In-situ solubility measurements of ionizable drugs and precipitation behaviour in the presence and absence of Plasdone™ Povidone and Copovidone crystallization inhibitors

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Purpose

To study in real-time the crystallization tendency of drug compounds from super-saturated solutions using novel pH-metric solubility methods and investigate the ability of Plasdone™ Povidone and Copovidone to inhibit crystallization.

Methods

Ionizable drug compounds were studied using the CheqSol solubility method which allows for the determination of the solution concentration of the free (acid or base) form of a compound during an acid-base pH titration using the principles of mass and charge balance. Ionizable compounds were dissolved at an appropriate pH, with and without the presence of Plasdone™ polymers, and titrated towards the sample's pK_a until the neutral species precipitates. The precipitation behaviour is then monitored to provide a picture of the crystallization tendency of the drug.

Results

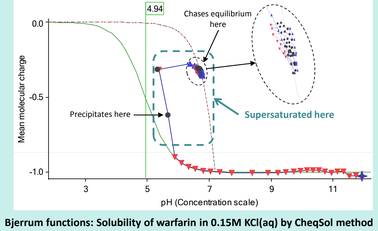
The effects of different grades of Plasdone Povidone crystallization inhibitors were evaluated in experiments with ketoprofen, warfarin, metoclopramide, niflumic acid and piroxicam. All PVP grades at 1:1 w/w polymer:drug ratio kept ketoprofen in solution for more than three hours at concentrations well above the crystalline solubility of the compound. PVP grade K-25 was able to sustain ketoprofen in solution in metastable form(s) for sustained periods at polymer:drug ratio as low as 1:50. K-29/32 and S-630 maintained supersaturation of warfarin for at least 2 hours. For metoclopramide, both the extent and duration of supersaturation increased with an increasing S-630:metoclopramide ratio. Although for niflumic acid and piroxicam the duration of supersaturation lasted for relatively a short period of time in presence of Plasdone polymers, the final solubility of the compounds were 3.3x and 5x the solubility of their relevant crystal forms, respectively.

Conclusion

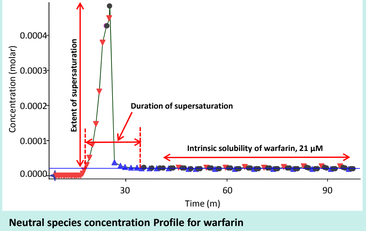
A technique for studying precipitation behaviour and monitoring the potential of different grades of Plasdone polymers as crystallization inhibitors has been described, providing useful insights into precipitation kinetics. Povidone and Copovidone were proven to be efficient in increasing the extent and/or duration of supersaturation of tested compounds.

Supersaturation behaviour of ionizable compounds: Example - warfarin

In the CheqSol solubility method [1], ionizable compounds are dissolved in charged form and titrated towards the pK_a to produce the neutral form. While the compound is in solution, the titration follows the Bjerrum function shown below left (solid green line). Before it precipitates, it first forms a supersaturated solution. Later, the compound crystallizes and the concentration falls towards the intrinsic solubility. The Bjerrum function shifts to a new position determined by the solubility. The data can be re-plotted as concentration of the neutral acid vs. time, showing the extent and duration of supersaturation.



Bjerrum functions: Solubility of warfarin in 0.15M KCl(aq) by CheqSol method

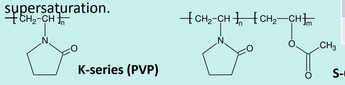


Neutral species concentration Profile for warfarin

Using SiriusT3 to investigate solubility enhancement

Solubility enhancement can be studied in real-time using the SiriusT3 instrument. This poster illustrates the behaviour of five compounds with various grades of Plasdone polymers from ASI. Plasdones are synthetic, water soluble N-vinyl-2-pyrrolidone (VP) mono- or co-polymers which inhibit crystallization and prolong supersaturation.

Plasdone Polymers	K-Value (Kinematic Viscosity)	Typical Weight Ave. Mol. Wt.
Plasdone K-12	10.2 - 13.8	4,000
Plasdone K-17	15.5 – 17.5	10,000
Plasdone K-25	24 – 26	34,000
Plasdone K-29/32	29 – 32	58,000
Plasdone K-90	85 - 95	1,300,000
Plasdone S-630	26 - 29	40,000

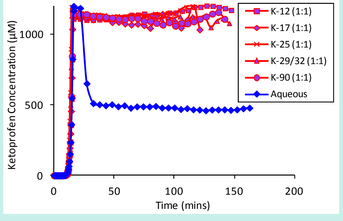


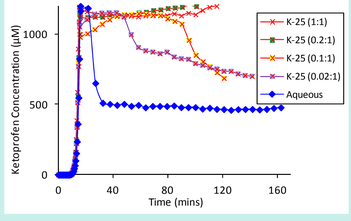
K-series (PVP)

S-630 (PVP-vinyl acetate copolymer) n:m = 6:4

Ketoprofen solubility enhanced threefold for two hours

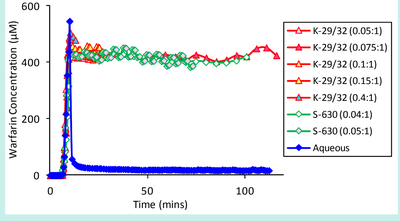
All K grades of Plasdone Povidone at 1:1 ratios keep ketoprofen in solution at much higher concentrations than the aqueous solubility of 460 µM. The concentration is maintained close to 1200 µM for at least 2 hours. It is likely that the polymers stabilize the amorphous form of ketoprofen. Plasdone K-25 was selected for further study. The duration of supersaturation increases with K-25:ketoprofen ratio; even at 0.1:1 and 0.02:1 ratios there was a delay before the onset of crystallization.





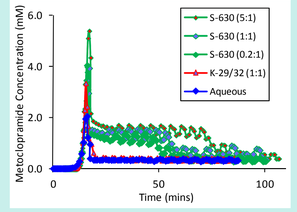
Warfarin solubility 20 times higher

Plasdone™ K-29/32 and S-630 keep warfarin in solution at much higher concentrations than the final solubility of 21 µM determined in aqueous conditions. The concentration is maintained for the duration of the experiments (up to 2 hours) at a solubility close to 430 µM. It is likely that the polymer stabilizes the amorphous form of warfarin, and even low polymer:warfarin ratios did not reduce the extent and duration of supersaturation.



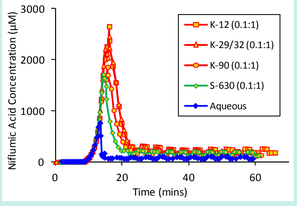
Metoclopramide: metastable form persists for one hour

Under aqueous conditions, the extent of metoclopramide supersaturation reaches 2 mM, around six times higher than the final solubility of 330 µM. Supersaturation is short-lived and is over in about three minutes. Supersaturation increases to 3.3mM at 1:1 drug:Plasdone K-29/32 ratio, but duration is still short. Plasdone S-630 shows a larger effect on both the extent and duration of supersaturation. Interestingly, both the extent and duration of supersaturation are increased with the increasing S-630:metoclopramide ratio, with evidence for a long-lived metastable form.



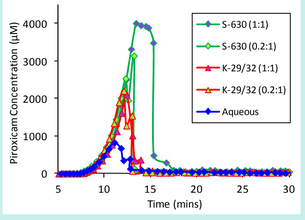
Niflumic acid: harder to achieve long-term solubility enhancement

Niflumic acid achieves concentration levels close to 750 µM before precipitating out under aqueous conditions, reaching a final concentration close to 60 µM. However, the supersaturation is short-lived, and once precipitation is induced the concentration reduces quickly over a few minutes. Different Plasdone grades significantly increase the kinetic solubility even at high drug loading, although supersaturation still remains relatively short-lived. In the best case, K-12, concentration levels of 2650 µM were achieved before reaching a final solubility of 200 µM in less than 10 minutes.



Piroxicam: dramatic enhancement but rapid decrease

Under aqueous conditions piroxicam has a supersaturation ratio greater than 45-fold when compared to the final solubility of 17 µM. However, supersaturation is short-lived and is over in a few minutes. Extent of supersaturation increases significantly in the presence of Plasdone polymers. S-630 shows a larger effect than K-29/32 and increases the extent of supersaturation to around 4000 µM at 1:1 piroxicam:S-630 ratio. Despite this, supersaturation is maintained for only 5 minutes and the final solubility is 4-fold higher than under aqueous conditions.



Reference

[1] Box, K.; Comer, J. E.; Gravestock, T.; Stuart, M., New ideas about the solubility of drugs. Chem Biodivers 2009, 6 (11), 1767-88.

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