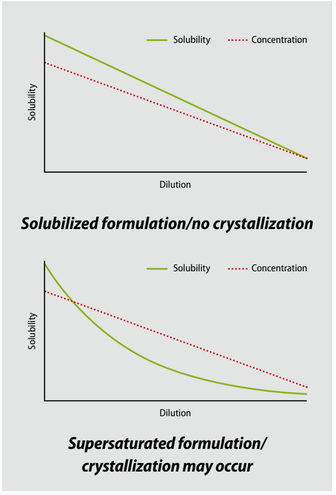
PREVENTING CRYSTALLIZATION WITH THE *Crystal16*™ FOR SUCCESSFUL PARENTERAL FORMULATION

Introduction

Many drug substances are formulated as parenteral formulations and administrated directly into the systemic circulation in animals and humans. In order to improve their stability and solubility, many parental formulations are formulated using a co-solvent. Ampule or vial dosage forms are often co-solvent concentrated formulations. These concentrates are finally diluted before administrated to the patient. Nevertheless, there are many cases known where dilution of drug formulations has the potential to generate conditions where drug concentrations are supersaturated. Under these circumstances, drug precipitation / crystallization is likely to take place. Drug precipitation after parenteral administration may cause mechanical or chemical irritation at the injection site, and potentially even more serious systemic effects.



Solubilized formulation/no crystallization

Supersaturated formulation/ crystallization may occur

Experimental

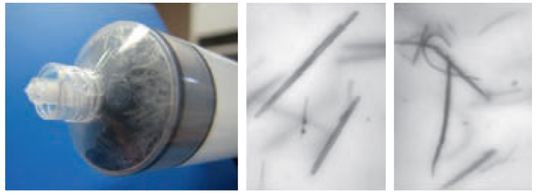
Simple ***Crystal16*** solubility measurements help avoid vulnerable formulations and foresee mechanical and chemical irritation at injection site. Additionally the particle visualization module of the ***Crystalline*** instrument can provide in situ information about the crystallization behaviour of a compound and the stability of a final formulation.

The ***Crystal16*** combines automation with integrated turbidity measurement to determine clear and cloud points resulting in solubility data and simple generation of solubility curves in a short time.

Results and Discussion

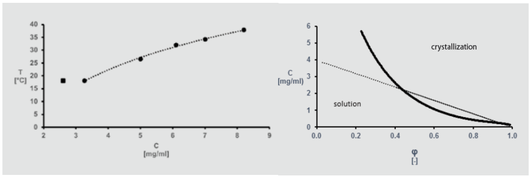
The commercial lorazepam solution is quite viscous and therefore dilutions with aqueous NaCl solution or 5% glucose are always prepared before injection. Nevertheless, upon administering lorazepam, obstruction of the infusion lines or syringe occurs frequently. Experiments to visualize the crystallization process of lorazepam were carried out in the ***Crystalline*** multiple reactor setup. Known volumes of the commercially available lorazepam solution and the aqueous glucose solution were added to prepare lorazepam solutions with known overall composition. The crystallization process of lorazepam could be followed in-situ with the help of the ***Crystalline*** particle visualization module.

Ter Horst et al observed that lorazepam crystals exhibit an extremely needle-like morphology when formed at or below a concentration of 0,5 mg/ml. Interestingly, at higher concentrations the needles were deformed and strongly curled.



Lorazepam cystallization during dilution in a syringe

These differences indicated that for a 1mg/ml solution, the supersaturation for crystallization is much larger than for a 0,5 mg/ml solution. All these results let ter Horst et al to investigate the phase behaviour of lorazepam in mixed solutions.



Measured saturation temperatures as a function of lorazepam concentration

Isothermal solubility diagram of lorazepam at 18°C

The authors determined the solid–liquid phase diagram for commercially available lorazepam in mixtures with aqueous glucose solution by performing simple solubility measurements on the ***Crystal16*** instrument. Known volumes of a commercially available lorazepam solution and a glucose solution in water were added to prepare 1 ml of a lorazepam crystal suspensions with known overall compositions.

Conclusion

The solubility diagram was constructed as a function of the volume fraction of glucose solution added when preparing the solution. The phase diagram showed that high lorazepam concentrations (low glucose solution volume fractions) lead to a stable solution in which no lorazepam crystallization will occur. This confirmed that the glucose solution acts as an anti-solvent, greatly reducing the lorazepam solubility in the infusion solution.

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