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Short communication

Effect of isopropyl alcohol and poloxamer 407 on gelation temperature and critical quality attributes of thermo-reversible gel formulation

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Introduction

Recently, thermo-gelling formulations composed of poloxamer 407 (P-407) have received much attention for drug delivery, mainly due to their low toxicity, ease of administration, spreadability and retention on the administration site. P-407 is a triblock copolymer with a center block of hydrophobic polypropylene oxide (PPO) surrounded by two hydrophilic polyethylene-oxide (PEO) blocks. The unique properties of the P-407 aqueous solution are the reversible gelation properties above a certain polymer concentration and temperature, as well as the ringing effect of the gel formulations. The thermo-gelling phenomenon is characterized by a sol-gel transition temperature ($T_{sol \rightarrow gel}$) and it occurs as a result of hydrophobic interactions between the P-407 copolymer chains resulting in a phase transition from the micellar solution to semisolid micellar cubic state.

However, the addition of solvents, such as isopropyl alcohol, to the P-407 formulation may increase or decrease $T_{sol \rightarrow gel}$ and affect the critical quality attributes (CQAs) of the gel formulation. In addition, depending on the manufacturing method (''hot'' or ''cold''), the poloxamer solution will remain fluid or become semi-solid below or above certain $T_{sol \rightarrow gel}$.

As the P-407 and isopropyl alcohol concentration are known formulation variables that affect the $T_{sol \rightarrow gel}$ and the CQAs of P-407-based gel formulation, the study aimed to optimize their concentration in the formulation, using a ''hot'' manufacturing method, and evaluate their effects on a few CQAs, such as pH, viscosity, cumulative transport, texture properties and $T_{sol \rightarrow gel}$ applying Design of Experiments (DoE) approach.

Materials and methods

In order to evaluate the effect of formulation variables – concentration of P-407 and isopropyl alcohol on CQAs of the gel formulations, a three-level full factorial quadratic design with two factors on three levels with three central points was performed. The experimental design was created and analyzed using Modde Go software version 12.0. The concentration of P-407 was studied at the following levels: 10% w/w (low), 12% w/w/ (medium) and 14% w/w (high), whereas the concentration of isopropyl alcohol was studied at the following levels: 16% w/w (low), 18% w/w (medium) and 20% w/w (high). The experimental range for the studied variables was predefined based on the screening experiments where it was observed that P-407 in concentration below 10 % w/w forms clear dense liquids at 20°C and above 14% w/w forms highly viscous and ''sticky'' gels. Formulations with more than 20% w/w isopropyl alcohol exist in a liquid state, whereas early hydrophobic interactions occur between PPO chains and a non-homogenous system is formed below 14% w/w.

The model was fitted using the PLS method and RSM was applied to estimate the non-linear multidimensional relationship between formulation variables and CQAs. Twelve experiments were generated by the software. The formulations were prepared by heating the purified water to 45 ± 2°C in a laboratory mixer, adding of the active substance solution, P-407 and slowly mixing until complete dissolving of P-407. Depending on the sol-gel transition of the formulation, the solution was cooled to a certain temperature. P-407

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(Kolliphor® P 407) was provided by BASF (Ludwigshafen, Germany). Isopropyl alcohol was purchased from Merck (Darmstadt, Germany) with Ph. Eur. grade. The model anti-inflammatory drug was purchased from BASF (Ludwigshafen, Germany) and purified water was of a Ph. Eur. grade.

The formulations were evaluated for appearance (visually), Tsol-gel transition temperature (DSC K2000, TA Instruments), pH (potentiometric method, pH meter SevenCompact), viscosity (rotating viscometer, Brookfield RVTDV-II viscometer, T-bar spindles), texture properties (TA-STF Spreadability Fixture, Brookfield Ametek Texture Analyzer), cumulative transport (Franz Diffusion Cell system) and ringing effect (manually).

Results and discussion

ANOVA analysis showed model significance (p value <0.05); lack of fit (p value >0.05), high R2 and Q2 values (>0.5). Poloxamer 407 - based formulations had a transparent and homogenous appearance. Two formulations were liquid at room temperature and the other ten formulations had the desired gel consistency. A strong ''ringing'' effect, distinctive for poloxamer gels, has been detected only in formulations with sufficiently high viscosity and hardness. DSC showed the temperature-induced transitions that happen in such formulations with thermosensitive polymer. The curves depict that the addition of higher concentrations of isopropyl alcohol decreases the critical micelle temperature indicating that the formation of micelles is favorable at a lower temperature. Hence, formulations with a low level of 16% w/w isopropyl alcohol (12% w/w and 14% w/w P-407) completed the micellization and the sol-gel transition occurs at 47°C, while formulations with a medium level of 18% w/w isopropyl alcohol shifted to lower micellization temperature range, resulting with lower $T_{sol \rightarrow gel}$ 37±2°C, making the formulation suitable for topical administration under normal storage conditions with optimum viscosity and texture properties. 20% w/w isopropyl alcohol concentration suppress the sol-gel transition at appropriate temperature by decreasing the degree of hydrogen bonding between micelles and reduction in gel strength, which results in liquid formulation. For *in vitro* release, a decrease in the release rate of the active substance is commonly interpreted by increase in P-407 concentration associated with an increase in gel viscosity.

The main effect plot showed that the most significant single model factor affecting cumulative transport, hardness, viscosity and adhesive force was P-407 concentration. Increasing its concentration to from low to high level provides firmer gel with greater viscosity and adhesive force, but decreased cumulative transport. Concentration of isopropyl alcohol showed a significant negative impact on $T_{sol \rightarrow gel}$, hardness and viscosity, hence with increasing its concentration from low to high level, shifting to the lower gelation temperatures has been observed, making the formulations soft gels or liquids at normal storage conditions.

Response Surface Plots showed that only concentration of P-407 has minor positive influence on pH, while concentration of isopropyl alcohol has negligible effect. In terms of $T_{sol \rightarrow gel}$, an interesting finding has been detected. Namely, the formulation trial with of 20% w/w isopropyl alcohol (high level) and 12% w/w P-407 (low level) showed decrease of the $T_{sol \rightarrow gel}$ and formulation still existed in liquid state even on 20-25°C. Further cooling to 7°C caused sol-gel transition and increased viscosity and strength of the formulation. However, this phenomenon was reversible and formulation returned to liquid state even with minor increase of the temperature above 8°C, making it unsuitable for use under normal storage conditions.

The sweet-spot showed that when the concentration of P-407 was varied between 11.2 – 12.5 % w/w and concentration of isopropyl alcohol was varied between 17.8 - 19.2 % w/w, the values for all evaluated CQAs of the formulation will be within the acceptable limits.

Conclusion

The concentration of isopropyl alcohol had the most significant effect on $T_{sol \rightarrow gel}$, an attribute related to the suitability for administration and storage of the dosage form. The concentration of P-407 had the most significant effect on the viscosity and hardness of the formulations, indicating that greater gel strength will be achieved with increased concentration. Since the release rate of the drug is mainly driven by the viscosity of the formulation, in vitro release rate was significantly affected in the formulations with high viscosity.

References

Djekic, L., Čalija, B., Medarević, Đ., 2020. Gelation behavior, drug solubilization capacity and release kinetics of poloxamer 407 aqueous solutions: The combined effect of copolymer, cosolvent and hydrophobic drug. Journal of Molecular Liquids, 303, 112639. doi: 10.1016/j.molliq.2020.112639

Tung, I.C., 1994. Rheological behavior of poloxamer 407 aqueous solutions during sol-gel and dehydration processes. International Journal of Pharmaceutics 107(2), 85-90. doi: 10.1016/0378-5173(94)90445-6