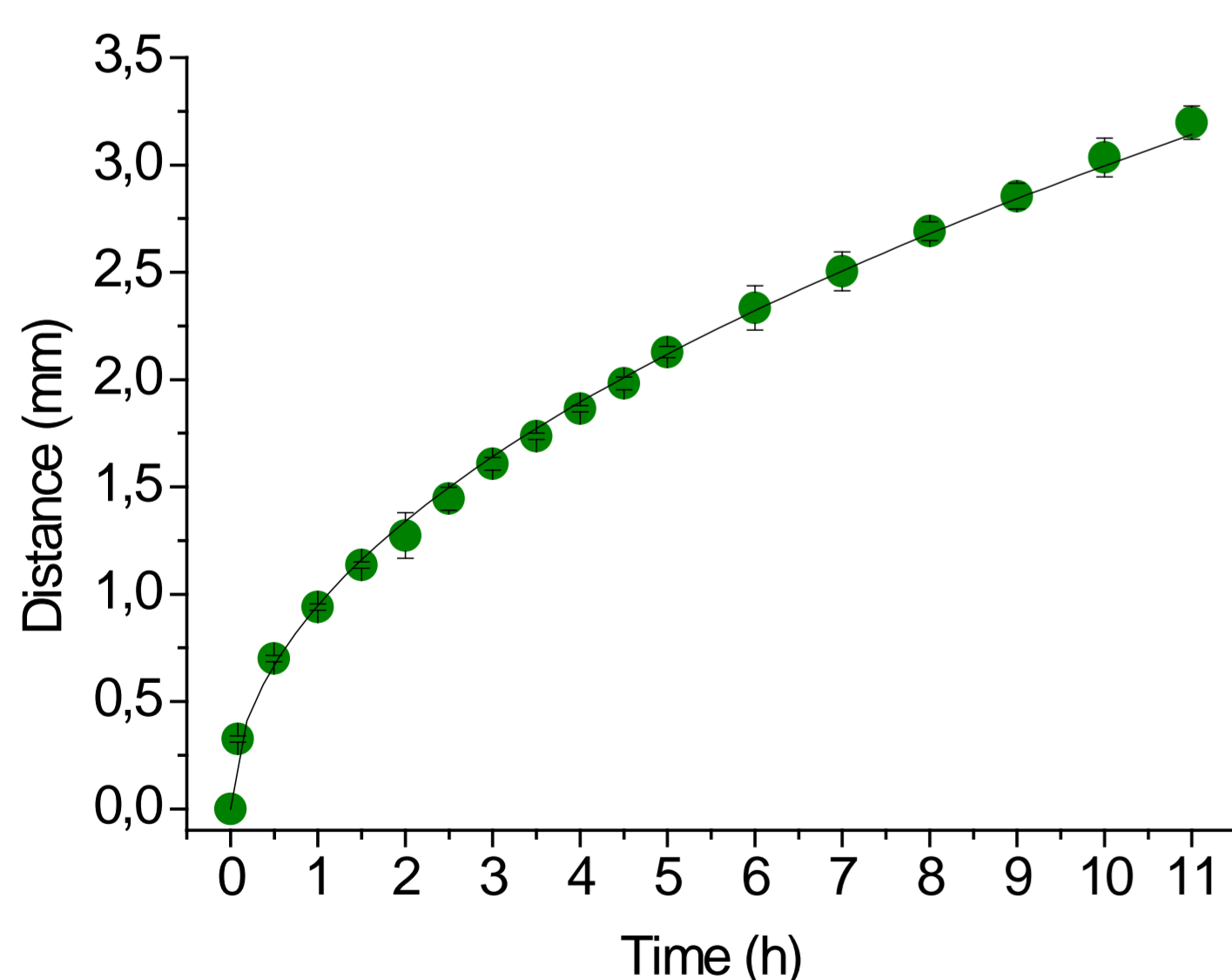


Fig. 4. Movement of the polymer hydration front.

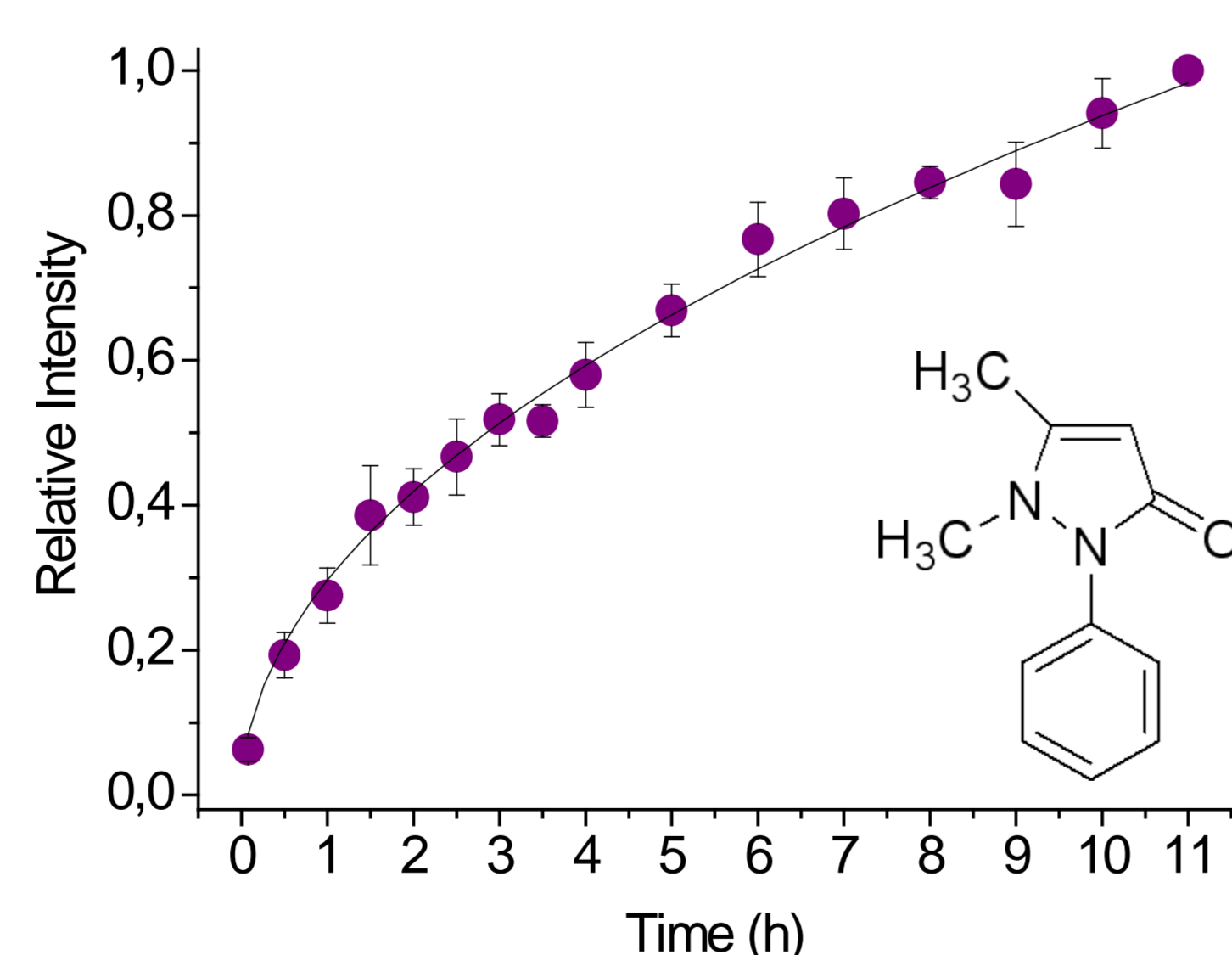


Fig. 5. Relative amount of antipyrine released from the tablets. The chemical structure of antipyrine is shown.

Spatial distribution of polymer carrier

The evolution of the distribution and hydration of the HPMC polymers of the tablets undergoing D_2O penetration is illustrated by ^1H NMR images shown in Fig. 3. As deuterated water penetrates further and further into the tablet, the polymers became more mobile and attain a longer T_2 value which leads to increasing image intensity. Further, the gel-like polymer layer on the top swells and enters into regions which initially contained no HPMC.

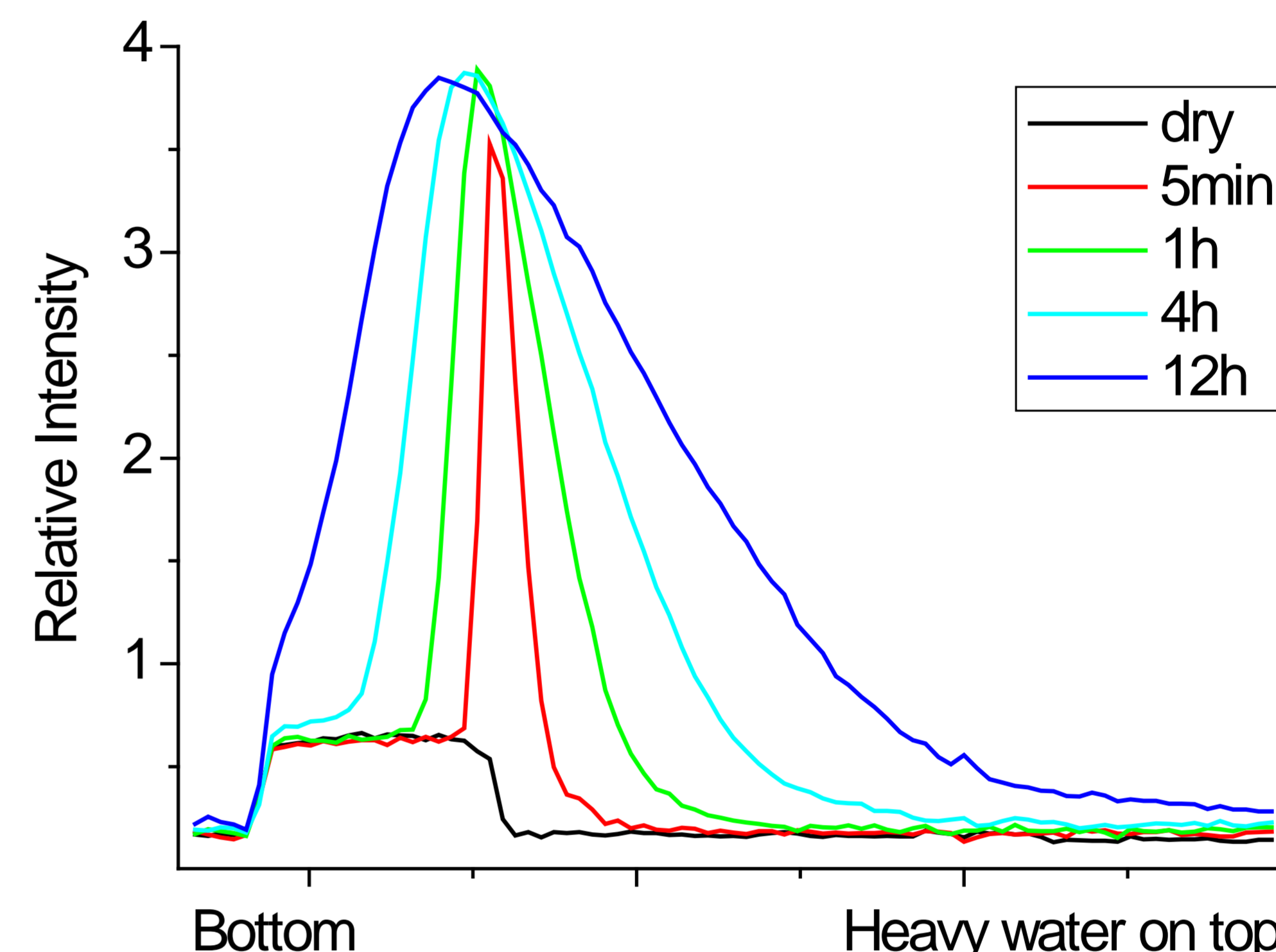


Fig. 3. ^1H NMR images illustrating the evolution of the distribution of the HPMC polymers during the swelling process for one tablet. The nominal spatial resolution is $59\ \mu\text{m}$.

The rate determining step for drug release

As can be seen in Fig. 6, all data recorded for the same tablet scale as a linear function of $t^{1/2}$, which indicates that swelling and release are diffusion controlled. This can be explained by assuming that the rate-determining step of release is the polymer swelling, compared to which the diffusion of the small and hydrophilic antipyrine across the formed gel layer is fast. The diffusion coefficient characterising the swelling and/or release processes was determined to $3 \times 10^{-10}\text{m}^2/\text{s}$.

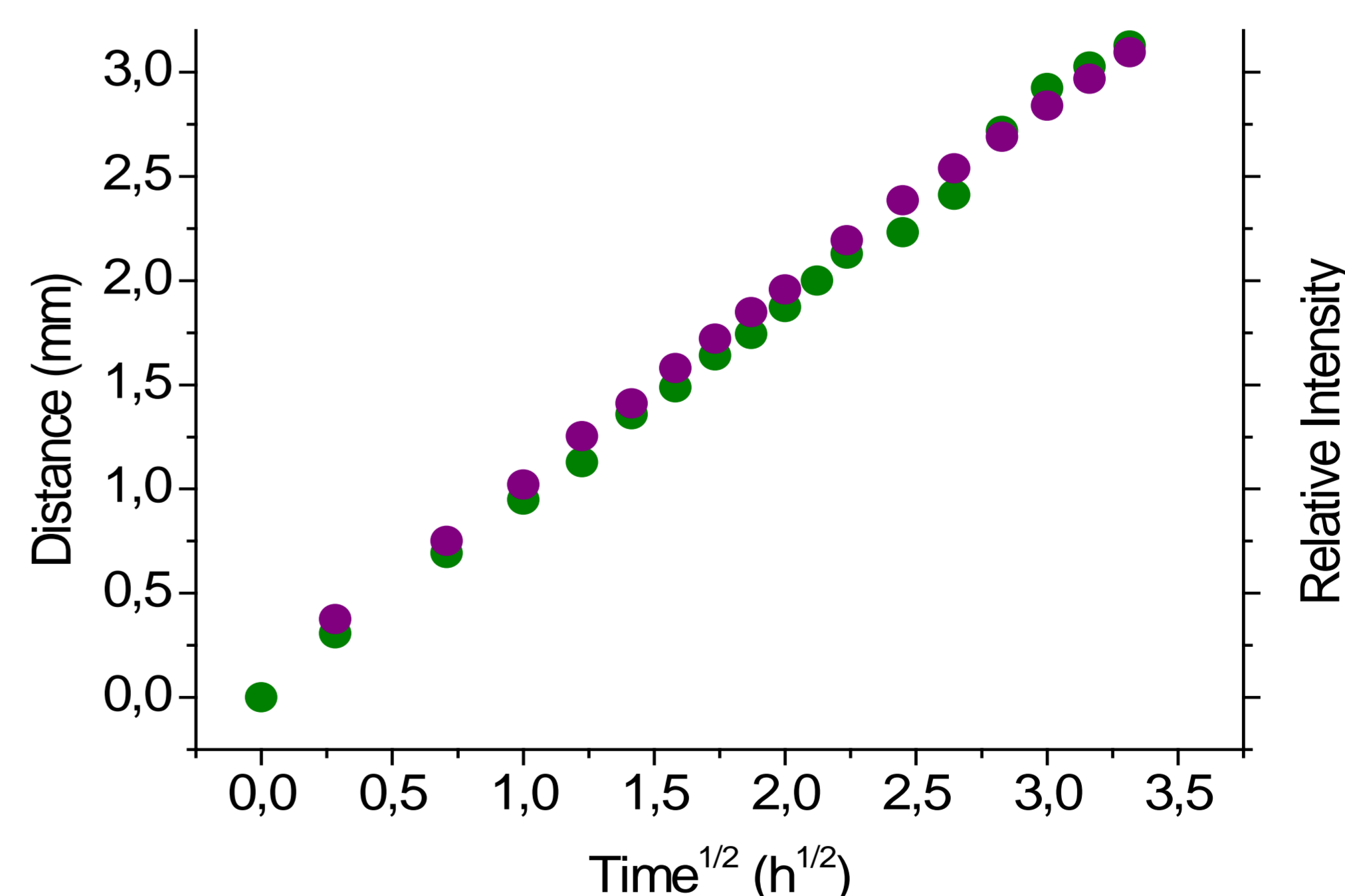


Fig. 6. Both the release data () and the swelling data () follow a linear function of $t^{1/2}$, indicating that both processes are diffusion controlled.

Conclusions

The ability of monitoring both the swelling and the drug release processes using the same experimental setup has important advantages when evaluating the drug-polymer-solvent interactions and their affects on drug release.

We demonstrated that in this specific system the swelling dynamics dominantly controls the drug release kinetics. This provides new opportunities for our understanding of tablet dissolution on a molecular scale [2].

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[1] S. Gravina and D.G. Cory, Sensitivity and Resolution of Constant-Time Imaging, J. Magn. Reson. 104(1) (1994) 53.
[2] C. Dahlberg et al., Polymer mobilization and drug release during tablet swelling. A ^1H NMR and NMR microimaging study, J. Cont. Rel. In press (2007)