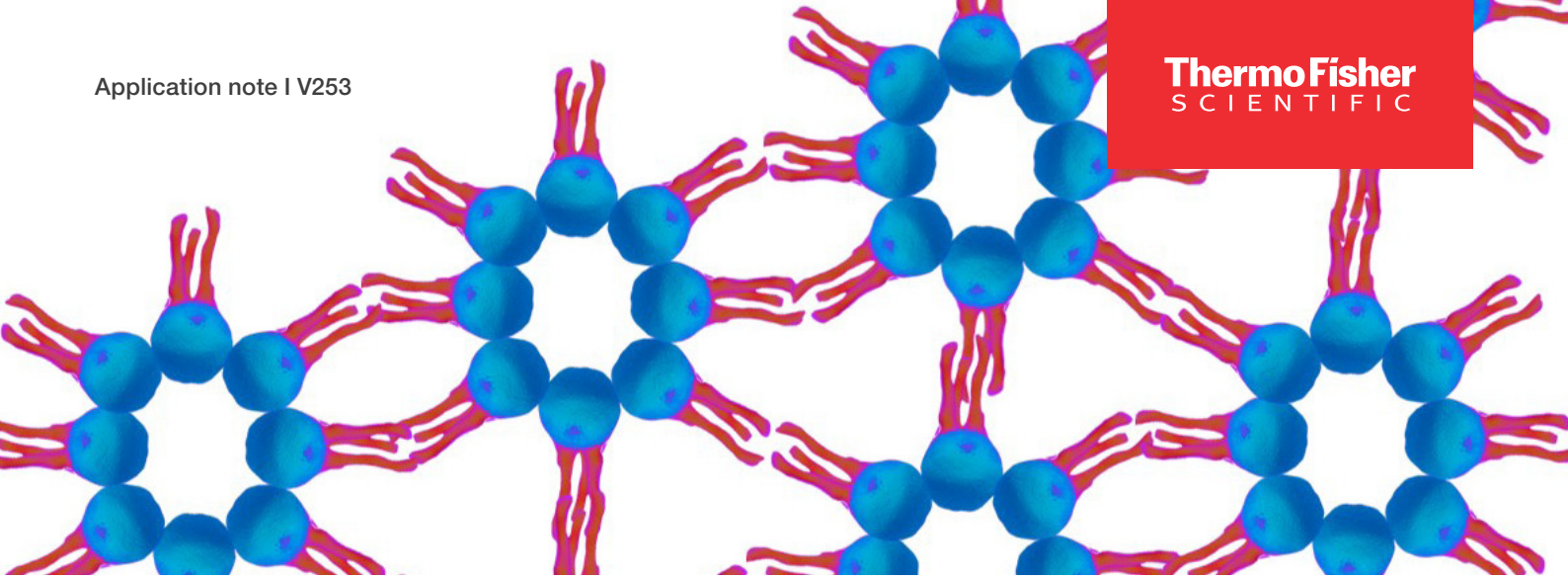

Influence of sodium chloride concentration on gel temperature and gel properties of poloxamer blends

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Key words

Sol/Gel transition, Gel point, Gel strength, Molecular weight, Salt concentration

Introduction

Different liquid pharmaceutical applications require a defined gel formation at temperatures of the human body. Poloxamers such as 188 or 407 offer this characteristic behavior, whereas both sol/gel transition temperature and gel strength are affected by various parameters (e.g. poloxamer concentration in the aqueous system) (1).

It has been described in literature that additives such as active ingredients are influencing the gel system as well (2). This may lead to a quite complex gel system. From the rheological point of view, oscillatory temperature sweeps must be applied for its characterization (1, 3, 5, 6).

The aim of this work was the rheological characterization of aqueous solutions of poloxamer mixtures holding different amounts of sodium chloride as model substance. Particular focus was laid on gel point temperature and strength of the formed gel.

Materials and methods

Materials

For the investigation, poloxamer 188 (Lutrol® F68) and poloxamer 407 (Lutrol® F127), both BASF SE, Ludwigshafen, Germany and sodium chloride (NaCl), Merck, Darmstadt, Germany were used.

Formulations

Various aqueous solutions of poloxamer 188 and 407, including mixtures were prepared in combination with various NaCl concentrations (Table 1). According to common practice, "cold water" preparation was used (4). The poloxamer was stirred in, using a magnetic stirrer. In order to ensure both low viscosity and homogeneous distribution, the solution was left for 2 days at refrigerated conditions (5 °C). After that, salt was directly added as a powder.

Table 1. Compositions tested – listed, the amount of poloxamer (w/w) present in the individually formulated aqueous solution.

	Poloxamer 188	Poloxamer 407	NaCl
1-A		20.0 %	
1-B		20.0 %	0.5 %
1-C		20.0 %	1.0 %
1-D		20.0 %	2.0 %
2-E	5.0 %	10.0 %	
2-Es	5.0 %	10.0 %	4.0 %
2-F	10.0 %	10.0 %	
2-Fs	10.0 %	10.0 %	4.0 %
3-G	10.0 %	20.0 %	
3-Gs	10.0 %	20.0 %	4.0 %
3-H	20.0 %	10.0 %	
3-Hs	20.0 %	10.0 %	4.0 %

Equipment

Complex dynamic viscosity from oscillatory testing was measured using a Thermo Scientific™ HAAKE™ Rheometer, with a 60 mm parallel plate measuring geometry – all equipment: Thermo Fisher Scientific, Karlsruhe, Germany.

Methods

After sample loading, each sample was equilibrated at 15 °C for 3 minutes. For the investigation of gel point and gel strength, a temperature ramp (15 - 80 °C) was used with a heating rate of 2 K/min. For oscillatory testing, controlled deformation mode with an amplitude of 1.0 % and a frequency of 1.0 Hz was adjusted.

Results and discussion

By means of oscillatory temperature sweeps, a distinct gel point temperature (GPT) could be determined for all formulations. In the first investigation, lower NaCl concentrations (0.5, 1.0 and 2.0 %) were adjusted in an aqueous solution containing 20 % of poloxamer 407.

It was found that the additive NaCl reduced the GPT markedly while hardly affecting the strength of the formed gel (Figure 1). However, the reduction of GPT clearly depended on the NaCl concentration in the solution (about 6 K with 2 % NaCl). Each measurement was duplicated, revealing a very good reproducibility.

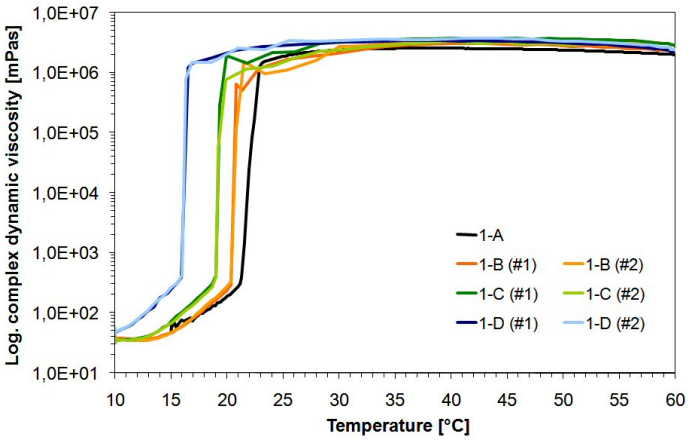

Figure 1: Complex dynamic viscosity and gel formation as function of temperature and NaCl concentration (0.0, 0.5, 1.0 and 2.0 %) in an aqueous solution containing 20 % poloxamer 407.

The goal of further investigations was to achieve both, a higher concentration of salt in the solution as well as a GPT in the temperature range in which the dosage form is usually intended to be applied.

Earlier investigations showed, that poloxamer 188 offered a distinctively higher GPT than poloxamer 407 (1). Therefore, mixtures of poloxamer 407 and 188 were used in order to adjust higher GPTs (2). The GPT increase achieved by partly replacing poloxamer 407 by poloxamer 188 can be seen in Table 2.

Table 2. Gel point temperatures (GPT) of aqueous poloxamer solutions containing 20 % polymer of different ratios of 188 and 407.

Formulation		
Poloxamer 188	Poloxamer 407	GPT [°C]
0.0 %	20.0 %	22
2.5 %	17.5 %	29
5.0 %	15.0 %	34
10.0 %	10.0 %	44
15.0 %	5.0 %	46
20.0 %	0.0 %	47

The depression of GPT caused by NaCl was investigated comparing NaCl concentrations of 0 % and 4 % (Figure 2). The addition of NaCl to mixtures of the two poloxamer grades also led to a reduction in GPT. However, the present amounts of poloxamer 188 shifted the GPT to higher temperature values. The mixture of both polymers is therefore recommendable to adjust the GPT.

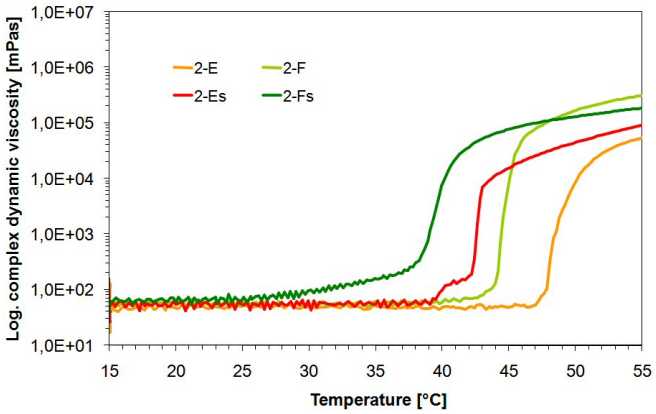

Figure 2: Complex dynamic viscosity and gel formation as function of temperature (15 % and 20 % poloxamer concentration).

The shape of the sol/gel transition as well as the gel strength (represented by the viscosity level) was depending on the poloxamer concentration. Solutions with 20 % poloxamer 407 showed a very sharp sol/gel transition with a gel strength reaching immediately a high level (Figure 1). Much more time to reach a high gel strength is required for solutions containing just 10 % poloxamer 407 (Figure 2, Figure 3).

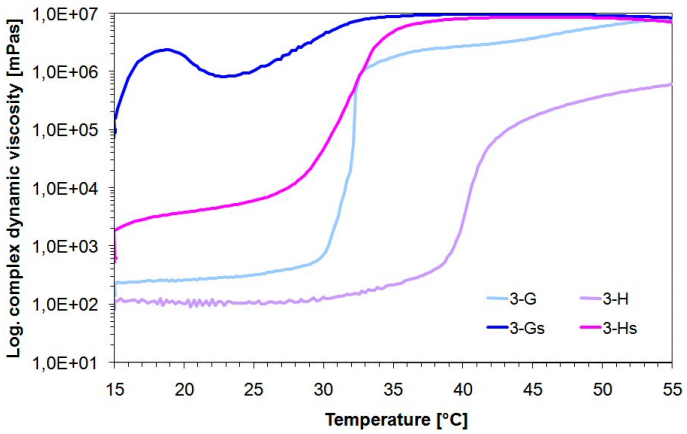

Figure 3: Complex dynamic viscosity and gel formation as function of temperature (30 % poloxamer concentration).

As soon as total poloxamer concentrations of 30 % were used, the resulting gel system was found to become quite complex (Figure 3). The increased concentration of poloxamer 407 reduced the GPT distinctively, yet also increased the sol viscosity at ambient temperatures.

This data suggests that a well selected combination of the two poloxamers 188 and 407 can alter both the initial viscosity of the system at ambient temperature and the GPT.

Conclusion

When NaCl was added to an aqueous solution containing poloxamers, the gel point temperature (GPT) of the system was markedly reduced. For solutions containing only poloxamer 407, GPT below ambient conditions could easily be realized.

To alter a gel point temperature to an applicable range of about 37 °C, poloxamer mixtures of both grades tested (Lutrol® F68 and Lutrol® F127) had to be used. The sol viscosity of the solution could be altered by selecting a proper ratio of the two poloxamer grades.

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