Surfactant-polymer complexation & competition on drug crystal surfaces controls crystallinity

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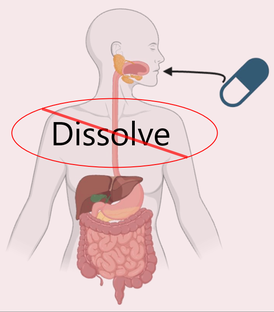
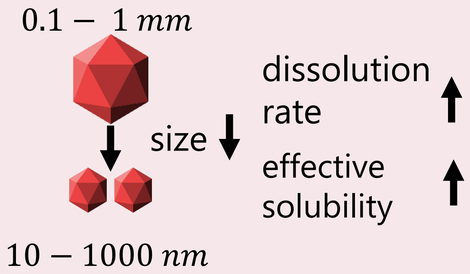
DOYLE GROUP SOFT MATTER ENGINEERING

1 Processing changes drug nanocrystal structure

Problem: 90 % of candidates are hydrophobic

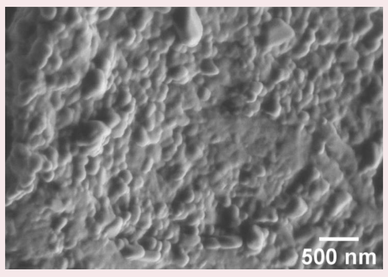


Solution: nano-size drug crystals

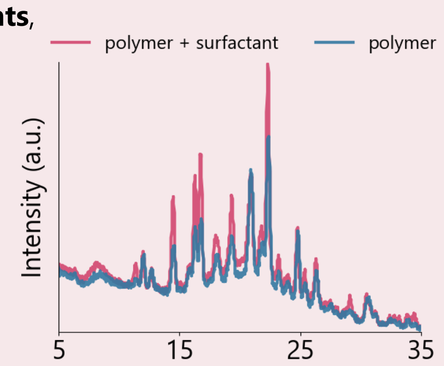


Nano-sizing drug crystals improves the low oral bioavailability of hydrophobic small molecule drugs

Nanocrystal are processed with **excipients**, particularly **polymers** and **surfactants**



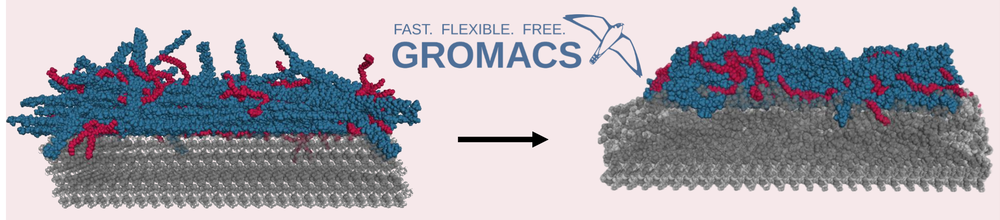
Drug nanocrystals dispersed throughout solid polymer matrix



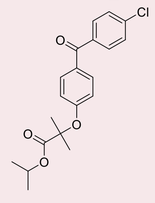
Crystalline signal increases when drug is processed with surfactant

Goal: understand how processing drug nanocrystals with polymers and surfactants controls crystal structure

2 We simulate nanocrystal surfaces using MD

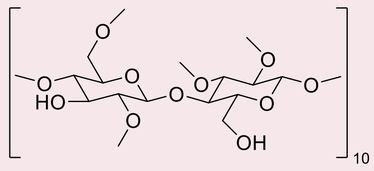


Drug



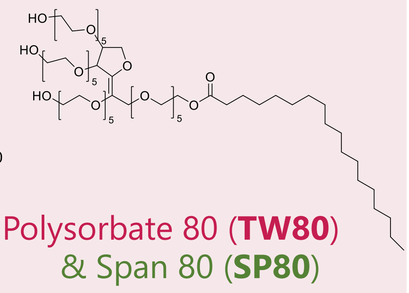
Fenofibrate (**FEN**)

Polymer



Methylcellulose (**MC**)

Surfactant



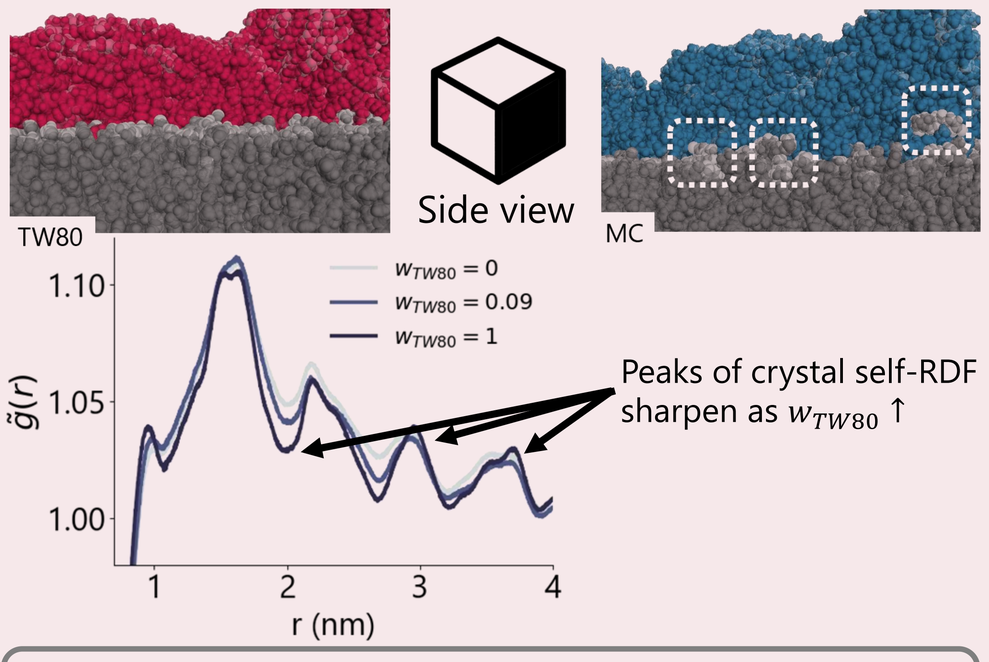
Polysorbate 80 (**TW80**) & Span 80 (**SP80**)

Match **surfactant**:**polymer** ratio in simulation to realistic experimental conditions

$$w_{TW80} = \frac{m_{TW80}}{m_{TW80} + m_{MC}}$$

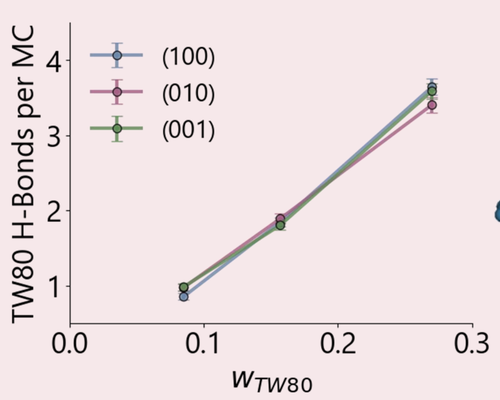
We simulate self-assembly of polymers and surfactants on nanocrystal surfaces using realistic compositions

3 Excipients modify drug surface structure

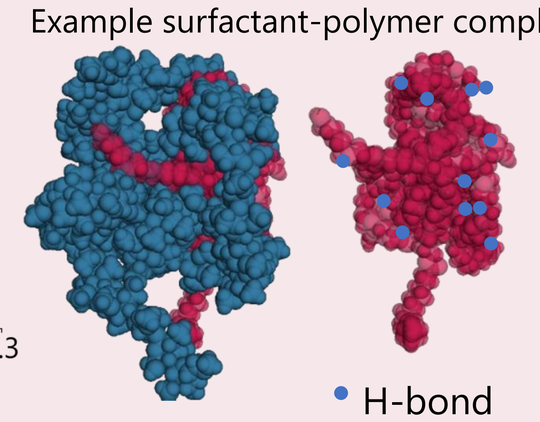


Surfactant preserves structure, while polymer **destructures** crystal

4 Polymer and surfactant complex and compete on nanocrystal surface



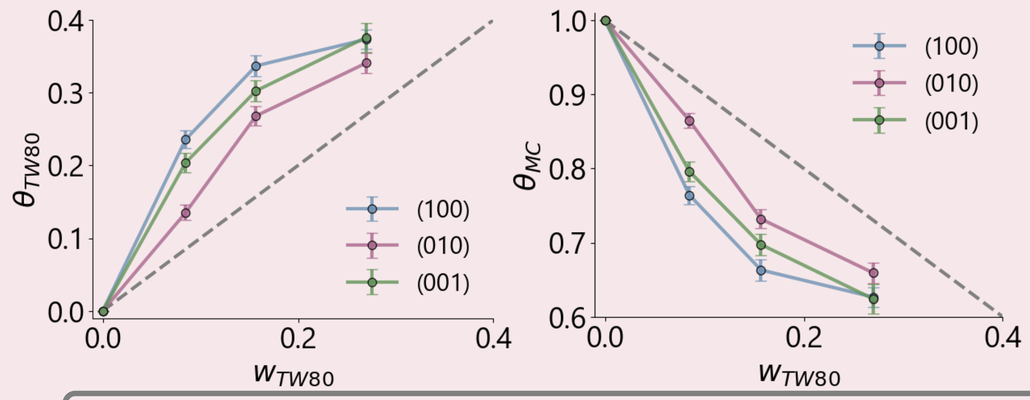
Example surfactant-polymer complex



Surfactant-polymer complexation delocalizes polymer from surface

Relative surface coverage (θ_{MC} & θ_{TW80})

$$\theta_{MC} = \frac{\langle H_{MC} \rangle}{\langle H_{MC} \rangle + \langle H_{TW80} \rangle} \qquad \theta_{TW80} = \frac{\langle H_{TW80} \rangle}{\langle H_{MC} \rangle + \langle H_{TW80} \rangle}$$

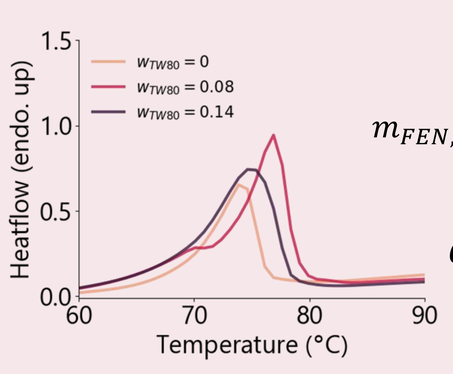


$\langle H_{MC} \rangle$ = time-averaged polymer-drug H-bonds

$\langle H_{TW80} \rangle$ = time-averaged surfactant-drug H-bonds

Surfactant chemisorption screens polymer-drug interactions

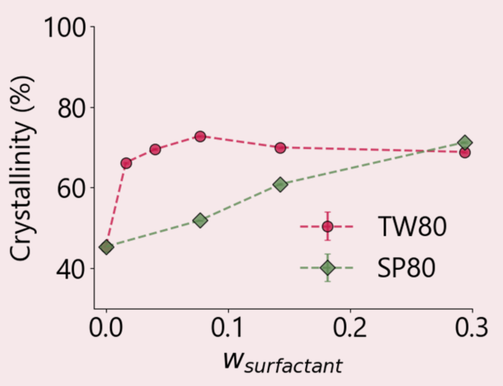
5 Crystallinity varies with surfactant fraction



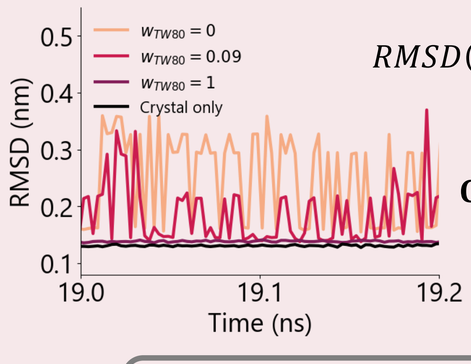
Experiment

$$m_{FEN,crystalline} = \int_{-\infty}^{\infty} \frac{\dot{H}\, m_{sample}}{\dot{T}\, \Delta H_{fusion}}\, dT_{mp}$$

$$\textbf{Crystallinity} = \frac{m_{FEN,\text{crystalline}}}{m_{FEN}}$$

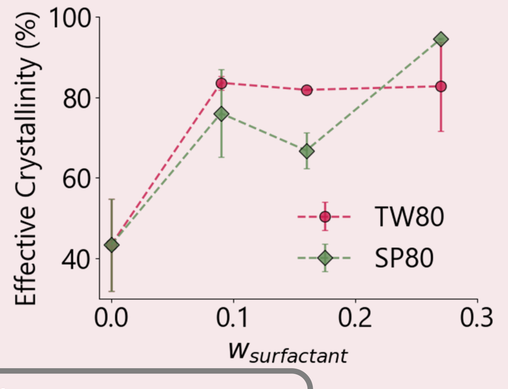


Simulation



$$RMSD(t) = \left[\frac{1}{N}\sum_{i=1}^{N} \left|\left| r_i(t) - r_i^{ref}(0) \right|\right|^2\right]^{\frac{1}{2}}$$

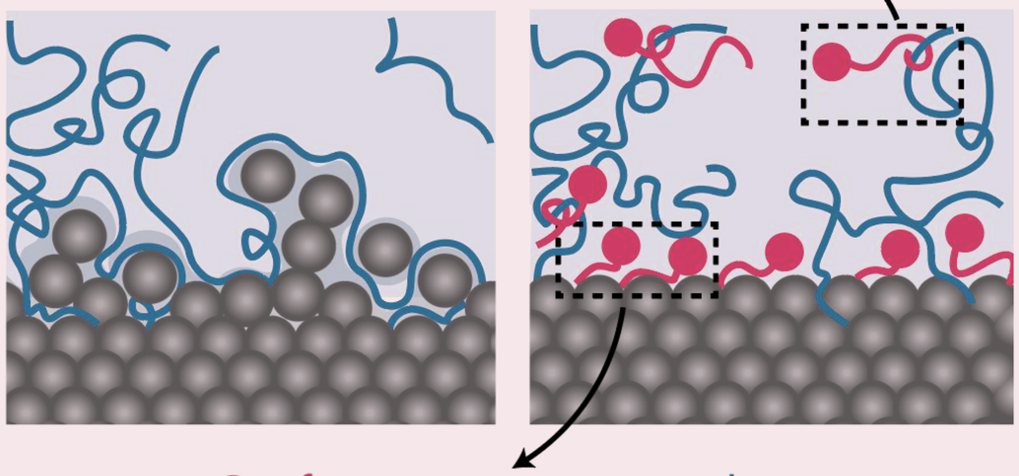
$$\textbf{Crystallinity} = \frac{\frac{a}{2} - \langle RMSD(t) \rangle}{\frac{a}{2} - \langle RMSD_0(t) \rangle}$$



Crystallinity increases with surfactant fraction, then saturates.
Crystallinity predictions from simulations agree with experiments.

Summary

Surfactant complexes polymer above drug surface



Surfactant screens polymer from drug surface

Attia, et al. *ACS Appl. Mater. Interfaces* (in review)

Acknowledgements

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