Experimental report

15/09/2019

Proposal: 9-13-795 **Council:** 10/2018

Title: Diffusion of active pharmaceuticalingredients in supra-molecular gels

Research area: Other...

This proposal is a resubmission of 9-13-754

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Samples: Paracetamol in 7:3 water/ethanol gel
Paracetamol in 7:3 water/ethanol solution
Ibuprofen in 7:3 water/ethanol gel
Ibuprofen in 7:3 water/ethanol solution
Tetracycline HCl in 7:3 water/ethanol solution
Tetracycline HCl in 7:3 water/ethanol gel

Instrument	Requested days	Allocated days	From	To
IN16B Si 111 BATS	6	6	08/07/2019	14/07/2019

Abstract:

This is a continuation proposal to 9-13-634. In this earlier experiment on IN16B we measured the diffusion of three different drug compounds within a supramolecular gel at 265 and 270 K, and found that depending on their charge and size the diffusion coefficient is either larger, smaller or equal to that found in the solution. We now propose to follow this experiment up with measurements in the new BATS mode on IN16B. Due to the larger energy range of this setup, we will be able to to measure the same samples at approximate body temperature of 310 K, which is pharmaceutically more important for drug delivery.

This proposed study on drug-loaded samples complements our already published study on the associated unloaded solvents and gels using both QENS and NMR [Chem.Comm., 2018, 54, 6340].

Importantly, neutron backscattering accesses unique time- and length scales that are not accessible by NMR. Due to the supramolecular scaffold in the gel samples, the different observation scales of backscattering and NMR are fundamentally important.

Experimental report to experiment 9-13-795

During the previous experiment (9-13-634) on IN16B, we were able to measure gels based on gelator 1 and 7:3 v/v water/ethanol, loaded with three different pharmaceutically relevant compounds: ibuprofen sodium, paracetamol and tetracycline hydrochloride. These show differences in size and charge and thus can interact differently with the gel scaffold. QENS data were collected to probe the pico- to nanosecond diffusion coefficients, which give us direct information about the interaction of the drug load with the gel fibre network. There is currently no other analytical technique giving us that information on the nanometer lengthscale.

Fitting the obtained data from the earlier experiment (Fig. 1 and 2) indicates a different diffusion behaviour for each of the three solute molecules, which one being faster diffusing in the gel, one slower diffusing in the gel and one without any detectable changes in diffusion behaviour. However, due to the restrictions on energy range on IN16B in normal mode, the errors on the fits are very large and thus we could not clearly define the diffusion model (jump diffusion vs Brownian diffusion).

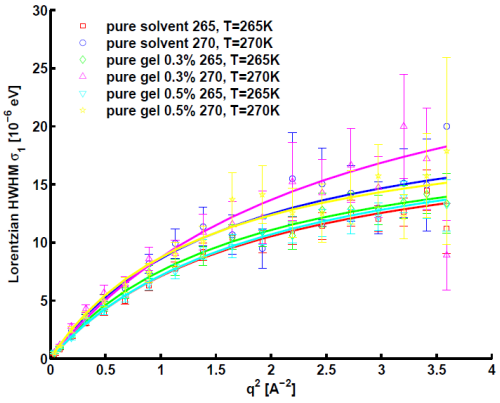

Figure 1 preliminary modelling of the pure solvent diffusion in bulk solvent and gel as modelled using a jump-diffusion model.

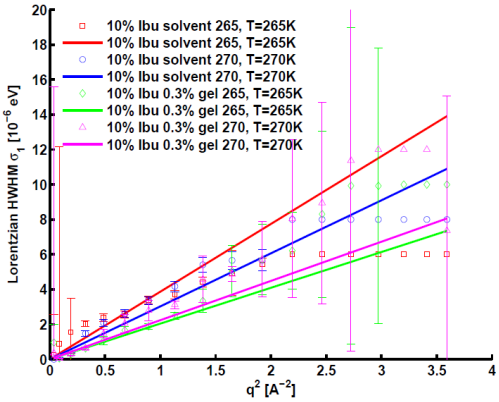

Figure 2 Preliminary modelling of ibuprofen sodium diffusion in bulk solvent and gel

In this continuation experiment, we have used the new BATS mode on IN16B, that enables us to probe a wider energy range with higher resolution. We measured the following samples:

Saample	Temperature
Pure 7:3 v/v D2O/EtOH-d6 solvent	270, 280, 290 and 310 K
3% w/v gel in 7:3 v/v D2O/EtOH-d6	270, 280, 290 and 310 K
5% Paracetamol in 7:3 D2O/EtOH-d6 solution	270, 280, 290 and 310 K
5% Paracetamol in 0.3% w/w gel in 7:3 D2O/EtOH-d6	270, 280, 290 and 310 K
5% Ibuprofen sodium in 7:3 D2O/EtOH-d6 solution	270, 290 and 310 K
5% Ibuprofen sodium in 0.3% w/w gel in 7:3 D2O/EtOH-d6	270, 290 and 310 K

Tetracycline as third guest molecule was abandoned due to time restrictions based on problems with the choppers. Since these stopped overnight in the beginning of the experiment leading to loss of experimental time. We thus decided to collect full datasets on two solute molecules.

Preliminary fits to the data of Ibuprofen sodium and Paracetamol are shown below (Fig. 3). With the increased energy window and better resolution, we can now confirm that the solute molecules follow a jump diffusion model, which can be clearly seen by the shape of the graphs. The data is much less noisy and thus much more reliable than the earlier data.
Furthermore, the diffusion behaviour of the solute molecules could be redetermined and matches our earlier observations. Figure 3 clearly shows a slower diffusion of paracetamol in the gel when compared to the bulk solvent, whilst ibuprofen sodium diffusion stays the same within the two phases.

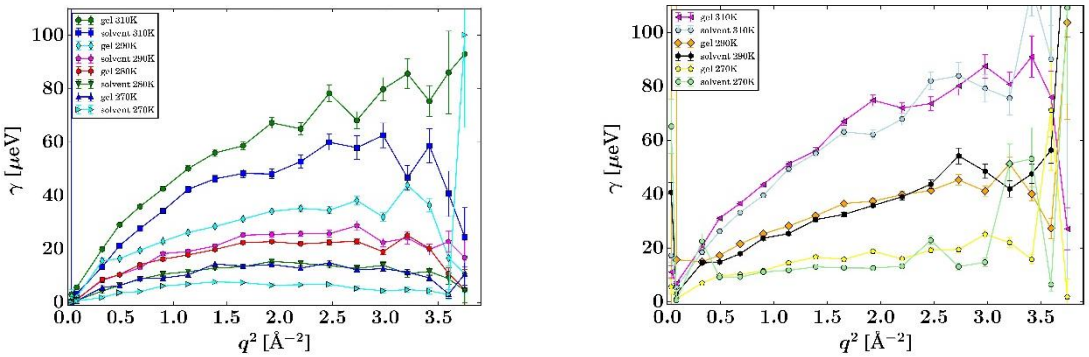

Figure 3 Preliminary modelling of paracetamol (PCM, left) and ibuprofen sodium (IBU, right) diffusion at different temperatures in bulk solvent and gel using a jump-diffusion model

Final fitting is still ongoing but the overall trend will most likely not change anymore and highlights the non-trivial behaviour of solute molecules in supramolecular gels.