Experimental report

13/09/2023

Proposal: 8-04-935 **Council:** 10/2022

Title: Drug release kinetics & water diffusion in a long-acting peptide hydrogel drug delivery implant for combined contraception & HIV prevention

Research area: Engineering

This proposal is a new proposal

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Samples: 5% peptoid-D-peptide MIV-150 + cabotegravir
Negative control (alkaline phosphatase 10.0 U/mL, buffer)
5% peptoid-D-peptide MIV-150 + etonogestrel
5% peptoid-D-peptide cabotegravir + etonogestrel
5% triple peptoid-D-peptide combination (MIV-150 + cabotegravir + etonogestrel)

Instrument	Requested days	Allocated days	From	To
IN5	5	5	19/05/2023	24/05/2023

Abstract:

We are developing a hydrogel implant for the combined delivery of HIV/AIDS and contraceptive drugs over a prolonged period e.g. 28 days. This implant is composed of tissue-like peptides for enhanced biocompatibility. Patients struggle to adhere to complex regimens of these medicines, which require a cocktail of drugs to be taken several times daily. Our therapy removes this need, improving adherence to medication. The objective of this project is to generate Quasi-Elastic Neutron Scattering (QENS) data using IN5 instrument to probe water diffusion within our hydrogels on the picosecond timescale in the presence of multiple model hydrophobic HIV/AIDS and contraceptive drugs. Dynamics/diffusion of water within our hydrogels are important in determining drug release kinetics. QENS data will support our rheology, microscopy, DOSY, spectroscopy and drug release and previous SANS data obtained at ILL. This will allow us to tailor diffusion within the gels to drug release kinetics for sustained 28-day delivery by modifying the chemical structure of our hydrogel forming peptide.

Garry Laverty. Experiment 8-04-935: Drug release kinetics and water diffusion in a long-acting peptide hydrogel drug delivery implant for combined contraception and HIV prevention.

Background: Our research group is developing a long-acting injectable formulation for the combined delivery of HIV and contraceptive drugs. The focus of this work is peptide-mimetic hydrogel composed of a low molecular weight peptoid-D-peptide molecule that responds to the presence of physiological enzymes (phosphatases) to form a hydrogel *in situ* upon injection. The ultimate goal is to provide HIV preventative and contraception protection to women in a discretely administered platform for ~84 days.

Aims/Objectives: In this study, we aimed to study whether the combined presence of two or more drugs (contraceptive + anti-HIV) has an impact on the diffusion and dynamics of water within the gel, as compared to bulk, on the picosecond timescale, using Quasi Elastic Neutron Scattering (QENS) on IN5. This data should inform drug release kinetics alongside our rheology, SANS, rheo-SANS, microscopy, spectroscopy and drug release studies.

Experimental: Time-of-flight QENS was performed using the IN5 instrument at the Institut Laue – Langevin, Grenoble, France. The following peptoid-D-peptides groups were studied: i) peptoid-D-peptide control with no drugs (S2), ii) three dual peptoid-D-peptide combinations a) MIV-150 + cabotegravir (1:1 ratio) (S3); b) MIV-150 + etonogestrel (9:1 ratio) (S4); c) cabotegravir + etonogestrel (9:1 ratio) (S5), iii) a triple peptoid-D-peptide combination of ratio 4.5: 4.5: 1 (MIV-150: cabotegravir: etonogestrel) (S6). Gels were formulated by the addition of be studied at a total concentration of 5% w/v peptoid-D-peptide, across four temperatures (275 K, 285 K, 295 K, 305 K) and neutron incident wavelengths of 5 and 8 Å. A negative control containing all components except peptoid-D-peptide (S1) was measured at the same conditions to ensure that the diffusion coefficient is not influenced by other components (e.g. phosphatase enzyme, D_2O) and provided additional bulk behaviour comparison. Samples were house in thin annular aluminium cans relevant to the minimization of effects like multiple scattering and absorption. Data reduction and analysis was performed using ILL software tools.

Preliminary Results: Triple drug peptoid-D-peptide (S6) data relating to a) temperature dependent Q-averaged data (5 Å), b) Q-dependent data at 305 K (5 Å) and (c) Q-dependent data at 305 K (8 Å) is shown in Figure 1, alongside some preliminary data (d) for all samples at 305 K (5 Å, Q=1.1 $Å^{-1}$).

On-going Progress: Our peptide and peptide-mimetic molecules form gels that are proven to effectively scatter neutrons.[1] Figure 1 demonstrates clear QENS trend as a function of temperature and momentum transfer observed within the instrumental time window. Careful analysis should be performed to disentangle dynamics related to the different samples' components. In this context, the large amount of data generated is currently being processed including a plot of fitted diffusion coefficients for each sample vs. temperature of bulk solvent. This will offer significant insight into the interactions between multiple solutes (drug combinations, peptoid-D-peptide) and supramolecular material structures. We are correlating QENS data to related observations for experiments conducted in our lab, especially Diffusion Oriented Nuclear Magnetic Resonance Spectroscopy (DOSY) which is being used to study diffusion kinetics of water at a longer nanosecond timescale. This dataset will form the basis of a research paper the experimental team will submit to a high quality journal.

Next Step: We intend to use QENS to study individual drugs, too decipher whether there is a difference in diffusion and dynamics of water within the gel for specific drugs and how this needs to be taken into account when optimising the pharmaceutical formulation structural/molecular design of peptoid-D-peptide long-acting injectable products for combined HIV prevention and contraception.

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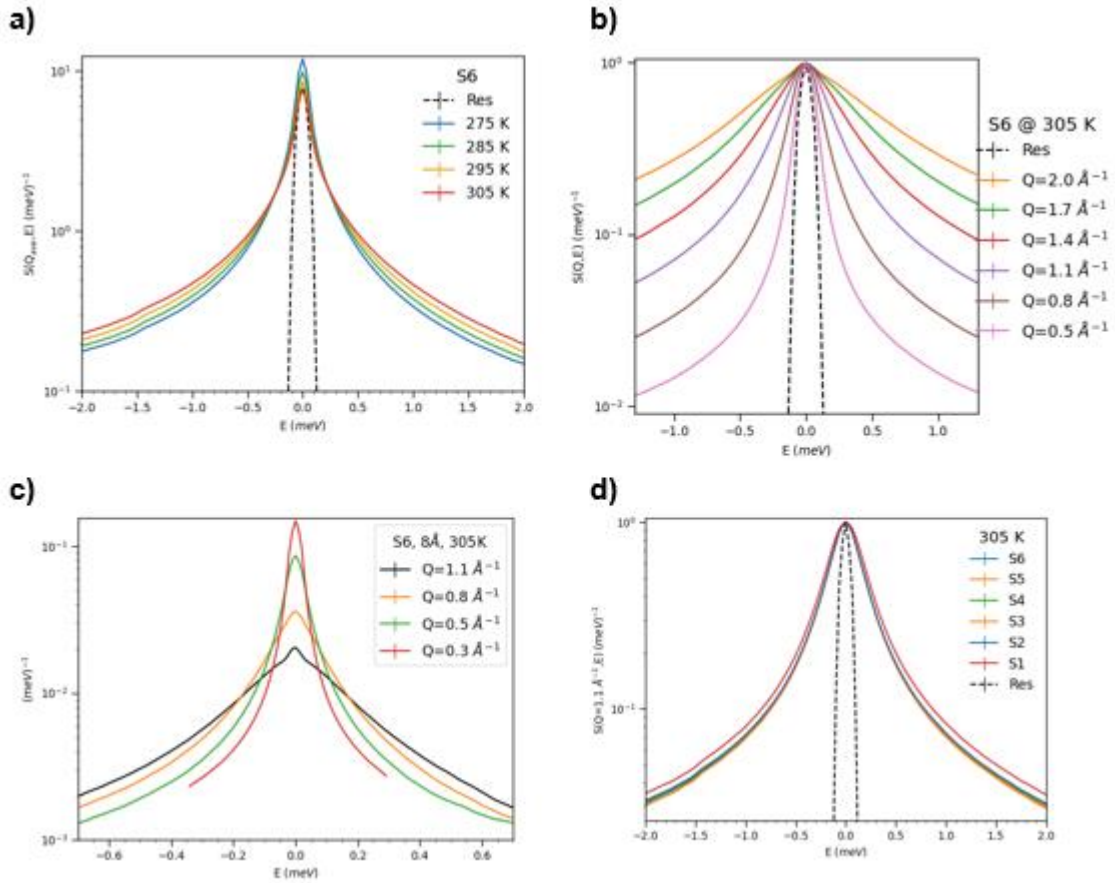

Figure 1. Time-of-flight QENS data from IN5 measurements plotted for S6 = the triple peptoid-D-peptide combination of ratio 4.5: 4.5: 1 (MIV-150: cabotegravir: etonogestrel) **a)** Temperature dependent, Q-averaged time-of flight-based spectra at neutron incident wavelength of 5 Å, **b)** Q-dependent data at 305 K and 5 Å, **c)** Q-dependent data at 305 K and 8 Å, **d)** QENS data for all samples and Q=1.1 $Å^{-1}$ at 305 K and 5 Å. S1 = negative control, S2 = peptoid-D-peptide alone (no drug), S3 = peptoid-D-peptide + MIV-150 + cabotegravir, S4 = peptoid-D-peptide + MIV-150 + etonogestrel, S5 = peptoid-D-peptide + cabotegravir + etonogestrel, Res = instrumental resolution.

References: [1] S.M. Coulter, S. Pentlavalli, L.K. Vora, Y. An, E.R. Cross, K. Peng, K. McAulay, R. Schweins, R.F. Donnelly, H.O. McCarthy, G. Laverty, Enzyme-Triggered l-α/d-Peptide Hydrogels as a Long-Acting Injectable Platform for Systemic Delivery of HIV/AIDS Drugs, Advanced Healthcare Materials, 12 (2023) 2203198.