

Econazole-Cyclodextrin Complexes: Of Solubility & Supercriticality

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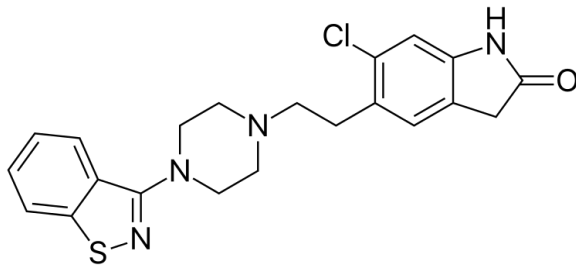
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The Prologue

Ziprasidone – antipsychotic.

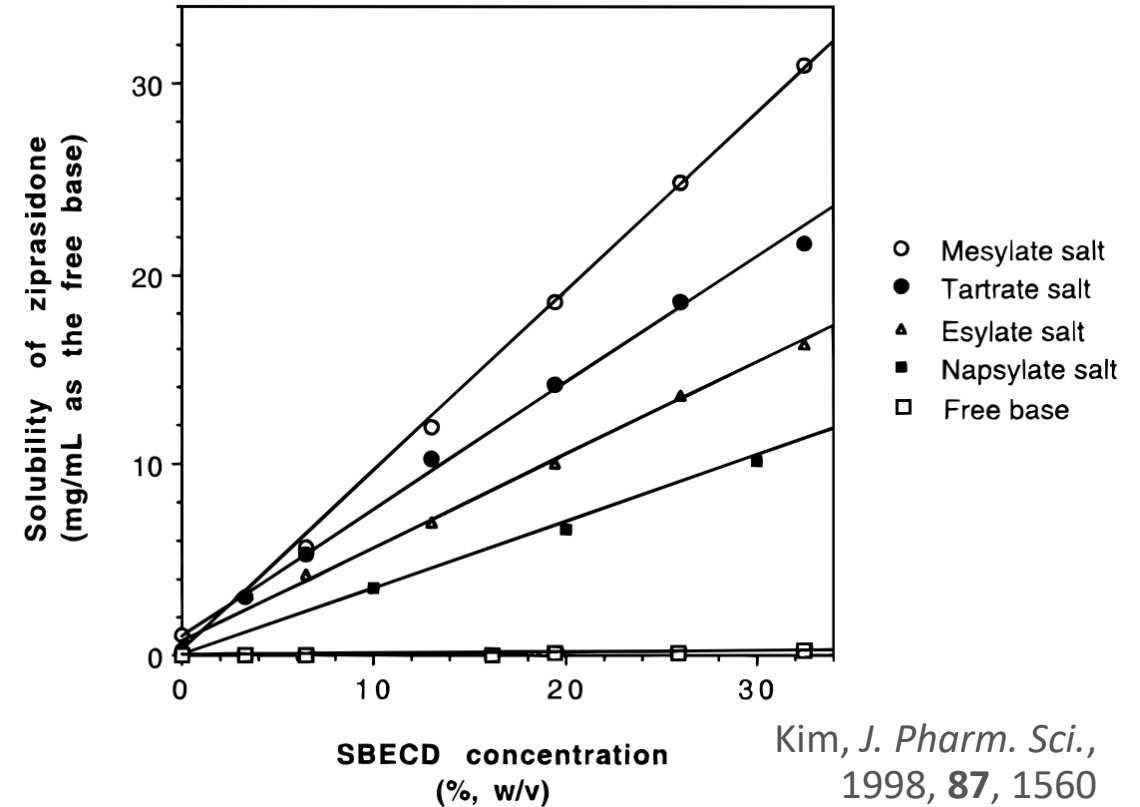
Oral = HCl salt, $210 \mu\text{g ml}^{-1}$



IM = mesylate salt, 0.89 mg ml^{-1}

sulfobutylether β -cyclodextrin,

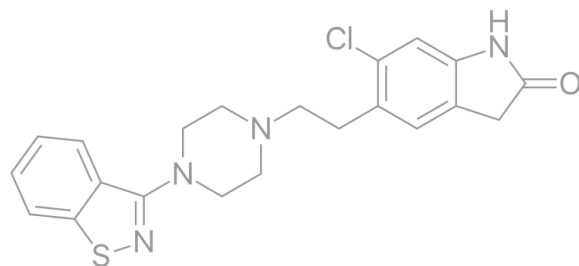
“the counterion is somehow involved in the complexation”



The Prologue

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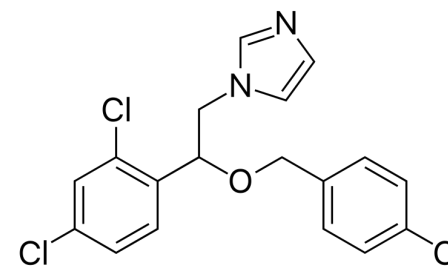


IM = mesylate salt, 0.89 mg ml^{-1}

sulfobutylether β -cyclodextrin,

Econazole – antifungal.

nitrate salt, 0.42 mg ml^{-1}

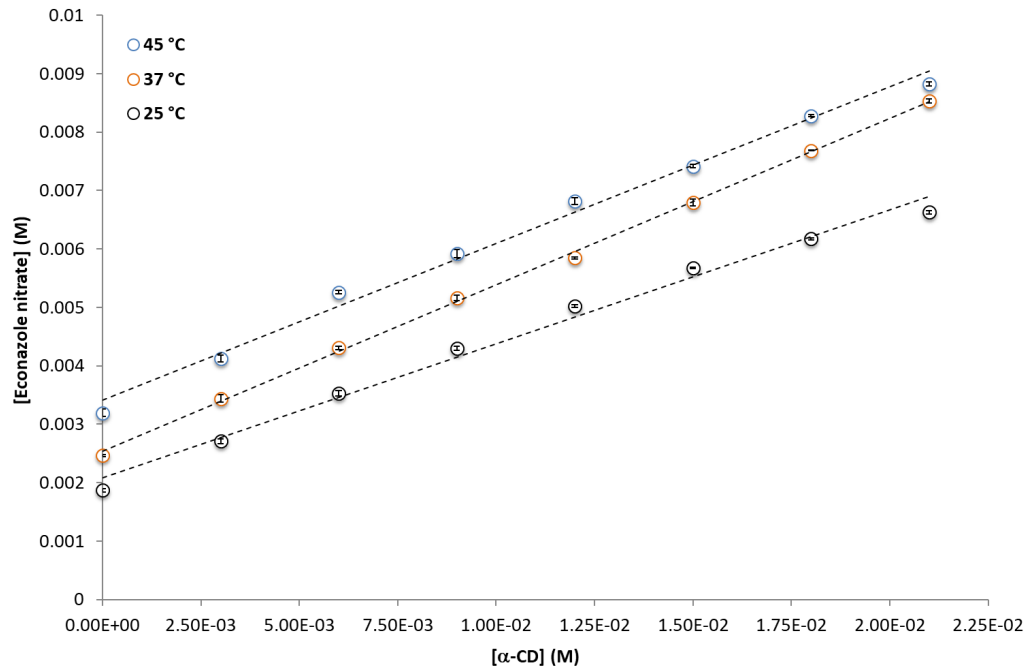


Other salt forms readily
accessible

“the counterion is somehow involved in the complexation”

Phase Solubility – α -Cyclodextrin

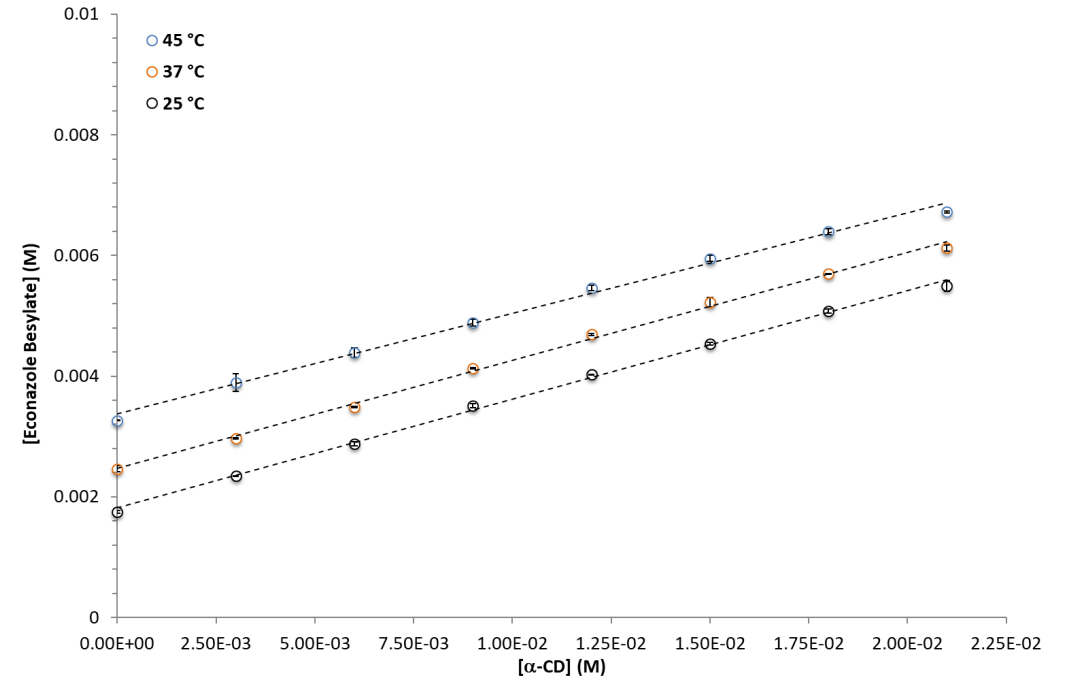
Econazole nitrate



$$K_{1:1} = 480.7 \text{ M}^{-1}$$

Again, counterion involved in complexation

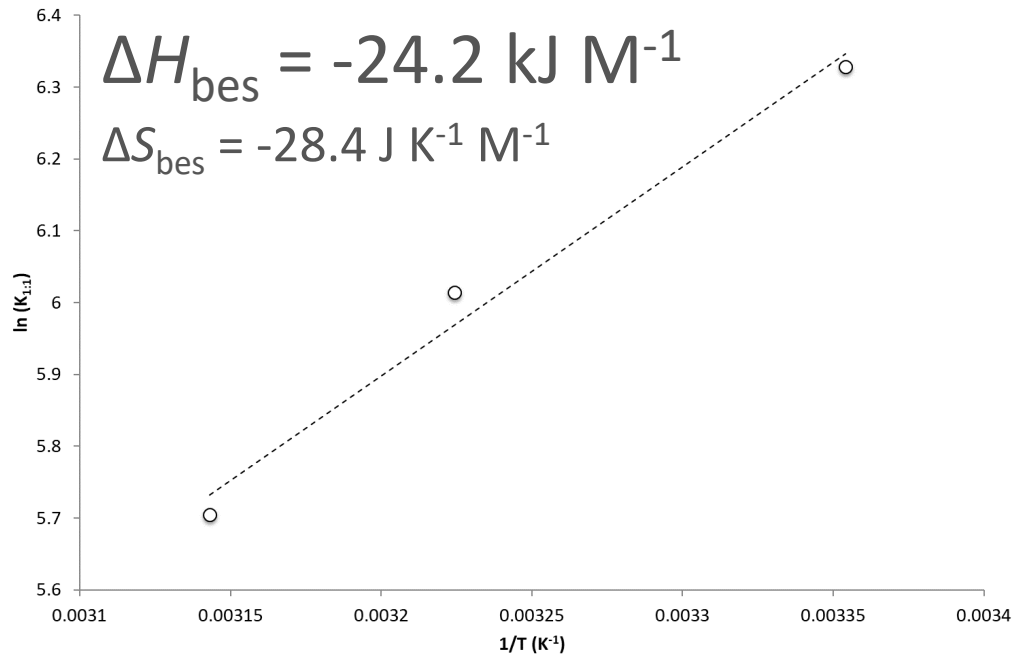
Econazole besylate



$$K_{1:1} = 560.3 \text{ M}^{-1}$$

Phase Solubility – α -Cyclodextrin

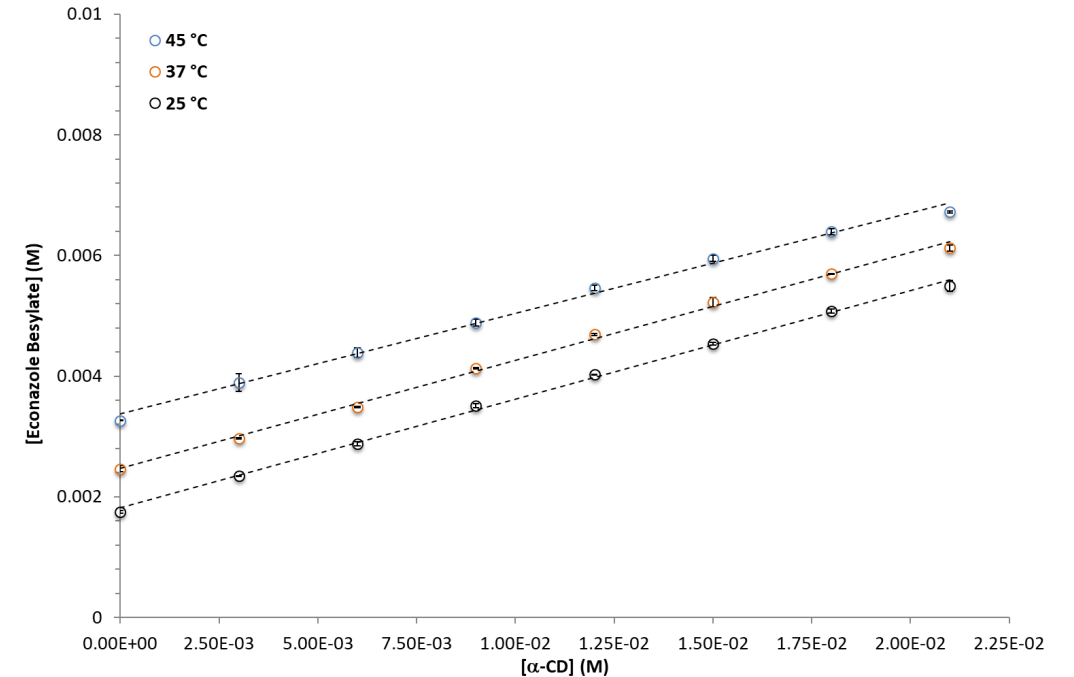
van't Hoff



$$\Delta H_{\text{NO}_3} = -18.9 \text{ kJ M}^{-1}$$

$$\Delta S_{\text{NO}_3} = -11.9 \text{ J K}^{-1} \text{ M}^{-1}$$

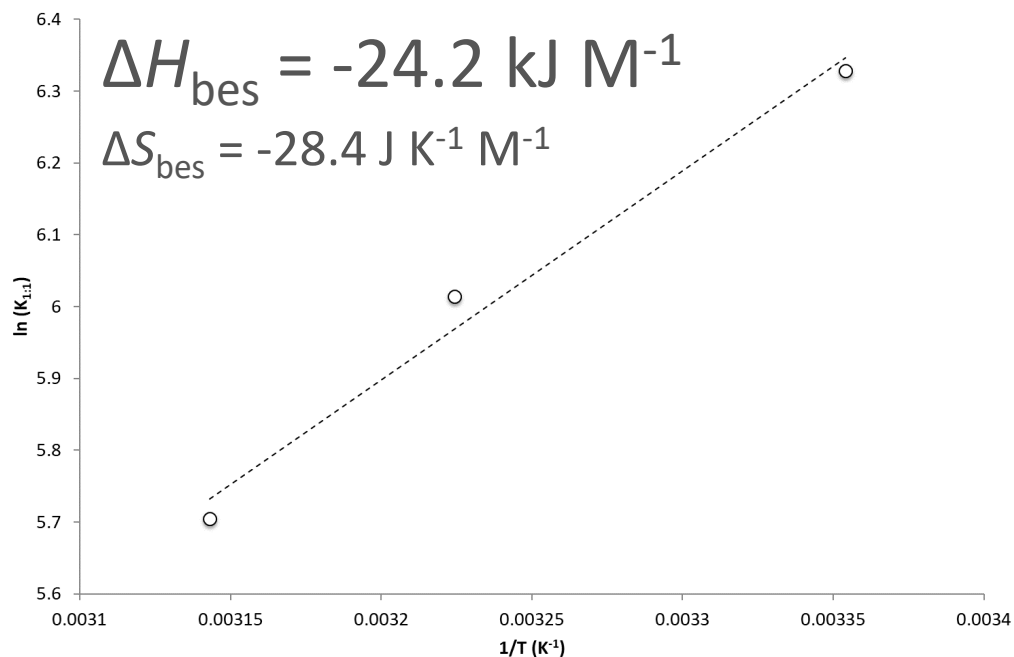
Econazole besylate



$$K_{1:1} = 560.3 \text{ M}^{-1}$$

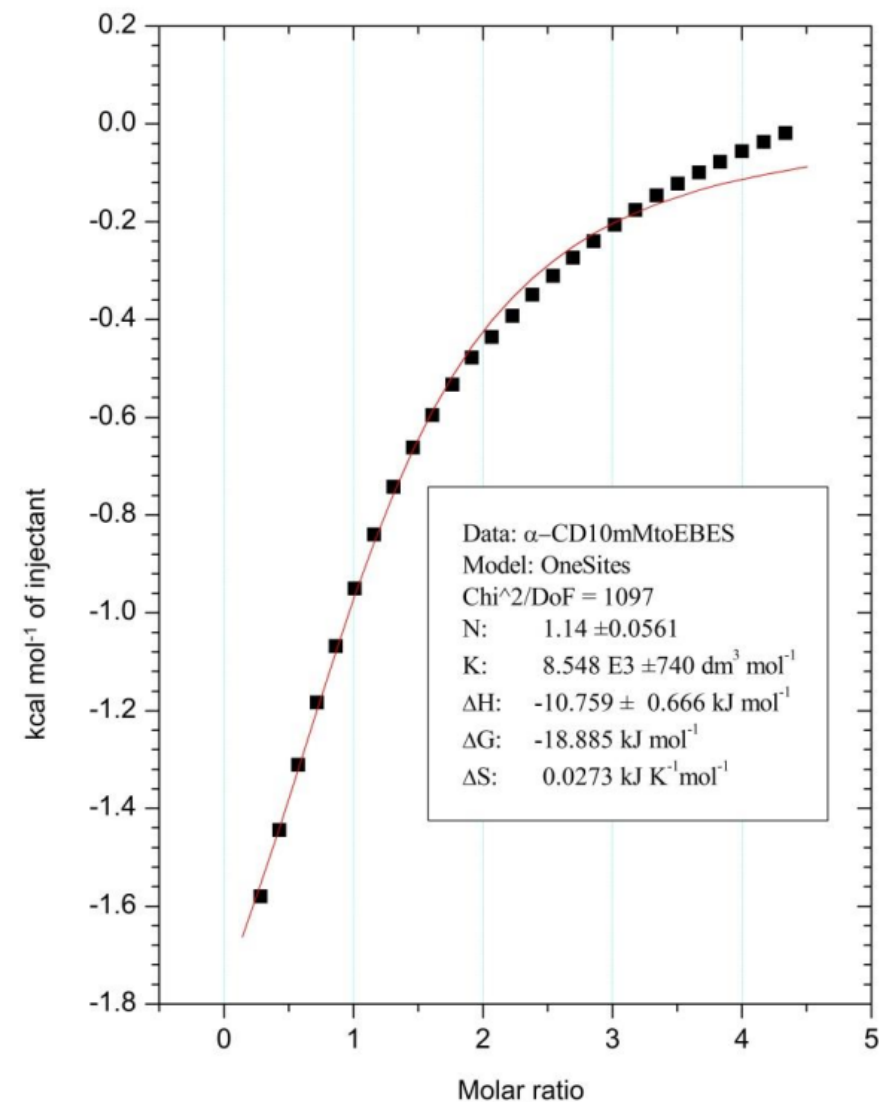
Phase Solubility – α -Cyclodextrin

van't Hoff



1:1 stoichiometry fits

$$\Delta H_{\text{ITC}} = -10.8 \pm 0.7 \text{ kJ M}^{-1}$$

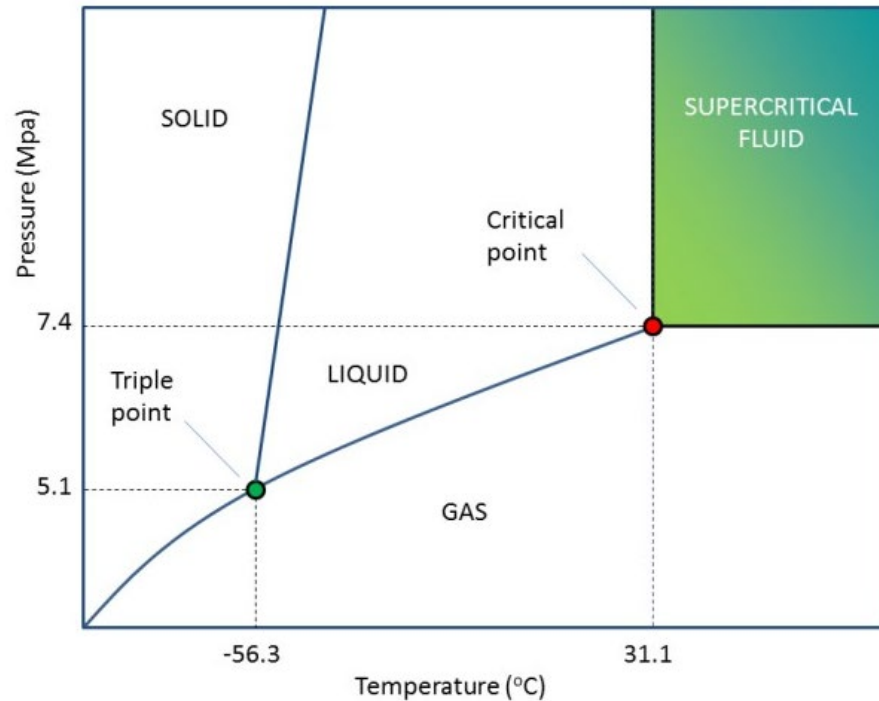


More Thermodynamics?

The four stages of reaction when you suggest doing some molecular dynamics

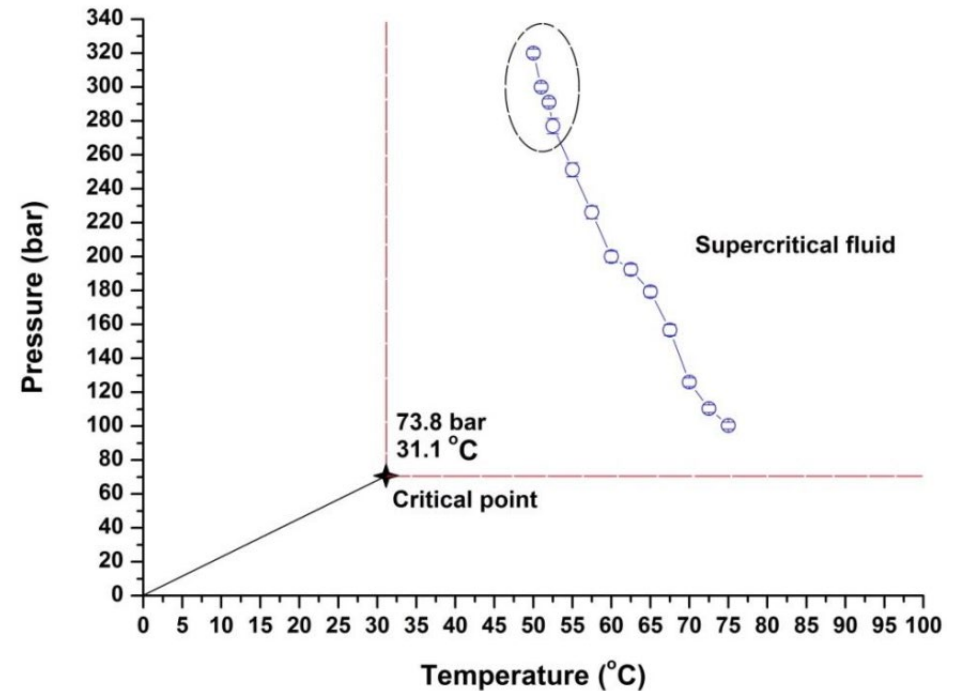


Supercritical CO₂ processing



Green solvent

Low temp & easy to remove

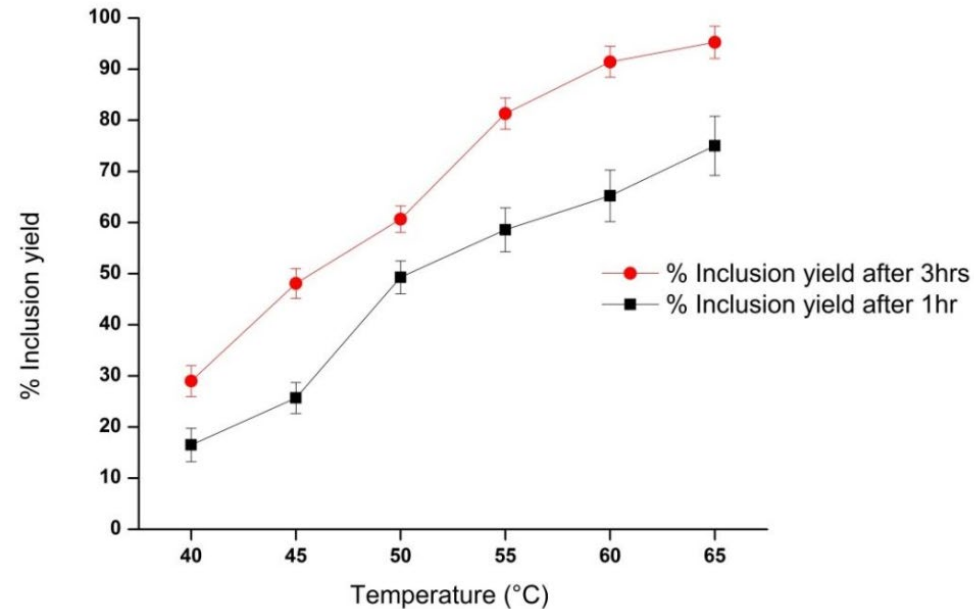


Econazole (base) $T_m = 92\text{ °C}$

T_m drops by 42 °C

So what else is new...?

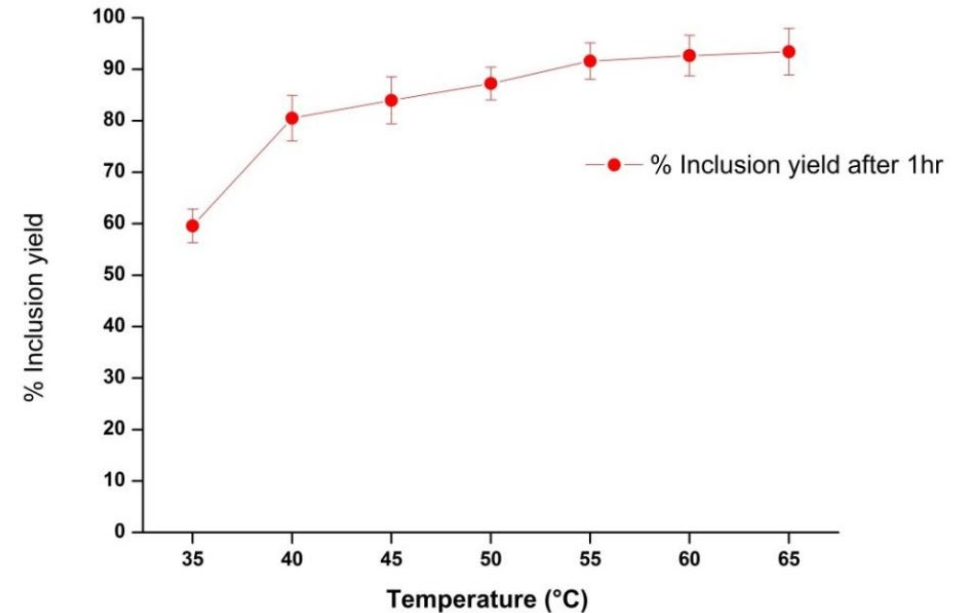
Econazole (base)- α -CD



Time improves yield

Increased P also helps

Econazole (base)-Me- β -CD

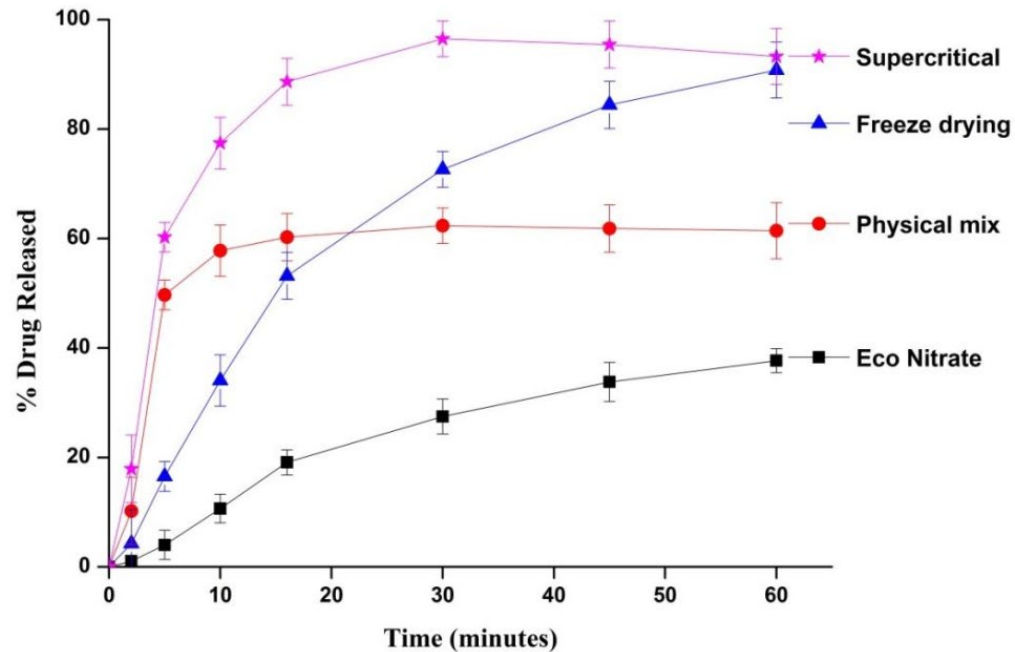


$P = 150$ bar

Me- β -CD melts ≈ 42 °C

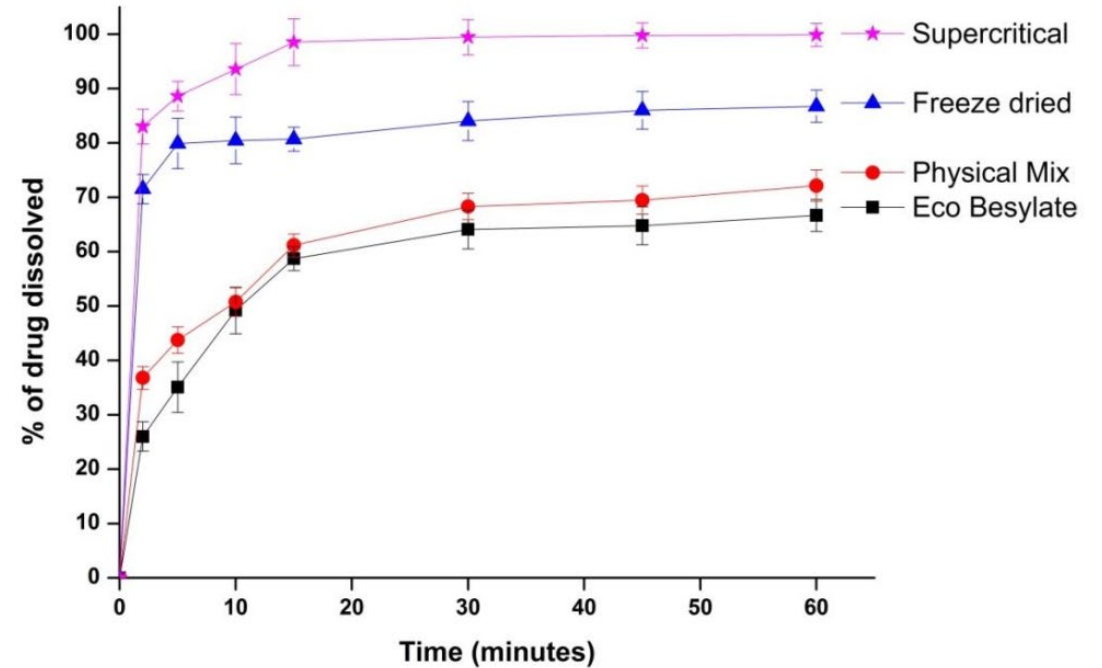
Other Implications

Effect of processing



Significantly amorphous

Econazole besylate- α -CD



Faster disso.

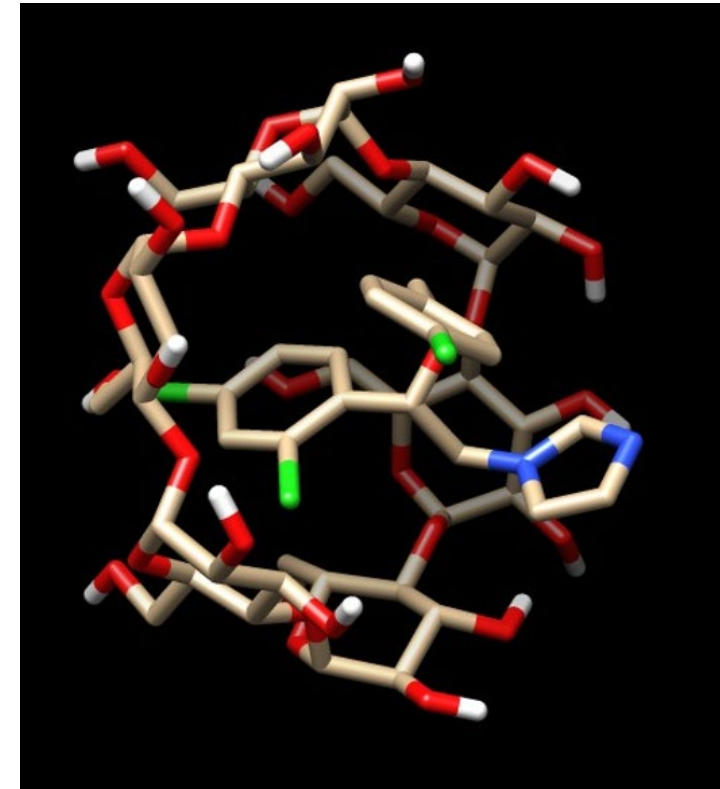
Conclusions

Salts

- Counter-ion involved in complexation
- Thermodynamics suggests 1:1 complex
- Complexation exothermic
- What is the role of the salt?

Supercritical CO₂

- Increase T & P to increase inclusion yield
- Choice of CD helps (melting)
- Induces amorphous content
- Faster dissolution



Acknowledgements

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**Medway Centre for Pharmaceutical
Science**

What are you doing now? mentimeter

Kim, *J. Pharm. Sci.*,
1998, **87**, 1560

