

Investigating the impact of phosphate buffer on the gel point temperature of aqueous poloxamer solutions

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INTRODUCTION

Various liquid pharmaceutical dosage forms call for a temperature initiated gel formation. The skin temperature of the human body for instance can be used to transfer these formulations from a low viscous sol into a strong gel. Poloxamers such as 188, 237, 338 or 407 offer this characteristic behaviour. However, 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 pharmaceutical ingredients influence the gel system as well [2, 3]. This may lead to a quite complex gel system. From a rheological point of view, oscillatory temperature sweeps have to be applied for its characterisation [4, 5].

The aim of this work was the investigation of the impact of phosphate (PP) buffer onto the rheological features of aqueous poloxamer solutions. Particular focus was laid on gel point temperature (GPT) of the formed gel.

MATERIALS AND METHODS

Throughout this investigation the following poloxamers were tested: 188 (Kolliphor® P 188), 237 (Kolliphor® P 237), 338 (Kolliphor® P 338), and 407 (Kolliphor® P 407), all BASF.

Of each individual poloxamer, aqueous solutions (20%, m/m) were prepared either using purified water or phosphate buffer (prepared with K₂HPO₄, Sigma Aldrich) pH 6.8 (adjusted with NaOH). According to common practice, 'cold water' preparation was used [6].

A HAAKE MARS III (Figure 1) was used to determine the complex dynamic viscosity of the samples by means of oscillatory testing. A cone plate measuring geometry was assembled for the investigation with the following specifications: cone C60/1° CS L and lower plate TMP 60. The whole measuring device was covered with a sample hood (POM) to reduce the amount of water evaporating during the heating phase and to allow a more homogeneous temperature distribution.

After sample loading, each sample was equilibrated at 5°C for 3 minutes (oscillation mode: CD-AS, amplitude: 10.0%, frequency: 1.00 Hz). For the investigation of gel point and gel strength, a temperature ramp (5–70°C) was used with a heating rate of 2 K/min (oscillation mode: CD-AS, amplitude: 1.0%, frequency: 1.00 Hz).



Figure 1. HAAKE MARS (Modular Advanced Rheometer System) III with Peltier plate and active hood.

RESULTS AND DISCUSSION

In order to gain reliable results, the structure of a gel must not be disturbed when it is rheologically characterised. Therefore, shear stress is a crucial parameter and needs to be both precisely adjusted and controlled. This inherently excludes rotational rheometers from any kind of investigations on either gel formation or gel characteristics. However, oscillatory measuring can be employed as a rheological tool to get clearly defined and reproducible measurements. If complex dynamic viscosity is plotted as a function of temperature, a distinctive onset in viscosity indicates the GPT of the system under test [4, 6].

For all samples a distinct GPT could be defined (Figures 2–5). Generally, all poloxamer solutions appear as low viscous liquids at

low temperatures. Thus, an extraordinary broad viscosity window starting from only 10 up to >1.000.000 mPas has to be covered with the same measuring job settings during the measurement, resulting in a comparatively high noise in the viscosity reading in the sol state.

Solutions containing 20% of either poloxamer 237 or 407 already formed a ringing gel at room temperature (Figures 3, 5). Generally, the rheological characteristics of the two polymer solutions were very similar regarding both gel point temperature and strength of the gel formed. Poloxamer 338 (Figure 4) showed similar gel characteristics, but a slightly higher gel point temperature by some 5 K, resulting in a liquid solution at room temperature.

Compared to the other polymers, poloxamer 188 revealed different rheological characteristics (Figure 2). Firstly, gel point temperature was found to be markedly higher and secondly, the process of gel formation appeared to be different as the shape of the viscosity curve was pretty straight. The other poloxamers seemed to have two levels of gel formation which was indicated by a different steepness in the onset of the viscosity curve. Thirdly, with a complex dynamic viscosity of below 1.000.000 mPas, the strength of the formed gel was distinctively lower.

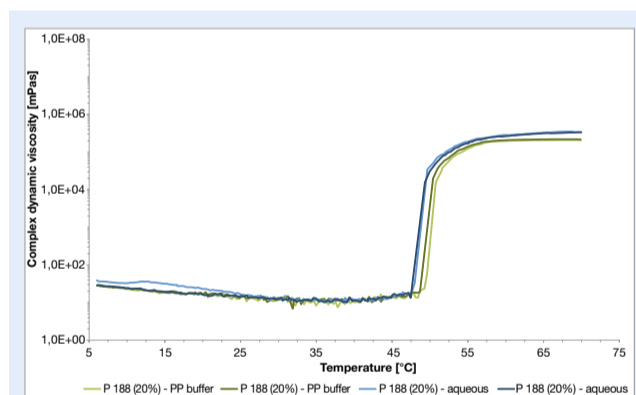


Figure 2. Complex dynamic viscosity of different poloxamer 188 solutions as function of temperature.

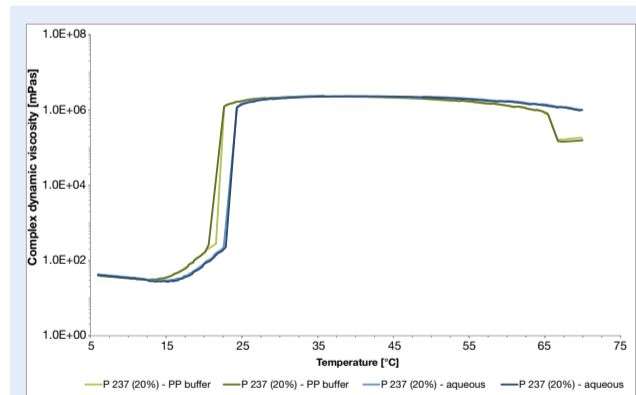


Figure 3. Complex dynamic viscosity of different poloxamer 237 solutions as function of temperature.

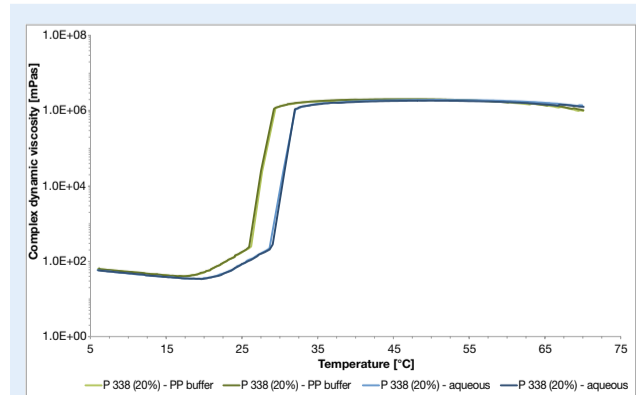


Figure 4. Complex dynamic viscosity of different poloxamer 338 solutions as function of temperature.

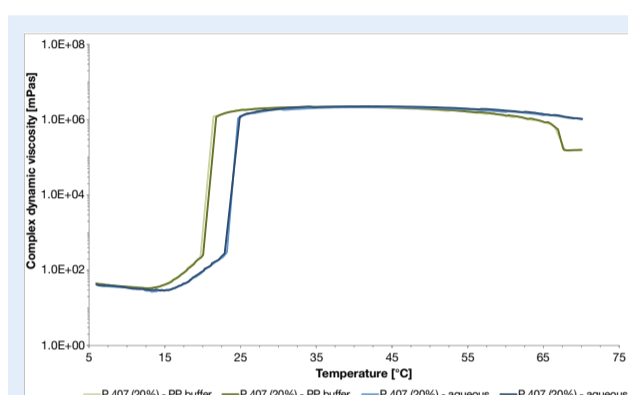


Figure 5. Complex dynamic viscosity of different poloxamer 407 solutions as function of temperature.

The results show clearly that GPT depends on the kind of poloxamer (and its concentration) in the aqueous media. Yet, it should be considered that GPT changes with further components added to the formulation [2, 3]. Compared to the effect of other additives, the impact of PP buffer was relatively small (Table 1). Eventually, for all samples GPT changed by merely 2–3 K.

Table 1. Summary of the gel point temperatures (GPT) found for the different poloxamers in purified water and PP buffer.

Polymer	GPT (water / PP buffer)
Poloxamer 188	47°C / 49°C
Poloxamer 237	23°C / 21°C
Poloxamer 338	29°C / 26°C
Poloxamer 407	23°C / 20°C

CONCLUSION

By means of oscillatory testing, a distinct gel point temperature (revealed as a sharp onset in the measurement of complex dynamic viscosity, $|\eta^*|$) could be determined for all poloxamers solutions. Switching the media from purified water to PP buffer changed the gel point temperature. With a difference of merely 2–3 K, this effect was found to be comparatively small.

REFERENCES

- [1] Agnese, Th.; Bang, F.; Cech, Th.; Haberecht, M.; Soergel, F.; Temperature initiated gel forming characteristics of different poloxamers; 9th Central European Symposium on Pharmaceutical Technology; Sep. 20–22, 2012; Dubrovnik, Croatia
- [2] Dumortier, et al.; A review of poloxamer 407 pharmaceutical and pharmacological characteristics; Pharm. Research, Vol. 23, No.12, 2006
- [3] Agnese, Th.; Cech, Th.; Herting, M.G.; Soergel, F.; Investigating the influence of sodium chloride on the gel point of poloxamer formulations by means of oscillatory temperature sweeps; 3rd PharmSciFair; June 13–17, 2011; Prague, Czech Republic
- [4] Schramm, G.; A practical approach to rheology and rheometry; 2nd edition; 2004; Thermo Fisher Scientific; Karlsruhe, Germany
- [5] Cech, Th.; Herting, M.G.; Soergel, F.; et al.; Determination of the gel point of poloxamers using different rheological methods; 7th PBP World Meeting; March 8–11, 2010; Valetta, Malta
- [6] Agnese, Th.; Cech, Th.; Herting, M.G.; Soergel, F.; Influence of preparation method on viscosity of different poloxamers; 7th PBP World Meeting; March 8–11, 2010; Valetta, Malta

PRESENTED AT:

1st European Conference on Pharmaceuticals, April 13–14, 2015; Reims, France
Pharma Ingredients & Services | G-ENP/ET448