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Cyclodextrins: Determination of the stability constant of Warfarin, Dipyridamole and Piroxicam and the impact on solubility in the presence of Cavasol® and Captisol®

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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.

METHOD

Three drugs with different structures were studied; Warfarin (acidic pK_a), Dipyridamole (basic pK_a) and Piroxicam (ampholyte).

Studies were performed on SiriusT3 (figure 1); 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 pK_as in the presence of varying quantities of cyclodextrin to determine the stability constants according to the method of Connors et al. [1]:

$$\frac{K_a}{K_a'-K_a} = \frac{1}{[L](K_{12}-K_{11})} + \frac{K_{11}}{(K_{12}-K_{11})} \quad \text{(eq. 1)}$$

Solubility: The kinetic solubility and intrinsic solubility of the selected compounds were measured in the absence and presence of cyclodextrins, using Sirius Cheqsol technology [2], 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 ratios of 5: 1 cyclodextrin:API.

RESULTS

Stability constant: The results show that increasing the quantity of cyclodextrins present in the assay shifted the pK_as compared to the aqueous values (figure 2). Complexation of the compounds with the cyclodextrins showed the largest shift in pK_a for Warfarin, followed by Dipyridamole and then Piroxicam, indicating the largest binding constants were obtained for Warfarin (Table 1).

Solubility: The results showed different effects on solubility depending on the drug studied (figures 3-5). It was observed that increasing the amount of Captisol or Cavasol, leads to an increase in the extent and duration of the supersaturated state for all the drugs studied. Warfarin in the presence of Cavasol showed the biggest effect on the extent and duration. However, it was observed that Piroxicam showed an enhancement in kinetic solubility, but a smaller effect on the extent and duration of the supersaturated state.

Stability constant

Figure 2 displays the pK_a shifts of Warfarin, Dipyridamole and Piroxicam as a function of the Cavasol, concentration. The described shift in pK_as has been overlaid with the Connors model [1], allowing for the calculation of the stability constant (equation 1).

Warfarin: The acidic pK_a of Warfarin shifted to a higher pH value upon complexation with the cyclodextrin molecules. The calculated stability constants indicated that the protonated, neutral species of the acidic drug binds more strongly to the cyclodextrin than the deprotonated, anionic species, reflected in the neutral form's higher stability constant (354 M^{-1}) versus that of the ionic form (107 M^{-1}).

Dipyridamole: The basic pK_a of Dipyridamole shifted to a lower pH value upon complexation with the cyclodextrin molecules. The calculated stability constants indicate that the deprotonated, neutral species of the basic drug binds more strongly to the cyclodextrin than the protonated, ionic species, as seen in the neutral form's higher stability constant (60.3 M^{-1}) versus that of the ionic form (13.5 M^{-1}).

Piroxicam: The calculated stability constants indicated that the most strongly binding form of the ampholytic drug was the anionic species since the acidic pK_a shifted to lower values. The stability constant of this complexation was found to be 2.87 M^{-1}, showing that Piroxicam only binds very weakly with Cavasol.

Solubility

Figures 3-5 display the change in the solubility of Warfarin, Dipyridamole and Piroxicam in the presence of cyclodextrins; Cavasol and Captisol, as characterised by the Sirius Curve Fitting Method [2].

Warfarin: The intrinsic solubility of Warfarin exhibited approximately a six fold increase in the presence of Cavasol, whereas Captisol caused approximately a threefold increase.

Dipyridamole: This drug exhibited an approximate two fold increase in intrinsic solubility in the presence of both cyclodextrins.

Piroxicam: Even this drug showed an improvement in solubility with the presence of the cyclodextrins studied, definitely it was the smaller impact determined in comparison with warfarin and dipyridamole.

Fig. 1: SiriusT3 platform used for pK_a and solubility analysis.

SiriusT3 is designed for compound screening and detailed PhysChem characterisation. It measures pK_a, logP/D and solubility of ionisable drugs and small molecules, requiring only small amounts of sample.

Table 1: pK_a of Dipyridamole, Piroxicam and Warfarin under aqueous conditions and their calculated stability constant in the presence of Cavasol (K_{11}=neutral, K_{12}=ionic species).

Compound	pK_a	K_{11}	K_{12}
Warfarin	4.97	356 M^{-1}	107 M^{-1}
Dipyridamole	6.19	60.3 M^{-1}	13.5 M^{-1}
Piroxicam	5.31	No binding	2.87 M^{-1}

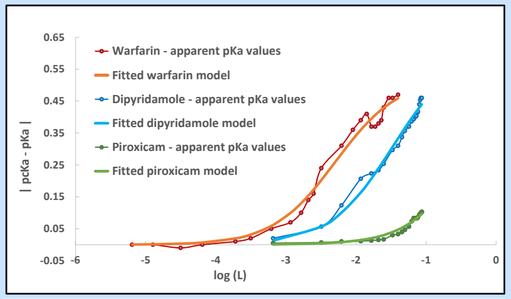

Fig. 2: Shift in pK_a with increasing Cavasol concentration for Dipyridamole, Piroxicam and Warfarin.

Table 2: Improvement of the Intrinsic solubility of the compounds studied in the presence of Cavasol and Captisol with the aqueous media.

Compound	Media	Intrinsic Solubility (µg/mL)	Δ
Warfarin	Aqueous	3.13	
	Cavasol	19.1	16
	Captisol	10.1	7.0
Dipyridamole	Aqueous	3.81	
	Cavasol	6.27	2.5
	Captisol	8.25	4.4
Piroxicam	Aqueous	7.38	
	Cavasol	7.90	0.5
	Captisol	10.3	2.9

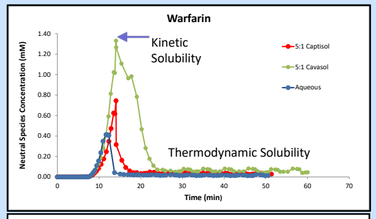

Fig. 3: Supersaturation of Warfarin in the absence and presence of cyclodextrins.

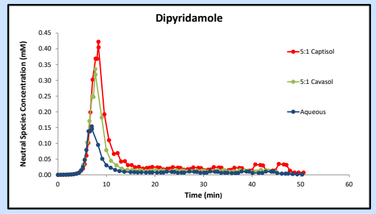

Fig. 4: Supersaturation of Dipyridamole in the absence and presence of cyclodextrins.

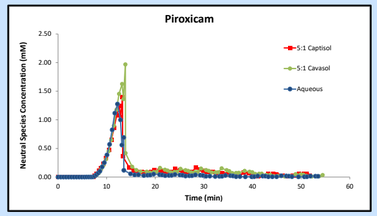

Fig. 5: Supersaturation of Piroxicam in the absence and presence of cyclodextrins.

CONCLUSION

Addition of cyclodextrins disturbs the equilibrium of ionisable compounds; the magnitude of the shift in the pK_as can be related to the binding constants of the drugs. In this study, we showed that the uncharged species bind more strongly for Warfarin and Dipyridamole, whereas the anionic species had the highest binding constant for Piroxicam. Moreover, we showed that cyclodextrins affect the intrinsic solubility of the compounds, and alter the extent and duration of supersaturation.

REFERENCES

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