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Thermorheology of polaxamer 407: effect of alcohols and drugs

A. F. BROWN, D. S. JONES AND A. D. WOOLFSON

Pharmaceutical Devices Group, School of Pharmacy, The Queen's University of Belfast, Medical Biology Centre, 97 Lisburn Road, Belfast BT9 7BL

Thermal gelation coupled with low toxicity makes poloxamers useful in a range of drug delivery applications. Several authors have used continuous shear methods to characterise their flow properties and sol-gel transitions (Miller and Drabik, 1984; Tung, 1994; Cho *et al.*, 1997). However, these techniques are sample destructive and yield little information on their structural properties. Surprisingly, the use of non-destructive techniques which provide information on the structural properties of materials in their rheological ground state has, to date, been neglected. The aim of this study was, therefore, to employ a non-destructive technique to investigate the effects of alcoholic solvents and drugs on the thermorheological properties of poloxamer gels. These were made using the cold method as described by Schmolka (1972). All samples contained poloxamer 407 25%w/w in co-solvents of water and alcohol (ethanol, propylene glycol or glycerol) in various proportions - 75/0, 70/5, 65/10, 60/15, 55/20 or 50/25 (water/alcohol as %w/w). For the aqueous system, the effects of various drugs were also investigated. These were chlorhexidine (CHX, 5%), tetracycline (TC, 5% as HCl) and amethocaine (AMC, 4% as HCl). Oscillatory analyses were performed using a CarriMed CSL rheometer with a 4cm diameter parallel plate geometry and a 1mm gap. A strain of 1.5×10^{-1} was found (by torque sweep) to lie within the linear viscoelastic region for all gels and was used for subsequent analyses. These were performed in triplicate using a temperature range of 5-40°C at an oscillation frequency of 0.5 Hz. The sol-gel transition temperature (T_m) was identified as a sudden rise in the storage modulus (G'). In water, a sharp sol-gel transition was observed at 16.87±0.38 °C. This was significantly reduced to 14.40±0.20 and 12.40±0.20°C with the inclusion of ethanol 5 and 10% respectively. Above T_m there was no significant difference in G' for these three samples. With 15 and 20% ethanol the sharp sol-gel transition was lost. Instead, there was a less sharp transition superimposed on a gradually increasing G'. The resulting gels had significantly lower G' values. In the sample containing 25% ethanol, gelation did not occur and only a small and gradual increase in G' was seen. Propylene glycol and glycerol also produced significant reductions in T_m. Unlike ethanol, higher concentrations did not destroy the gel. In fact, with 20% or more, T_m was reduced to below 5°C and samples existed as gels over the entire temperature range observed.

	5%	10%	15%	20%	25%
EtOH	14.40 ± 0.20	12.40 ± 0.20	*	*	*
PG	14.30 ± 0.17	10.73 ± 0.29	6.53 ± 0.21	< 5	< 5
Glyc.	13.43 ● 0.25	8.47 ± 0.31	5.23 ± 0.25	< 5	< 5

Sol-gel transition temperatures in °C. (*indicates that no sharp sol-gel transition was observed).

The inclusion of TC or AMC produced significant increases in T_m to 17.85±0.19 and 20.83±0.23°C respectively whilst CHX produced a significant reduction to 14.87±0.15°C.

In aqueous solution, poloxamer chains are surrounded by a hydrogen bonded sheath of water molecules at low temperatures and they behave as elastoviscous liquids. As the temperature is increased these bonds are cleaved and desolvation occurs. Polymer entanglement and intermolecular hydrogen bonding of the polymer chains causes gelation, observed as a sudden increase in G'. Reductions in T_m indicate that desolvation occurs more readily in the presence of alcohols. This may be due to hydrogen bonding of the alcohol to either the water or the polymer molecules. The degree of suppression of T_m appears to be related to the polarity of the co-solvent, with the greatest suppression caused by glycerol, a triol. Each of drugs used, produced a change in T_m which may be attributed to interference with the micellisation process. Increases with TC and AMC may be due to disruption of poloxamer micelles whilst CHX (itself a surfactant) may promote micellisation, causing a reduction in T_m. Here, we have used non-destructive rheological analysis to show that incorporation of non-aqueous solvents and drugs can have significant effects on the thermal gelation of poloxamers. These should be considered during formulation to ensure products with the appropriate properties.

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