Soluplus solutions as thermothickening materials for topical drug delivery.

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Abstract

Soluplus is a pharmaceutical excipient used primarily in the manufacture of solid dispersions. The polymer also exhibits interesting rheology in aqueous solution, increasing in viscosity as the solution is warmed. This material could have application topical drug delivery to sites including the skin, vagina, rectum or nasal mucosa, where the increase in viscosity allows for improved retention. However, there exists very little information surrounding this "thermothickening" phenomenon and the effect of solution composition on temperature-dependent rheology. In this study the effect of soluplus concentration, salt concentration, salt type (NaCl, KCl, and guanidine HCl), pH and ethanol addition on the thermothickening of soluplus solutions is explored with a view to developing topical dosage forms which thicken on application to the body surface. The rheology of the solutions was unaffected by pH over the range tolerated by the skin (pH 4-7), but the inclusion of ethanol rapidly negated the thermothickening effect. "Salting out" of the solutions resulted in a depression of gelation temperatures, and an increase in both storage and loss moduli of the solutions. 30 % (w/v) soluplus in 1 M NaCl or KCl was identified as a potential thermothickening agent for topical drug delivery.

Introduction

Soluplus is a poly(N-vinyl caprolactam) – poly(vinyl acetate) – poly(ethylene glycol) graft copolymer manufactured by BASF (figure 1). It is principally used as a pharmaceutical excipient, as a matrix for the formation of solid dispersions, and as a surfactant to enhance the aqueous solubility of poorly water-soluble drugs (1). What has been poorly explored is that aqueous solutions of soluplus undergo an increase in viscosity upon warming. This "thermothickening" phenomenon could have application in topical drug delivery, where drugs are administered to the skin or mucosal sites such as the vagina, rectum, and eye. These thermothickening dosage forms could flow through an applicator or syringe, before hardening after application to the body. For example, in intravaginal drug delivery, the poor retention of semi-solid dosage forms leads to messiness and leakage of medicines, lowering efficacy and reducing patient compliance with treatment (2). Thermothickening

solutions could flow through an applicator, reducing messiness, before thickening in the vagina, enhancing retention (2). Soluplus is attractive as a thermothickening agent due to its safety, documented by its manufacturer. Many novel temperature-responsive materials reported in the literature are based on poly(N-isopropylacrylamide) (3–5), but this polymer produces cytotoxic hydrolysis products (6). There is a need to explore macromolecules with known safety profiles to produce temperature-responsive materials capable of translation into medicines. Soluplus has been tested according to OECD guidelines for acute toxicity, irritation, and sensitization, and did not elicit these ill effects (7).

Thermothickening in soluplus solutions is likely a result of the poly(N-vinyl caprolactam) component of the copolymer, which possesses a lower critical solution temperature (LCST) in water (8). The LCST is a critical temperature above which the polymer undergoes a demixing from aqueous solution, resulting in collapse of the polymer into a globule, and precipitation from solution. It is known that block copolymers of poly(N-vinyl caprolactam) and poly(ethylene glycol) in aqueous solution transition from a hydrophilic to amphiphilic state upon warming above the LCST of poly(N-vinyl caprolactam) (~34-36 °C), which results in self-assembly and gelation (9). It is possible that a similar mechanism occurs in soluplus, which contains regions of poly(ethylene glycol) and poly(N-vinylcaprolactam).

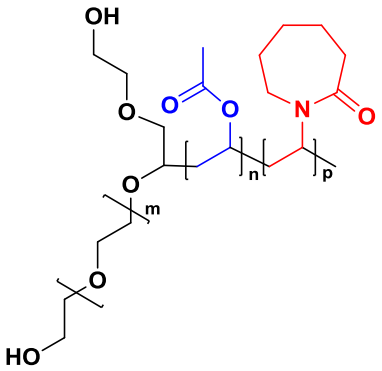

Figure 1. The structure of soluplus, containing poly(ethylene glycol) (black), poly(vinyl acetate) (blue), and poly(N-vinyl caprolactam) (red) blocks. Structure proposed by the supplier, BASF (1). Please note that the polymer has a graft-type structure.

To the authors knowledge, only a single peer-reviewed article describes the thermothickening of soluplus (10). Cespi et al (10) investigated the effect of temperature on the rheology of soluplus solutions between 5 and 35 % (w/w). It was found that at concentrations above 20 % (w/w) the solutions exhibit a sol-gel transition upon warming above a critical temperature ranging from 45 – 37 °C as concentration increased to 35 % (w/w). The properties of the gelled material indicate a viscous solution without a clear network structure.

The aim of this research is to investigate soluplus solutions as thermothickening materials, for use in topical drug delivery. This focusses on the effect of solution composition on the thermothickening effect, studied by rheometry. The effect of concentration between 20-50 % (w/v) on temperature-dependent rheology will be investigated, as will the inclusion of salts, buffers, and ethanol co-solvent. The effect of ions which “salt out” or “salt in” the soluplus are explored, and a candidate thermothickening material for topical drug delivery is identified.

Materials and Methods

Materials

Soluplus was a gift from BASF (Germany). Salts and absolute ethanol were purchased from Sigma-Aldrich (U.K.). Phosphate buffered saline (PBS) was purchased as tablets from Oxoid (U.K.). All materials were used without further purification.

Dynamic light scattering

Soluplus was dissolved in water to a concentration of 1 mg/mL. Dynamic light scattering measurements were taken on a Malvern Zetasizer Nano ZS with a scattering angle of 173 °.

Rheological evaluation – Temperature Ramp

A TA instruments AR1500ex rheometer equipped with a 40 mm parallel plate and 600 µm gap was used for all rheological tests. Oscillatory stress sweeps were initially conducted at 20 °C and 1 Hz over 0.01 – 100 Pa to identify an appropriate stress within the linear viscoelastic region at which to conduct temperature ramps. Temperature ramps were then performed at 1 Pa and 1 Hz between 20 and 60 °C at a ramp rate of 5 °C per minute.

Sample preparation

Effect of soluplus concentration on temperature-responsive gelation

Soluplus was dissolved in deionised water at sufficient quantity to prepare 20 mL of 20, 30, 40, and 50 % (w/v) solutions. All samples required stirring overnight to ensure complete dissolution. Temperature ramps were then performed as previously described.

Effect of salt concentration and type on temperature-responsive gelation

NaCl solutions were prepared at 1, 1 x 10^{-1}, 1 x 10^{-2} and 1 x 10^{-3} M. KCl and guanidine hydrochloride solutions were prepared at 1 M in deionised water. Soluplus was then dissolved to 30 % (w/v) in 20 mL salt solution. All samples required stirring overnight to ensure complete dissolution. Temperature ramps were then performed as previously described.

Effect of pH on temperature-responsive gelation

PBS was prepared and adjusted to pH 4, 5, 6, and 7 with 0.15 M HCl. Soluplus was then dissolved in the solutions to 30 % (w/v). All samples required stirring overnight to ensure complete dissolution. Temperature ramps were then performed as previously described.

Temperature-responsive gelation in water-ethanol mixtures

Hydroalcoholic solutions were prepared with ethanol and deionised water at 0, 25, 50, 75, and 100 % (v/v) ethanol content. Soluplus was then dissolved in the solutions to 30 % (w/v). All samples required stirring overnight to ensure complete dissolution. Temperature ramps were then performed as previously described.

Further rheological evaluation of 30 % (w/v) soluplus in 1 M NaCl

30 % (w/v) soluplus solutions in 1 M NaCl were prepared as described above and analysed by several rheological tests in addition to the temperature ramp. Oscillatory stress sweeps were conducted at 35 °C and 1 Hz between 1 and 1000 Pa. Frequency sweeps were conducted at 35 °C and 1 Pa (within

the linear viscoelastic region) between 0.1 and 10 Hz. Flow rheology was conducted at 35 °C between shear rates of 10 and 100 s^{-1}. To mimic application of the solution to a topical site, the solution was held at 20 °C for 1 min, then 35 °C for 4 min. These measurements were taken in oscillation mode at 1 Pa and 1 Hz.

Statistical analysis

Data is presented as means (n = 3) ± standard deviation. Statistical analysis is typically conducted by one-way analysis of variance (ANOVA) with Bonferroni post-hoc, unless specified otherwise. $p < 0.05$ is accepted to be statistically significant.

Results and discussion

Dynamic light scattering indicates that soluplus forms aggregates at 20 °C with hydrodynamic diameter 64.86 ± 1.58 nm and a polydispersity index (PDI) of 0.08 ± 0.01 (figure 2a). The concentrations used are above the critical micelle concentration (7.6 mg/L) (1). These aggregates are the result of the amphiphilic nature of soluplus at this temperature, with hydrophilic poly(ethylene glycol) and poly(N-vinyl caprolactam) components, and hydrophobic poly(vinyl acetate) regions. As temperature increases, these aggregates appear to increases in size and polydispersity above 36 °C (figure 2b). It is believed that this is triggered by the reduced solubility of poly(N-vinyl caprolactam) as temperatures surpass its LCST, which results in rearrangement of aggregates and a more random aggregation. This aggregation may be a trigger for the thickening at elevated temperatures which is reported for soluplus.

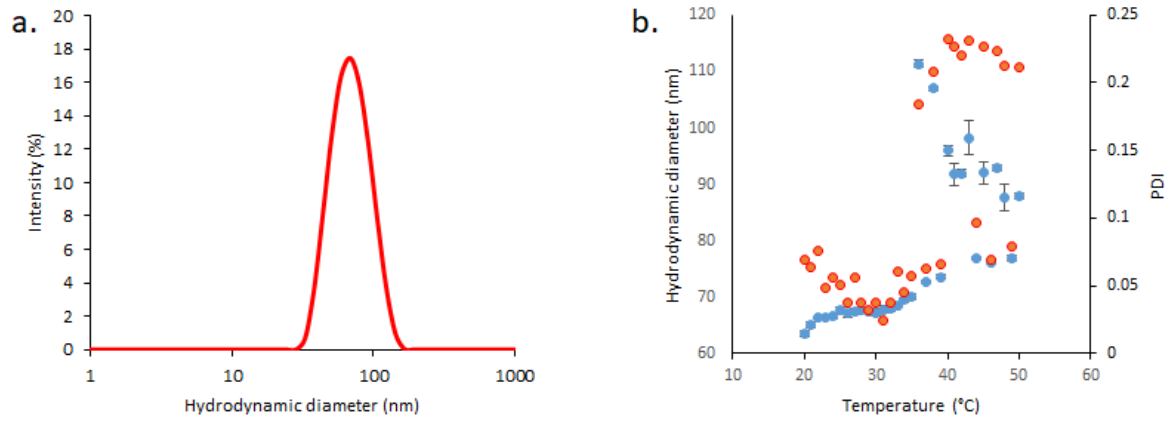

Figure 2. a. Size distribution of 1 mg/mL soluplus at 20 °C. b. effect of temperature on hydrodynamic diameter (blue) and PDI (red)

The effect of concentration on G’ and G’’ between 20 and 60 °C are shown in figure 3. Increases in the G’ and G’’ are seen with temperature at all concentrations. Gelation temperatures (TGels), defined as the first temperature when the sample transitions from G’’ > G’ to G’ > G’’, were seen in the 20, 30, and 40 % samples. TGels for the 20, 30 and 40 % samples were determined to be 40 ± 0.0, 39.7 ± 0.5, and 37.5 ± 0.0 °C respectively, indicating a small but significant ($p < 0.0001$) decrease in TGel at 40 %. The 50 % soluplus solution never reached G’ > G’’ , but reached a minimum loss tangent (G’’/G’) of 1.02 ± 0.01 at 40 °C indicating near-equivalent elastic vs viscous flow behaviour. LCSTs are generally reduced at high polymer concentration due to a decreased number of polymer-water interactions, allowing polymer-polymer interaction to dominate (11). Absolute values of G’ and G’’ increased below 30 °C with concentration, indicating that the solutions became increasing

viscoelastic and resistant to flow. The maximum values of G' (G'_{max}) reached were 288.6 ± 19.1, 450.7 ± 132.9, 964.5 ± 114.7, and 1461.3 ± 19.9 Pa for 20, 30, 40, and 50 % (w/v) polymer solutions, respectively. These G'_{max} values were reached at 54.2 ± 2.2, 51.1 ± 3.8, 53.6 ± 4.0, and 53.1 ± 3.2 °C, respectively. This demonstrates a significant effect of concentration on the elasticity of the materials, but not on the temperature at which G'_{max} is reached.

G' and G'' increase over a broad temperature range for all concentrations studied. This is likely due to a time-dependent thickening of soluplus, explored later in the manuscript. Additionally, as soluplus contains poly(N-vinyl caprolactam) copolymerised in a statistical manner, it is likely that a range of LCSTs are present within blocks of different lengths. Poly(N-vinyl caprolactam) exhibits type I (Flory-Huggins) demixing behaviour, and the LCST is dependent on block length (8,12).

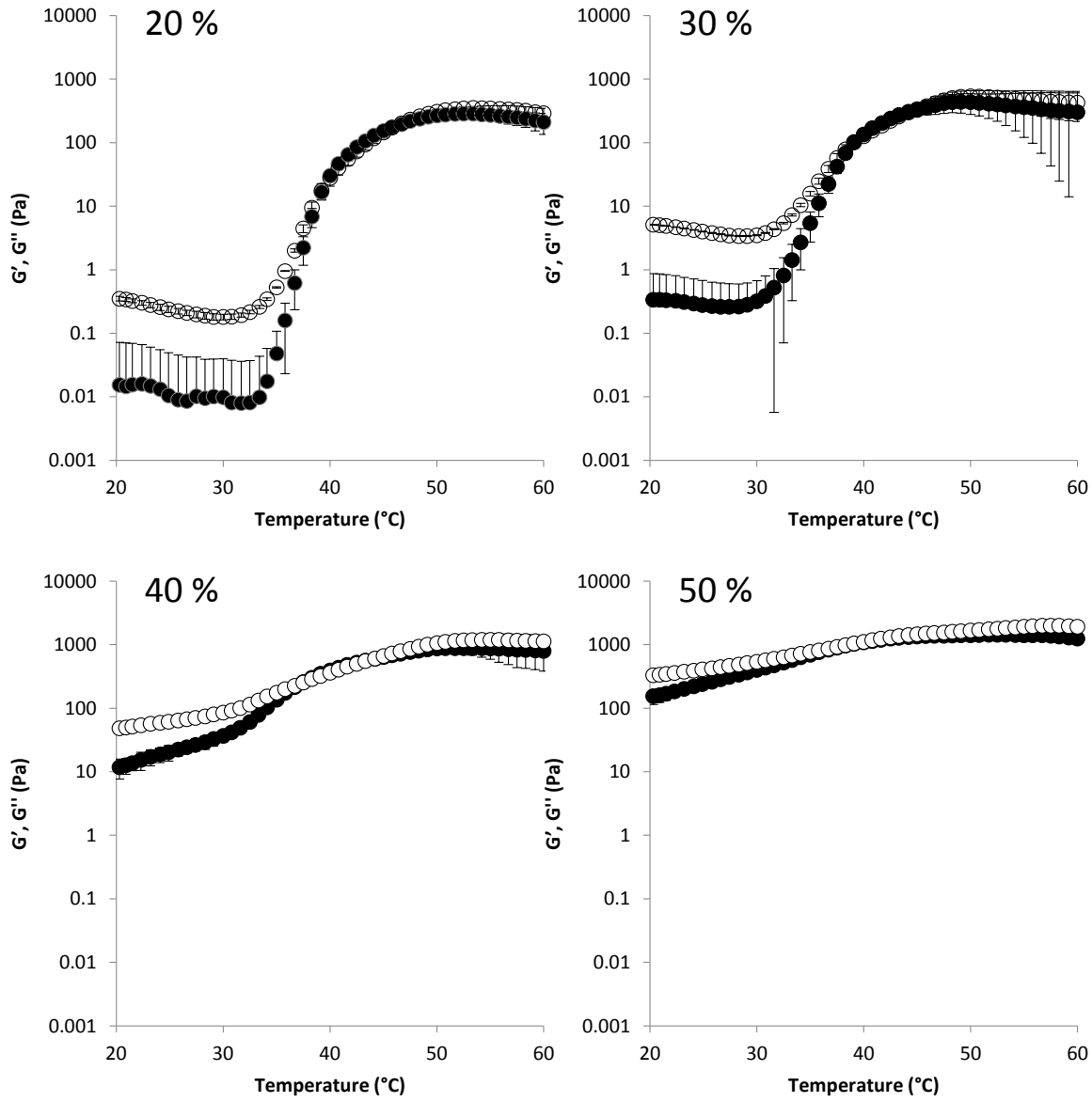

Figure 3. The effect of temperature on G' (closed circles) and G'' (open circles) with soluplus concentration.

The balance between the storage modulus, reflecting elastic-like behaviour, and the loss modulus, which expresses viscous flow may be expressed as the loss tangent (G''/G'). Gelation is typically defined as the point at which the loss tangent has a value less than 1. The effect of temperature and soluplus concentration on the loss tangent may be seen in figure 4. It is evident that at temperatures below 40 °C, the loss tangent decreases with increasing soluplus concentration, indicating an increase in entanglements within the system leading to increasingly elastic behaviour. Interestingly, the loss tangent plateaus at approximately 1 (G' = G'') above 40 °C for all polymer concentrations. A loss tangent of around 1 indicates that there is not a dramatic gelation occurring, but a behaviour consistent with a viscoelastic fluid.

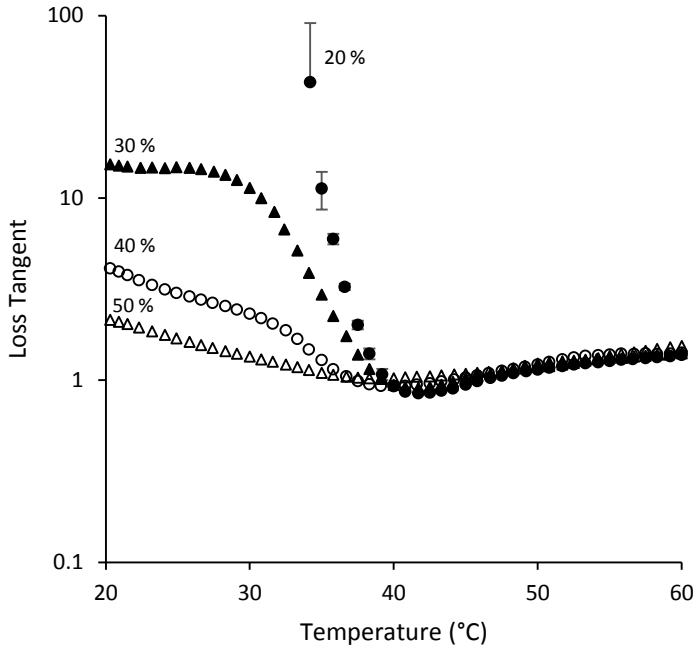

Figure 4. The effect of soluplus concentration (20 % - closed circles, 30 % closed triangles, 40 % - open circles, 50 % - open triangles) on loss tangent with temperature. Loss tangents for 20 % soluplus (closed circle) could not be measured at low temperature as G' approached 0.

The behaviour of soluplus in hydroalcoholic solutions was also investigated (figure 5), as ethanol is often included in topical formulations to alter solubility and thermodynamic activity of drugs. It was found that the inclusion of ethanol in aqueous solutions of soluplus at 30 % (w/v) dramatically supressed the thermoresponsive thickening seen. A negligible increase in G' and G'' was observed on warming with 25 % (v/v) ethanol inclusion, but by 50 % no thermoresponsive behaviour is seen. Increasing ethanol content made had no further effect (data not shown). It is likely that ethanol is able to solubilise Soluplus to a greater extent than water alone, supressing LCST type behaviour and reducing polymer-polymer interactions. It has been demonstrated in a previous report that inclusion of ethanol to > 20 mol% increases the LCST of poly(N-vinyl caprolactam) homopolymer to > 60 °C (8).

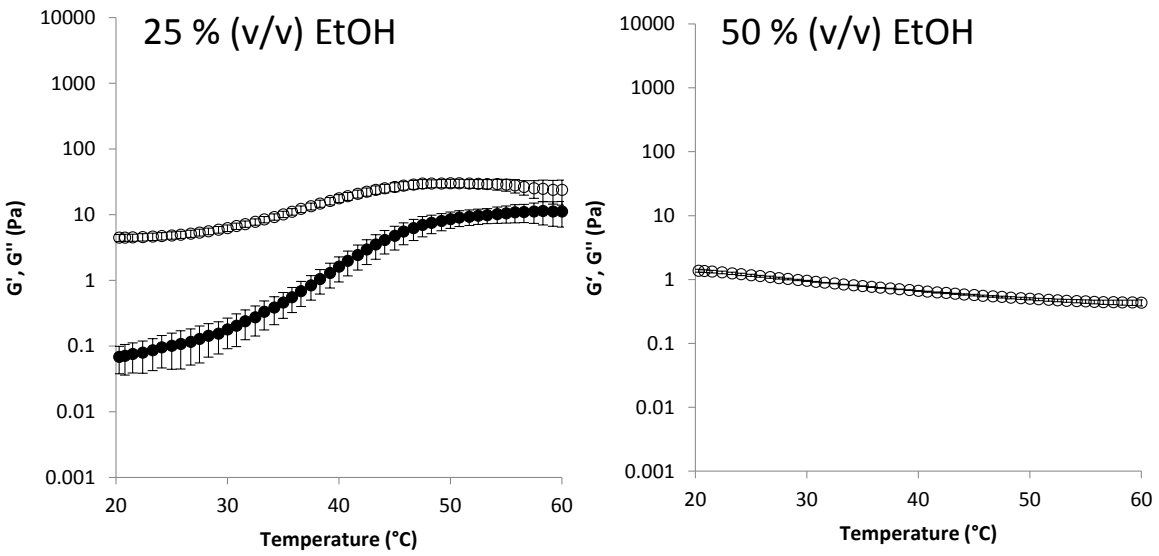

Figure 5. The effect of ethanol content and temperature on G' (closed circles) and G'' (open circles) at 30 % (w/v) soluplus concentration. Please note that a value of G' could not be measured for 50 % (v/v) ethanol solutions as it was below the limit of detection of the instrument.

Topical formulations are typically tolerated within a pH range of 4-7, either side of which irritation may occur. 30 % (w/v) soluplus solutions in PBS at pH 4, 5, 6, and 7 were evaluated by rheometry to understand how this variation in pH may affect thermoresponsive behaviour (figure 6). The gelation temperature was unaffected by pH, having values of 36.9 ± 0.5, 36.9 ± 0.5, 37.5 ± 0.0, and 37.5 ± 0.0 °C for solutions at pH 4, 5, 6, and 7, respectively. No dramatic changes were noted in the viscoelasticity of these solutions. Overall, rheological properties appear unaffected by pH over this range. Soluplus is a copolymer of N-vinylcaprolactam, vinyl acetate, and poly(ethylene glycol), and these functional groups do not contain functional groups likely to ionise within this range. It is evident that all solutions exhibited a reduced Tgel compared with 30 % soluplus in deionised water (39.7 ± 0.5 °C). This is likely a result of the different ionic strength of the PBS solutions relative to deionised water, thus there is a need to explore the effect of salt concentration on thermoresponsive behaviour. It has been demonstrated by Mikheeva et al (13) that the LCST of poly(N-vinyl caprolactam) is decreased by the presence of NaCl due to a "salting out" effect.

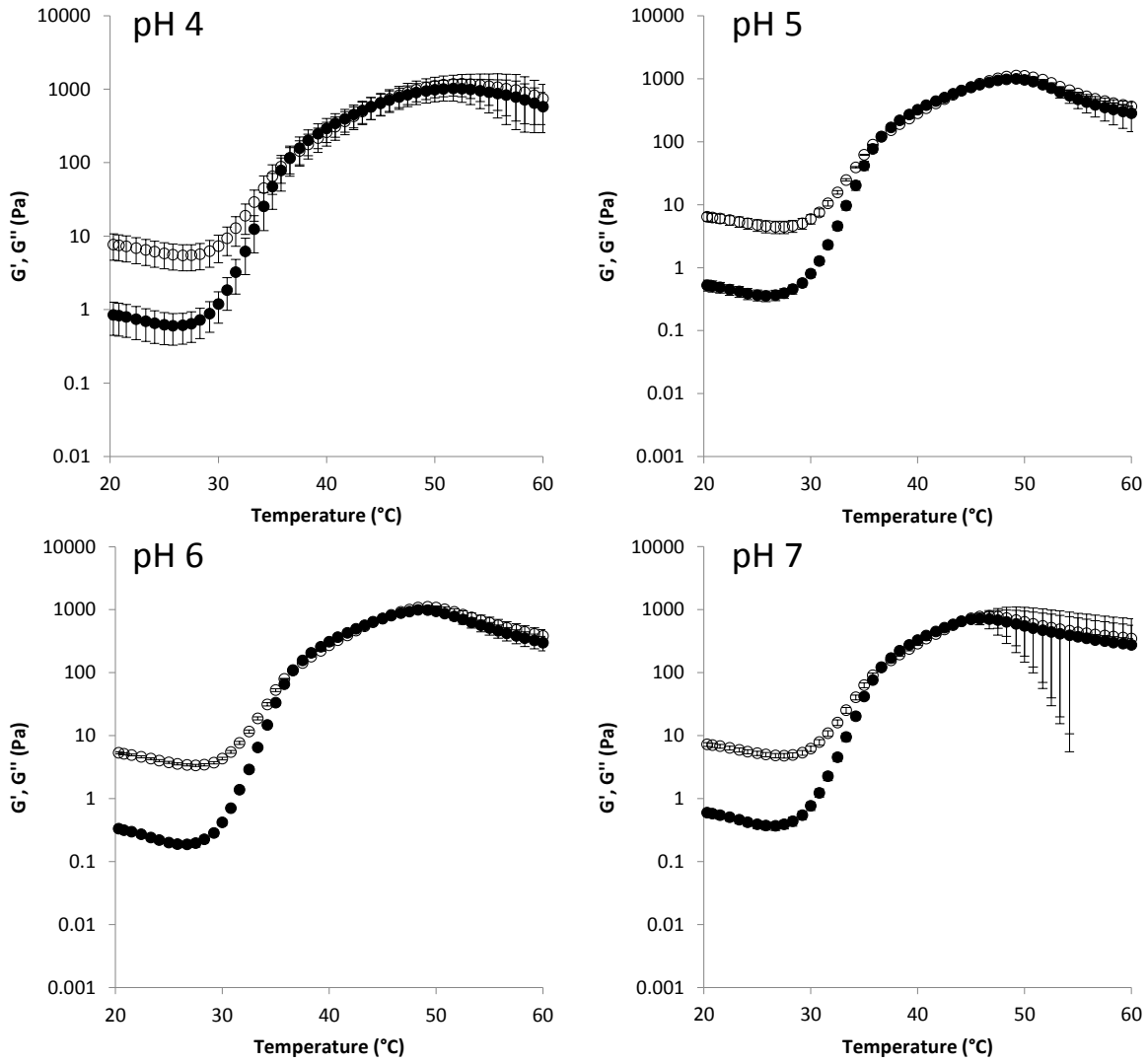

Figure 6. The effect of pH and temperature on G’ (closed circles) and G’’ (open circles) at 30 % (w/v) soluplus concentration.

The effect of salt concentration on the thermoresponsive nature of 30 % (w/v) soluplus solutions is shown in figure 7. NaCl concentrations of 0.001, 0.01, 0.1 and 1M resulted in gelation temperatures of 39.7 ± 0.5, 39.7 ± 0.5, 37.5 ± 0.0, and 28.9 ± 0.5 °C, respectively. It is clear that low concentrations of NaCl had no observable effect on gelation temperature, but at [NaCl] > 0.1 M this critical temperature was depressed. This effect was also seen in poly(N-vinyl caprolactam) homopolymer by Mamytbekov et al (14). The use of a 1 M NaCl reduced this temperature to below body surface temperature (34-35 °C), making this material a potential *in situ* gelator for topical use, transitioning from a thin to thickened state upon application to the body. The depression in gelation temperature is likely a result of the “salting out” of poly(N-vinyl caprolactam) blocks in soluplus, which exhibits an LCST. This 30 % (w/v) soluplus solution in 1 M NaCl had a G'_{max} of 1163.6 ± 280.1 Pa at 37.8 ± 0.5 °C, significantly higher than the other solutions at this temperature. G'_{max} values for 0.1, 0.01, and 0.001 M were 1035.6 ± 167.0, 793.6 ± 96.1, and 730.9 ± 98.5, at 58.3 ± 1.7, 59.2 ± 0.9, and 60.0 ± 0.0 °C, respectively. Increasing salt concentration appears to depress this maximum G’ value, and the temperature at which G'_{max} is reached. It is likely that the “salting out” effect which depresses the

LCST of N-vinylcaprolactam also promotes polymer-polymer interactions in the system, increasing G'_{max} through increased physical entanglement.

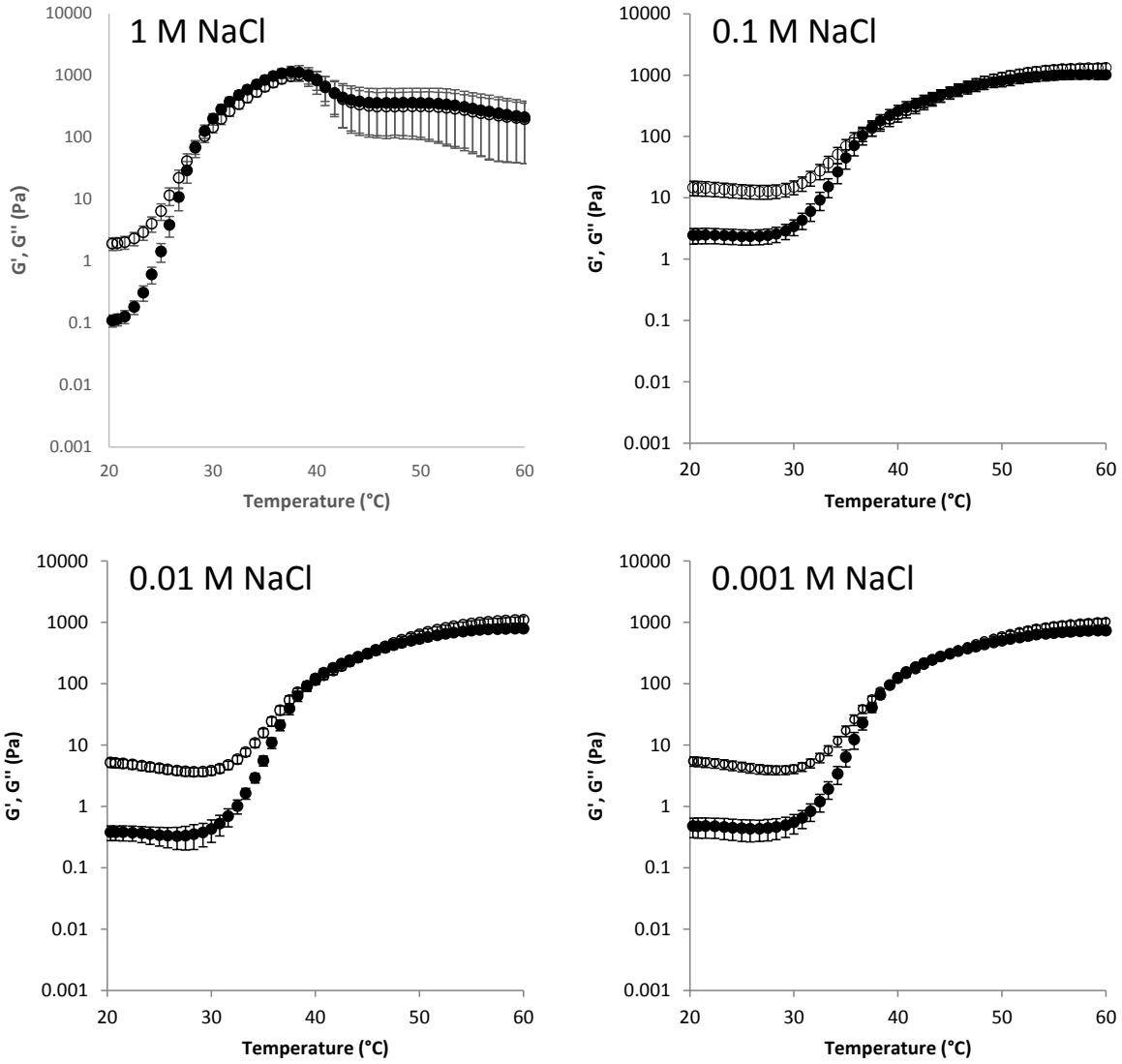

Figure 7. Effect of NaCl concentration on the thermoresponsive nature of 30 % (w/v) soluplus solutions. G' (closed circles) and G'' (open circles) shown.

"Salting out" describes a reduction in solubility due to an enhancement of hydrophobic interaction, whilst "salting in" describes the opposite effect – an increase in solubility due to decreased hydrophobic effects. The "salting in" or "salting out" power of ions can be described using the Hofmeister series (15). For the purpose of investigating the effect of "salting in" or "salting out" ions on the thermoresponsive rheological behaviour of soluplus, the properties of 30 % (w/v) soluplus in 1 M KCl and 1 M guanidine HCl was investigated and compared to 1 M NaCl. The Hofmeister series ranks K^+ ions as having a greater "salting out" effect than Na^+ (16). The guanidinium ion is a "salting in" agent, or "chaotrope"(16). For the purpose of this study we can rank from salting out to in as: KCl>NaCl>guanidine HCl. The effect of these cations on the rheology of 30 % (w/v) soluplus is shown in figure 8. Increasing salting out power increased absolute values of G' and G'' above ca. 25 °C, where the solutions had started to thicken. Relative to NaCl, gelation temperature is increased from

28.9 ± 0.5 °C in 1 M NaCl to 48.3 ± 0.0 °C by the salting in agent (guanidine HCl), and decreased to 26.6 ± 0.0 °C by the KCl, which has a greater salting out power (figure xb). The anion, Cl^- was kept constant, as was ionic strength, so that effects may be directly attributed to the cation. Decreased gelation temperature with increased ability to salt out may be related to an increase in the strength of hydrophobic effect, favouring polymer-polymer interactions, which leads to aggregation at lower temperatures. The increased favourability of polymer-polymer interactions could also be responsible for the increased in internal friction, manifesting as increases in overall values of G' and G''. Overall it is believed that salting out results in a more viscous gel, which forms at lower temperatures.

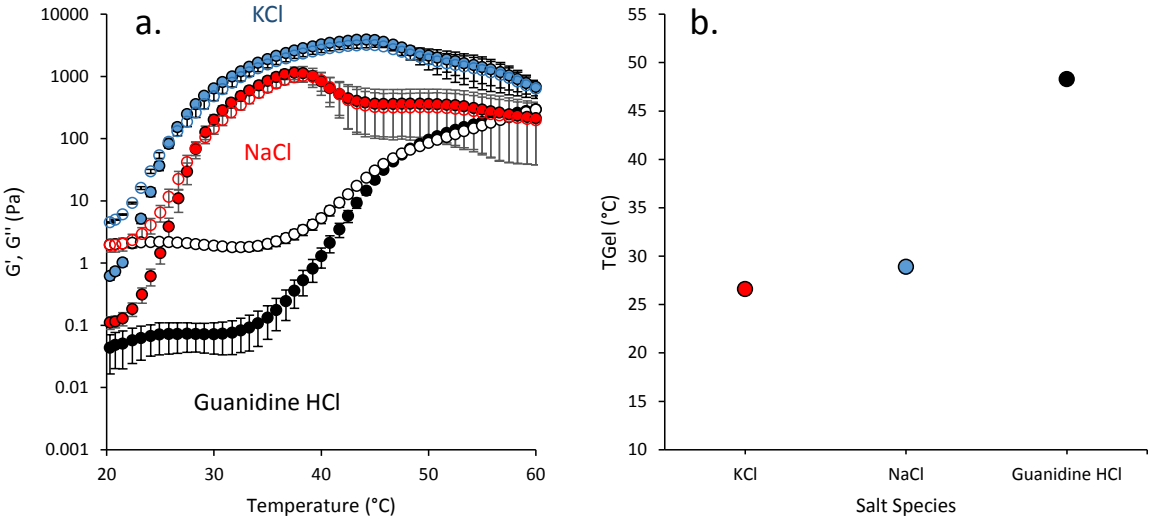

Figure 8. a. Effect of salt species and temperature on G' (closed circles), and G'' (open circles), using KCl (blue), NaCl (red), and guanidine hydrochloride (black). Na^+ and K^+ ions are "salting out" agents, whilst the guanidinium ion is a "salting in" agent, following the Hofmeister series K^+>Na^+> guanidinium. b. effect of salt type on TGel.

30 % (w/v) soluplus in 1 M NaCl has been identified as a potential thermoresponsive material with suitable rheological properties for topical application. This solution has an ideal gelation temperature of 28.9 ± 0.5 °C, and is expected to exist as a thin fluid at room temperature, which will increase in viscosity and elasticity by warming upon contact with the body. The loss tangent of the material at 35 °C is 0.77 ± 0.01, indicating a small dominance of elastic behaviour, but overall properties more analogous to a thickened fluid than a highly elastic hydrogel. The potential of this thermothickening solution for topical use was further evaluated by rheometry (figure 9). An oscillatory stress sweep of the 30 % (w/v) soluplus in 1 M NaCl demonstrated a linear viscoelastic region until a yield stress of ca. 10 Pa, where thinning was observed (figure 9a). A frequency sweep indicated a dependence of G' and G'' consistent with a thickened polymer solution rather than a strongly entangled solid-like material (figure 9b) (17). Flow rheology demonstrated shear-thinning behaviour, with a dynamic viscosity of 36.3 ± 9.8 Pa.s at a shear rate of 20 s^{-1} (figure 9c). Finally, the application of the 30 % (w/v) soluplus in 1 M NaCl solution to a topical site, such as the skin, was investigated by holding the material at 20 °C for 1 min, mimicking room temperature, then at 35 °C for 4 min, mimicking the surface of the body (figure 9d). It can be seen that at 1 min the material rapidly transitioned from a fluid-like state with G'' > G', to a thickened state with G'>G''. Gelation occurred after 18 s, and thickening was complete after ca. 30 s, where a plateau was reached. This

demonstrates that 30 % (w/v) soluplus in 1 M NaCl is suitable as a thermothickening fluid for topical application.

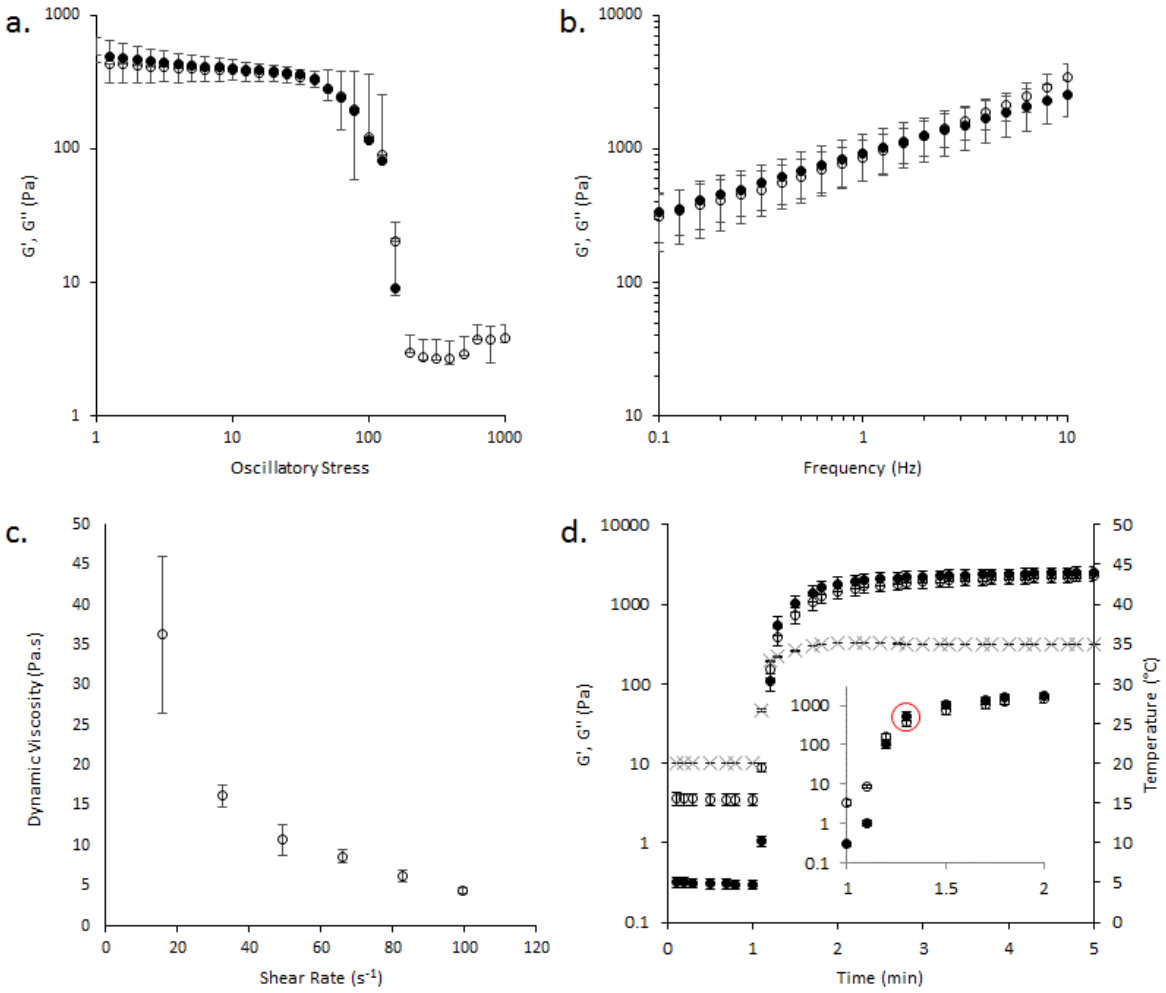

Figure 9. Rheological analysis of 30 % (w/v) soluplus in 1 M NaCl, including: a. oscillatory stress sweep at 35 °C and 1 Hz b. frequency sweep at 35 °C and 1 Pa c. flow rheogram at 35 °C and d. mimicking the application of an in situ gelling system by measurement of G' (closed circle) and G'' (open circle) at 1 Pa and 1 Hz at 20 °C for 1 min, then 35 °C for 4 minutes. Temperature shown as crosses. Insert: expanded region of the graph showing the time for gelation to occur, in red (18 s).

To demonstrate the macroscopic thickening of the 30 % (w/v) soluplus solution in 1 M NaCl, the solution was placed into a vial, warmed to ca. 35 °C and the vial inverted (figure 10). The soluplus solution flowed freely at room temperature, but formed an opaque white gel which did not flow under the force of gravity.

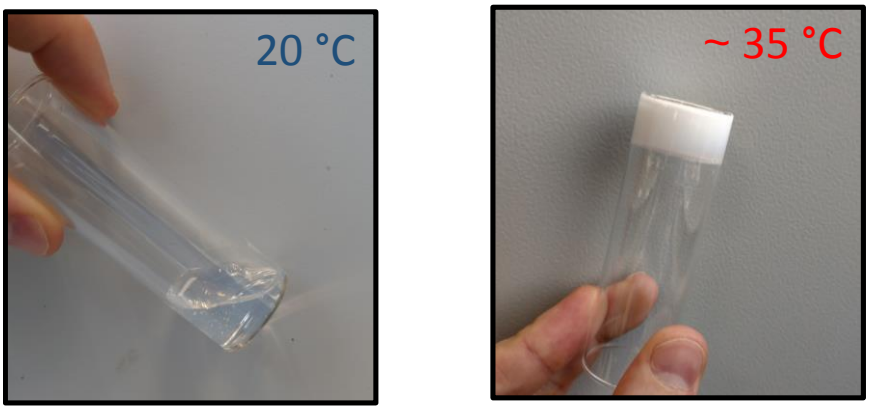

Figure 10. 30 % (w/v) soluplus solution in 1 M NaCl flows at room temperature (20 °C), but forms a viscous gel when warmed to 35 °C, representing the surface of the body.

Concluding remarks

Aqueous soluplus solutions increase in viscosity upon warming, which is believed to be a result of aggregation triggered by the demixing of poly(N-vinyl caprolactam) regions above their LCST. In water alone, the gelation temperatures were too high to produce solutions which thicken upon application to the body surface. Inclusion of 1 M NaCl or KCl drove gelation temperatures down to ca. 29 and 27 °C, respectively, and increased the viscosity of the gel formed. These effects are believed to be a result of the salting out of soluplus. 30 % (w/v) soluplus in 1 M NaCl or KCl was identified as a suitable platform for the production of *in situ* gelling systems for topical use. Soluplus is attractive as a thermothickening agent for topical use as it has multiple functionality which could be exploited for drug delivery. In addition to the thermothickening effect studied, soluplus can increase the equilibrium solubility of poorly water-soluble drugs relevant to topical drug delivery, including estradiol, clotrimazole, and itraconazole (1). It has also been shown to enhance intestinal absorption across the intestine in dogs and rats (18,19), and thus improve bioavailability.

1. Basf. Technical Information Soluplus. BASF, Pharma Ingredients Serv. 2010;(July):1–8.

2. Cook MT, Brown MB. Polymeric gels for intravaginal drug delivery. J Control Release.

3. Chen J, Liu M, Gong H, Huang Y, Chen C. Synthesis and self-assembly of thermoresponsive PEG-b-PNIPAM-b-PCL ABC triblock copolymer through the combination of atom transfer radical polymerization, ring-opening polymerization, and click chemistry. J Phys Chem B [Internet]. 2011 Dec 22;115(50):14947–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22082119

4. Filippov SK, Bogomolova A, Kaberov L, Velychkivska N, Starovoytova L, Cernochova Z, et al. Internal Nanoparticle Structure of Temperature-Responsive Self-Assembled PNIPAM-b-PEG-b-PNIPAM Triblock Copolymers in Aqueous Solutions: NMR, SANS, and Light Scattering Studies. Langmuir. 2016;32(21).

5. Topp MDC, Dijkstra PJ, Talsma H, Feijen J. Thermosensitive Micelle-Forming Block Copolymers of Poly(ethylene glycol) and Poly(N -isopropylacrylamide). Macromolecules [Internet]. 1997;30(26):8518–20. Available from: http://pubs.acs.org/doi/abs/10.1021/ma9710803

6. Vihola H, Laukkanen A, Valtola L, Tenhu H, Hirvonen J. Cytotoxicity of thermosensitive polymers poly(N-isopropylacrylamide), poly(N-vinylcaprolactam) and amphiphilically modified poly(N-vinylcaprolactam). Biomaterials. 2005;26(16):3055–64.

7. Safety Data Sheet Product: Soluplus . Saf Data Sheet. 2017;(1):1–9.

8. Cortez-Lemus NA, Licea-Claverie A. Poly(N-vinylcaprolactam), a comprehensive review on a thermoresponsive polymer becoming popular. Progress in Polymer Science. 2016. p. 1–51.

9. Negru I, Teodorescu M, Stanescu PO, Draghici C, Lungu A, Sarbu A. Poly(N-vinylcaprolactam) Triblock Copolymers Synthesis by ATRP and thermal gelation properties of the aqueous solutions. Mater Plast. 2010;35–41.

10. Cespi M, Casettari L, Palmieri GF, Perinelli DR, Bonacucina G. Rheological characterization of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®) water dispersions. Colloid Polym Sci. 2014;292(1):235–41.

11. Verbrugghe S, Bernaerts K, Prez FE Du. Thermo-Responsive and Emulsifying Properties of Poly (N-vinylcaprolactam) Based Graft Copolymers. Spectroscopy. 2003;1217–25.

12. Meeussen F, Nies E, Berghmans H, Verbrugghe S, Goethals E, Du Prez F. Phase behaviour of poly (N - vinyl caprolactam) in water. Polymer (Guildf). 2000;41(24):8597–602.

13. Mikheeva LM, Grinberg N V, Mashkevich AY, Grinberg VY, Thanh LTM, Makhaeva EE, et al. Microcalorimetric Study of Thermal Cooperative Transitions in Poly(N-vinylcaprolactam) Hydrogels. Macromolecules [Internet]. 1997;30(9):2693–9. Available from: http://dx.doi.org/10.1021/ma9615112

14. Mamytbekov G, Bouchal K, Ilavsky M. Phase transition in swollen gels 26. Effect of charge concentration on temperature dependence of swelling and mechanical behaviour of poly(N-vinylcaprolactam) gels. Eur Polym J. 1999;35:1925–33.

15. Hofmeister F. Zur Lehre von der Wirkung der Salze. Arch für Exp Pathol und Pharmakologie [Internet]. 1888;25(1):1–30. Available from: http://link.springer.com/10.1007/BF01838161

16. Hyde AM, Zultanski SL, Waldman JH, Zhong YL, Shevlin M, Peng F. General Principles and Strategies for Salting-Out Informed by the Hofmeister Series. Org Process Res Dev. 2017;21(9):1355–70.

17. Stokes JR, Frith WJ. Rheology of gelling and yielding soft matter systems. Soft Matter [Internet]. 2008;4(6):1133. Available from: http://xlink.rsc.org/?DOI=b719677f

18. Hou J, Sun E, Sun C, Wang J, Yang L, Jia X bin, et al. Improved oral bioavailability and anticancer efficacy on breast cancer of paclitaxel via Novel Soluplus®—Solutol® HS15 binary mixed micelles system. Int J Pharm. 2016;512(1):186–93.

19. Linn M, Collnot E-M, Djuric D, Hempel K, Fabian E, Kolter K, et al. Soluplus® as an effective absorption enhancer of poorly soluble drugs in vitro and in vivo. Eur J Pharm Sci. 2012;45(3):336–43.