Experimental report

05/06/2020

Proposal: 9-11-1905 **Council:** 10/2018

Title: Understanding aggregation in drug-conjugate gels

Research area: Materials

This proposal is a new proposal

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Samples: C32H32N2O5
C32H16D16N2O5

Instrument	Requested days	Allocated days	From	To
D11	3	2	15/07/2019	17/07/2019

Abstract:

Gels can be used for drug delivery as carriers for an encapsulated drug. An alternative approach is to make the actual gel matrix itself from the drug. As the gel breaks down, the drug is released. This allows a slow release, and also the gel can be used to fill space for example in invasive brain surgery. For this to work, it is necessary to build gels from drug-conjugates. These need to have the right self-assembled morphology to form a gel and also such that the degradation rate is correct. We have found that we can control the gel properties and degradation rate by functionalising a drug with a dipeptide; different properties can be tuned by the choice of dipeptide and (critically) the chirality. To tune and develop our systems, we need to link our data to the self-assembled structures which we will determine using SANS.

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Introduction Low molecular weight gels are formed when specific small molecules self-assemble in solution to form a permanent network of fibres. The small molecules used here are drug molecules functionalized with a dipeptide. The dipeptide directs the self-assembly to form the necessary fibrous structures that result in a gel. The free carboxylic acid terminus means that these dipeptides are dispersable in water at high pH, forming gels when the pH is lowered. Here, we wished to understand the packing at high pH and in the gel state at low pH.

Experimental Solutions of LMWG were prepared as described previously.[1] Solutions were prepared in D_2O at high pD at 10 mg/mL by the addition of one molar equivalent of NaOD (0.1 M), followed by stirring until the LMWG had dispersed to give a free-flowing solution. Gels were prepared by the addition of GdL[2] to these solutions. SANS experiments were performed on the D11 diffractometer, a neutron wavelength of λ= 10 Å was employed at three different detector distances, D = 1.2, 8 and 40 m, corresponding to a Q range from 1.0×10^{-3} to 0.31 $Å^{-1}$. All spectra were normalized and corrected using the scattering of the empty cell. Scattering data were corrected for electronic noise and incoherent background subtraction and normalized by the intensity scattered for a 1 mm H_2O sample corrected by the intensity scattered from the empty quartz cell.

Results We prepared a range of solutions at high pH (where micellar aggregates exist), at high pH in the presence of a calcium salt (which forms gels by cross-linking the micelles) and at low pH (where gels are formed in the absence of an added salt). We carried this out for a number of samples, based around a library of materials such as the example shown in Figure 1.

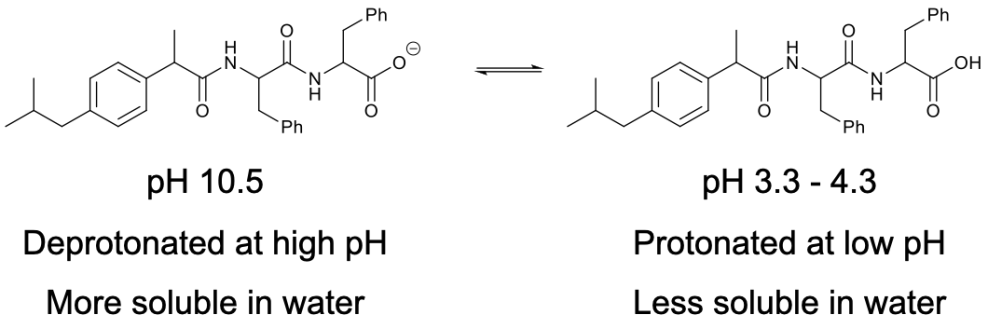

Figure 1. Chemical structure of a typical drug-conjugates used here. At high pH, the conjugate is deprotonated and can be dispersed in water. At low pH, a gel is formed due to the lower solubility.

The scattering was compared at high and low pH. In all cases, micellar aggregates were formed at high pH, with different structures formed at low pH. Typical data are shown in Figure 2.

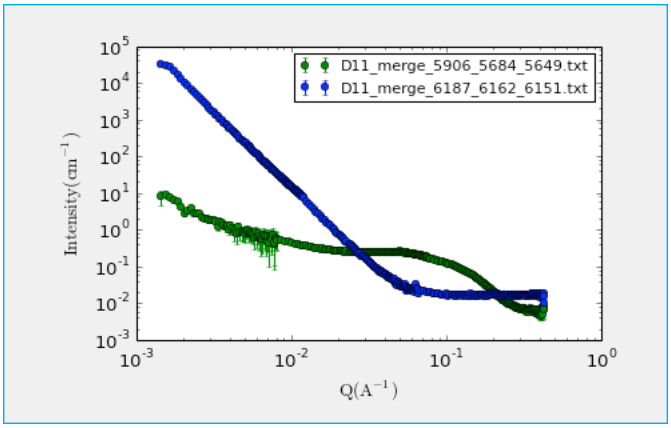

Figure 2. SANS data for a solution of a drug-conjugate at high pH (green data) and a gel of the same conjugate (blue data).

The data are currently being fitted and compared to viscosity and rheology data to understand the systems. In the example in Figure 2 for example, the high pH data can be fitted to a sphere combined with a power law and the gel phase to a cylinder model using SASView.

References

1. E.R. Draper, M. Wallace, R. Schweins, R.J. Poole and D.J. Adams, *Langmuir*, **2017**, 33, 2387–2395.
2. D.J. Adams, W.F. Frith, M. Kirkland, L. Mullen and P. Sanderson, *Soft Matter*, **2009**, *5*, 1856-1862.