Experimental report

27/09/2021

Proposal:	**9-11-2028**	**Council:**	10/2020

Title: Engineering thermoresponsive branched copolymer surfactants: Influence of the copolymer composition on thermoresponse

Research area: Materials

This proposal is a new proposal

Main proposer:	**Michael COOK**
Experimental team:	Lionel PORCAR
Local contacts:	Lionel PORCAR

Samples:
H2C=C(CH3)CO(OCH2CH2)nOH-C8H13NO
H2C=C(CH3)CO(OCH2CH2)nOH-CH2=C(CH3)COOCH2CH2N(CH3)2
H2C=C(CH3)CO(OCH2CH2)nOH-C7H13NO
H2C=C(CH3)CO(OCH2CH2)nOH-CH3(C6H11NO)nCH3

Instrument	Requested days	Allocated days	From	To
D11	1	1	26/03/2021	27/03/2021
D22	1	0		

Abstract:

Thermoresponsive hydrogels are promising materials that offer bespoke rheological behaviour triggered by mild temperature changes and have applications in advanced therapeutics, tissue engineering and emerging fields such as soft robotics. We have designed advanced thermothickening materials based on "engineered emulsions" stabilised by branched copolymer surfactants (BCS). These BCS are branched copolymers bearing thermoresponsive polymer chains terminated with short hydrophobic chain ends which are grafted with hydrophilic block. The properties of BCS and hence their ability to generate useful thermothickening materials depends on a hierarchical understanding of BCS assembly into nanoparticle structures and interactions between these particles. We propose to use SANS to achieve an understanding of the structure of these novel constructs at the nano-scale, both in sol and gel states. These experiments will give us a critical insight into BCS architecture both above and below the transition temperature, allowing us to correlate bulk properties with morphology to support rational development of novel high-performance thermothickening emulsions.

Introduction

Thermoresponsive hydrogels are promising materials that offer bespoke rheological behaviour triggered by mild temperature changes and have applications in advanced therapeutics, tissue engineering and emerging fields such as soft robotics.[1] Thermothickening materials, specifically, exhibit an increase in viscosity with heating and are of specific interest in this project for drug delivery, where medicines exhibit low viscosity during application (easing administration), before transitioning to a retentive viscous state when warmed by the body, thus prolonging local therapeutic effects and enhancing duration of absorption. In these systems, the macroscopic temperature response originates from nanoscale level changes in the supramolecular assemblies present in these materials. In order to obtain the desired response in a rational manner, a fine understanding of the supramolecular assembly is necessary. There is currently only a single excipient with regulatory approval for use in medicines which possesses this thermothickening property: poloxamer 407 (or Pluronic F127). In this project (funded by EPSRC grant # EP/T00813X/1), we have designed superior thermothickening materials based on “engineered emulsions”[2] stabilised by branched copolymer surfactants (BCS). These BCS are branched copolymers bearing thermoresponsive polymer chains terminated by hydrophobic chain ends, which are grafted with hydrophilic block. These BCS solutions are thermothickening in their own right. Furthermore, they are effective emulsifiers and BCS-stabilised emulsions are thermothickening. These materials are therefore strong candidates in “smart” formulations, which are able to flow through applicators and undergo a sol-gel transition upon application to the body whilst containing sizeable hydrophobic domains for drug solubilisation.

Experiments and discussion

In this proposal, we investigated the solution behaviour of selected BCS systems in order to establish correlations between structure and rheological behaviour. These BCS were divided in two group. In one group, the effect of PNIPAM-PEGMA BCS molecular weight was evaluated. Four PNIPAM-PEGMA systems were evaluated: 4.7 kDa (Low Mw), 5.5 kDa (Med Mw), 7.0 kDa (High Mw) and 7.7 kDa (Very High Mw). For this series, the optimal rheological behaviour desired, thermal-thickening, is shown by the High Mw BCS, while the Low Mw BCS shows thermal-thinning, so we have an evolution from undesired behaviour all the way to optimal behaviour and past. The second group was focused on the nature of the thermo-responsive polymer component. PNIPAM-PEGMA is taken as reference and the behaviour of PDEA-PEGMA, PDEG-PEGMA and PVCPL-PEGMA is compared. For both groups, data was collected at three temperatures: 25^0C, below transition, 40^0C, just above transition and 50^0C, above transition. At the current stage of this work, the analysis has been focused on the first group, and the discussion here will be focused on this dataset.

For the PNIPAM-PEGMA Low, Med, High and Very high Mw series, the data obtained could be satisfactorily fitted with using two ellipsoids above transition. Below transition temperature, a single ellipsoid at mid-high q range and the low q range dominated by a power law. However, in order to extract more information about the systems, a second model was used to fit the data, mass surface fractal.[3] The key difference between these two approaches is the ellipsoid+ellipsoid only assumes two independent scatterers centres, while the mass surface fractal describes a larger aggregate composed of smaller aggregates, which leads to two distinct shoulders in the data. The scattering in between the two shoulders is described by power law related to a mass fractal dimension. Curiously, the data for Med to Very High Mw was satisfactorily fitted using the mass surface fractal while the Low Mw couldn't. The current interpretation of thermo-thickening mechanism for these systems involves the formation of interconnected small aggregates, when above the transition temperature, will partially aggregate causing the system to jam which leads to the observed thickening. If they are not interconnected, instead of jamming, unconnected aggregates would form instead. Currently, we are working in obtaining SEM micrographs of these systems to clarify if the difference in the aggregation process is real or just incidental. The general trend observed from the fits results (Table 1) show that for all the four systems studied here, one object dominate the scattering below transition, and above, two objects can now be observed and their size increases as temperature increases, which suggests the transition triggers an aggregation of the BCS, and if the difference between Low Mw and the rest is correct, connectivity of the aggregates is the controls thermo-thinning/ thermo-thickening response.

		PNIPAM Low Mw			PNIPAM Med Mw			PNIPAM High Mw			PNIPAM Vhigh Mw	
	25^0C	40^0C	50^0C	25^0C	40^0C	50^0C	25^0C	40^0C	50^0C	25^0C	40^0C	50^0C
Radius/Model	**E**	**EE**	**EE**	**E**	**MSF**	**MSF**	**E**	**MSF**	**MSF**	**E**	**MSF**	**MSF**
Rp primary / Rg primary	24	33	35	24	52	72	24	41	115	15	76	72
Re primary	515	134	100	54			53			30		
Rp cluster / Rg cluster		219	117		182	357		121	186		103	357
Re cluster		593	406									

E – ellipsoid model, EE – ellipsoid+ellipsoid model, MSF – mass surface fractal model, Rp – polar radius, Re, equatorial radius, Rg, radius of gyration

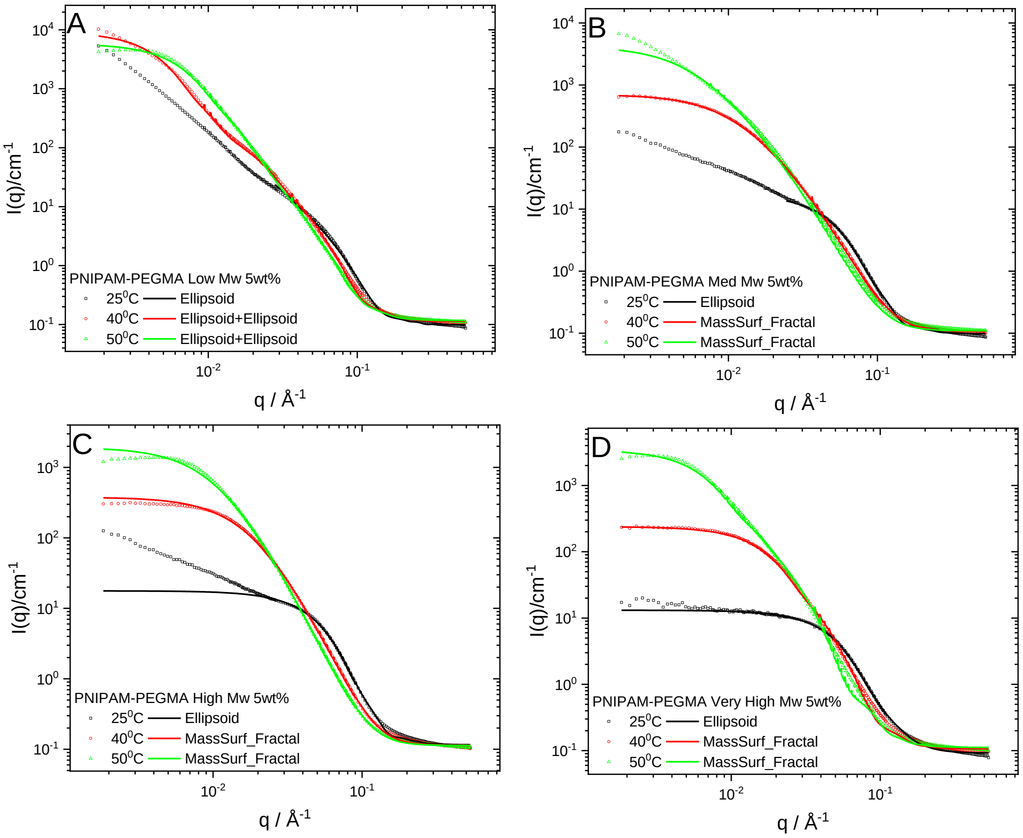

Fig. 1 – Neutron scattering patterns and fits for BCS solutions of PNIPAM-PEGMA (A) low, (B) med, (C) high and (D) very high Mw at 25, 40 and 50^{0}C.

References

[1] Stuart MAC, Huck WTS, Genzer J, Müller M, Ober C, Stamm M, Sukhorukov GB, Szleifer I, Tsukruk VV, Urban M, Winnik F, Zauscher S, Luzinov I, Minko S *Nat Mater* **2010** 9(2):101
[2] Weaver JVM, Rannard SP, Cooper AI Angew. Chem. Int. Ed. 2009, 48, 2131–2134
[3] Hurd AJ, Schaefer DW, Martin JE *Phys. Rev. A* **1987** 35:2361