Cyclodextrins; Determination of the stability constant of warfarin, dipyridamole and piroxicam and the impact on solubility in the presence of cavasol and captisol.

Breeze Outhwaite 1, Rebeca Ruiz 1, Karl Box 1, Jon Mole 2
1 Sirius Analytical Ltd. Forest Row, RH18 5DW, UK.
2 Sirius Analytical Inc. Sirius Analytical Inc., Beverly, MA, USA

Purpose
Cyclodextrins are a series of sugar molecules bound together in a ring which are used in drug delivery to increase the bioavailability and solubility of drugs, via the formation of an inclusion complex with the API. This study shows the determination of stability constants and the impact on the solubility of three medicinal compounds, warfarin, dipyridamole and piroxicam in the presence of the cyclodextrin derivatives cavasol and captisol.

Methods
Three drugs showing different structures were studied; warfarin (acidic pKₐ), dipyridamole (basic pKₐ) and piroxicam (ampholyte). Studies were performed on SiriusT3; an automated titration platform with in-situ UV fibre-optic spectroscopy. Measurements were performed in triplicate at 0.15M ionic strength, under aqueous conditions.

Stability constant: Several UV-metric titrations with a phosphate buffer present were carried out to determine the shift of the sample pKₐs in the presence of varying quantities of cyclodextrin to determine the stability constants.

Solubility: The intrinsic solubility and supersaturation profiles of the selected compounds were measured in the absence and presence of cyclodextrins, using Sirius Cheqsol technology, to study the enhancement on the solubility. The extent and duration of supersaturation of the compounds were determined in the presence of cavasol and captisol at different ratios.

Results
Stability constant: The results show that increasing the quantity of cyclodextrins present in the assay shifted acidic pKₐs (i.e. the -OH groups within piroxicam and warfarin) to a higher pH, as shown in figure 1. Conversely, an increase of cavasol present shifted basic pKₐs (i.e. pyridine group of piroxicam and the pyrimidine group in dipyridamole) to a lower pH. Complexation of the compounds with the cyclodextrins showed the largest shift in pKₐ for the lowest drug:cyclodextrin ratios, whilst further additions of cyclodextrin showed incremental increases which slowly decreased until a plateau was reached. For instance, the stability constant of the neutral form of warfarin in Cavasol was found to be 354 M⁻¹ and the stability constant of its ionised form was 107 M⁻¹.

Solubility: The results showed different effects on solubility depending on the drug studied. It was observed that increasing the amount of captisol leads to an increase in the extent and duration of the supersaturated state for dipyridamole (figure 2). However, it was observed that piroxicam showed a large enhancement in equilibrium solubility (by more than threefold in a 1:5 piroxicam:captisol ratio), but a smaller effect on the extent and duration of the supersaturated state.

Conclusion
Addition of cyclodextrins disturbs the equilibrium of ionisable compounds; acidic pKₐs shift to a higher pH whereas basic pKₐs shift to a lower pH and the binding constant of a drug can be calculated. In this study, we showed that the uncharged species bind more strongly than the
charged forms. Moreover, we showed that cyclodextrins affect the intrinsic solubility of the compounds, and alter the extent and duration of supersaturation. The selection of the type of cyclodextrins used and the drug: cyclodextrin ratios is important to obtain optimal results.

Figure 1: Shift in $pK_a$ with increasing cavasol concentration for warfarin

Figure 2: Extent and duration of the supersaturated state of dipyridamole in the presence of different ratios of captisol.