Solubilities of morphine analogs: crystallization vs. liquid-liquid phase separation (LLPS)

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Purpose

To gain insight into the behaviour of structurally similar compounds in solution before, during and after precipitation.

Methods

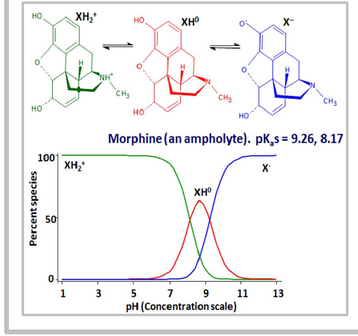
Two analogs of morphine were selected for study. Both compounds were ampholytes, with one acidic and one basic pK_a, and they were highly soluble in water at low and high pH. However they were less soluble at pH values between the two pK_as, where the molecules were unionised. The aqueous equilibrium solubilities of the unionised forms of each compound were measured by two independent CheqSol experiments, one starting at low pH and the other at high pH. In CheqSol, the pH of a stirred solution of analyte is adjusted by adding small volumes of HCl and KOH titrant solutions. The concentration of analyte in solution is calculated using principles of mass balance and charge balance. The onset of precipitation is sensed by an in-situ UV/vis dip probe.

Results

The solubilities of each compound measured in both experiments (low-to-high pH and high- to-low pH) agreed closely. However the behaviour of the two compounds during the experiments was different. Naloxone became supersaturated before precipitation in both experiments to a concentration that was nine times higher than the equilibrium solubility. After precipitation the concentration in solution fell rapidly and the solid crystallised. Diprenorphine immediately precipitated above a certain concentration (0.18 mg/mL) and the data showed that it remained in a form consistent with liquid liquid phase separation (LLPS) throughout both experiments. These observations of solid state form were confirmed using polarised light microscopy. Both molecules had 5 hydrogen bond acceptors and 2 hydrogen bond donors, but the polar surface area of naloxone was 11% higher than that of diprenorphine. It is proposed that the tendency for crystallization vs. phase separation is related to the differences in polar surface area of the two analogs.

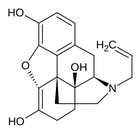
Conclusion

The solubilities of each compound measured in both experiments (low-to-high pH and high- to-low pH) agreed closely. Equilibrium solubility of ampholytes measured after pH-induced precipitation is independent of the direction of pH change. After precipitation, the form of the solid state appears to correlate with the molecule's polar surface area.



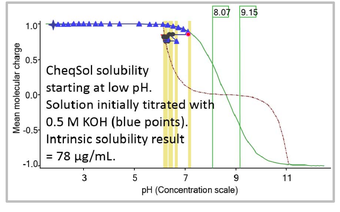
Solubility was investigated with the SiriusT3 instrument, using CheqSol and Curve Fitting methods.

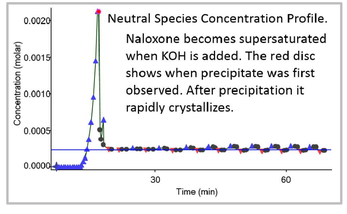
Solid state forms were observed using the Nikon Eclipse E200 polarised light microscope

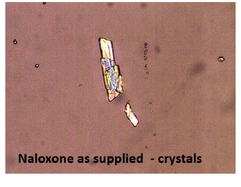


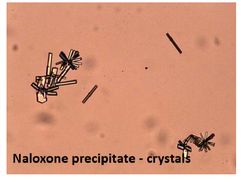
Naloxone

Naloxone is an opioid antagonist. It is used to counter the effects of opioid overdose, such as heroin or morphine. An antagonist is a drug that blocks the effect of another drug. Like diprenorphine, naloxone has 3 hydrogen bond acceptors and 2 hydrogen bond donors. Its topological polar surface area is 70 and its calculated log P is 0.61. Solubility measurements used sample weights of 5.5 – 11.8 mg, dissolved initially in 0.15M KCl solution (1.5 mL, adjusted to low or high pH). During measurement it behaves as a chaser.



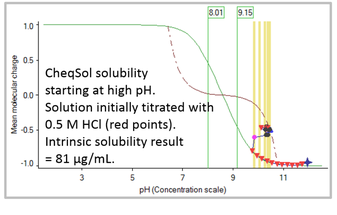


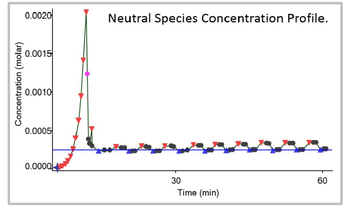




In solution, naloxone behaves like morphine. At low and high pH it is charged, and easily dissolves in 0.15M KCl. It is less soluble between its pK_as, and precipitates. The result measured by CheqSol is independent of the direction of titration.

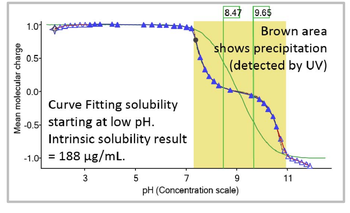
Above: titration low to high pH
Below: titration high to low pH

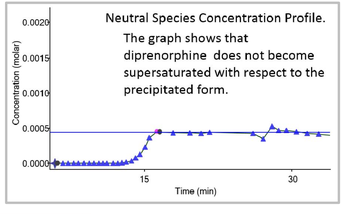




Diprenorphine

Diprenorphine is an opioid antagonist used to reverse the effects of the super-potent opioid analgesics such as etorphine and carfentanil that are used for tranquilizing large animals in veterinary medicine. Like naloxone, diprenorphine has 3 hydrogen bond acceptors and 2 hydrogen bond donors. Its topological polar surface area is 62.16 and its calculated log P is 2.82. Solubility measurements used sample weights of 4.5 – 5.1 mg, dissolved initially in 0.15M KCl solution (1.5 mL, adjusted to low pH). During measurement it behaves as a non-chaser.





Discussion

Both compounds were supplied in crystalline form. Naloxone rapidly crystallized after precipitation, and behaved as a chaser. However, diprenorphine appeared to undergo liquid-liquid phase separation (LLPS), and behaved as a non-Chaser. Although the structures of naloxone and diprenorphine share many features, naloxone is more polar and less lipophilic that diprenorphine. It is proposed that these differences in physicochemical properties lead to the different behaviours of the compounds after precipitation. A useful follow-up study would comprise experiments to determine the time for which diprenorphine persists in the LLPS form.

Reference

Hsieh, Y. L.; Ilevbare, G. A.; Van Eerdenbrugh, B.; Box, K. J.; Sanchez-Felix, M. V.; Taylor, L. S., pH-Induced Precipitation Behavior of Weakly Basic Compounds: Determination of Extent and Duration of Supersaturation Using Potentiometric Titration and Correlation to Solid State Properties. Pharm Res 2012, 29 (10), 2738-2753.

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