Poster #: W4018

A Novel *In Silico* Screening Protocol For The Selection Of Optimized Precipitation Inhibitor Systems For Supersaturable Formulations

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PURPOSE

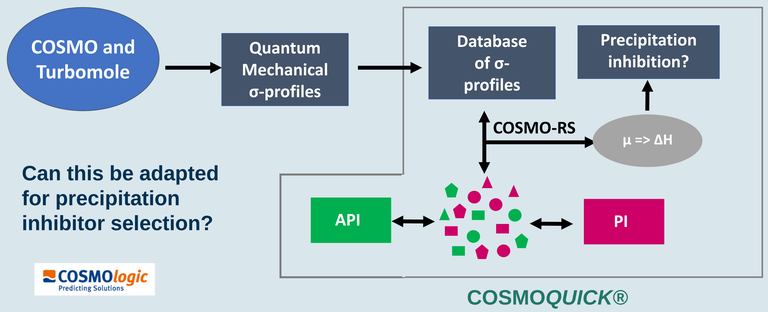
- Supersaturable formulations represent a viable option for improving bioavailability of poorly soluble active pharmaceutical ingredients (APIs).
- Given the metastable nature of the supersaturated state, precipitation inhibitors (PIs) are required to sustain API in solution for physiologically relevant time scales.
- PI selection is currently very 'trial-and-error' based
- This study aimed to develop a novel *in silico* screening protocol for precipitation inhibitor systems, allowing for a more scientific and efficient selection process

METHODS

- Glibenclamide Loaded Silica (GBLSi), prepared using the solvent impregnation method, was used as a model supersaturable formulation.
- Screening for theoretical enthalpy of interaction between glibenclamide and 52 precipitation inhibitors was carried out using the COSMO*quick*® software[1]
- The enthalpy 'rank-order' was used as a parameter for the selection of a range of precipitation inhibitors, which were then physically blended with the formulation (API : PI, 1 : 3)
- A small-scale single-medium FaSSIF (pH 6.5) dissolution and biorelevant transfer dissolution (SGF, pH 2.0→FaSSIF, pH 6.5) was performed on formulations at 37°C to assess the correlation between the COSMO*quick*® prediction and the actual dissolution performance. Precipitation residues from dissolution experiments were subjected to PXRD for solid-state characterization.
- Physical mixtures of glibenclamide with selected polymers were analyzed for their dissolution characteristics to rule out any innate solubility enhancement effects only by the polymer.

COSMO*QUICK*®: HOW DOES IT WORK?

COSMO*quick*® is used for co-crystal screening, utilising the excess enthalpy of a mixture of API and co-former as a selection parameter[1]



RESULTS AND DISCUSSIONS

COSMOQUICK® SCREEN

- Eduragit E100 (EU) was predicted to have the most significant enthalpy of interaction **(Figure 1).**
- The polymers: HPMCAS, HPMC and PVP, commonly used in the trial and error approach, were predicted to interact less strongly.
- EU, Pluronic (PLR), PEG, HPMCAS, PVP and HPMC were selected for the formulations.

SINGLE-MEDIUM FASSIF DISSOLUTION

- GBLSi generated significant supersaturation (*ca.* 15-fold), after which precipitation and re-crystallization occurred rapidly **(Figures 2 and 3).**
- EU, PLR and HPMCAS act as successful 'parachutes' with varying degrees of success **(Figures 2 and 3).**
- The AUCs of the curves correlated well with the rank-order predicted by COSMO*quick*® except for PEG **(Table 1)**. The PI effect of PEG is likely to be dependent on bound water which is not considered in COSMOquick® predictions.
- The most effective PI system, EU, showed no crystallinity in the post-dissolution residues, compared to the other formulation residues, which showed some partial-crystallinity (**Figure 4).**
- Furthermore, the EU formulation resulted in a 20-fold sustained supersaturation in a biorelevant transfer model (***not shown)*** compared to only a 2-fold effect for HPMCAS.
- Physical mixtures of API and polymers showed no enhanced dissolution ***(not shown)-*** supporting the PI mechanism, as opposed to solubility enhancement.

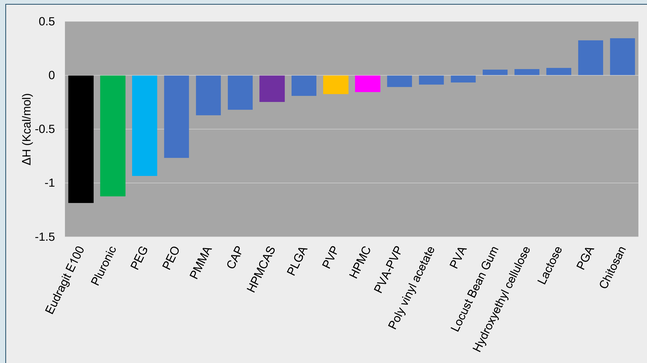


Figure 1. Theoretical enthalpy of association for glibenclamide with a database on commercially available polymers (not all shown). Polymers selected for formulation testing: EU (black), PLR (green), PEG (light blue), HPMCAS (purple), PVP (yellow) and HPMC (pink)

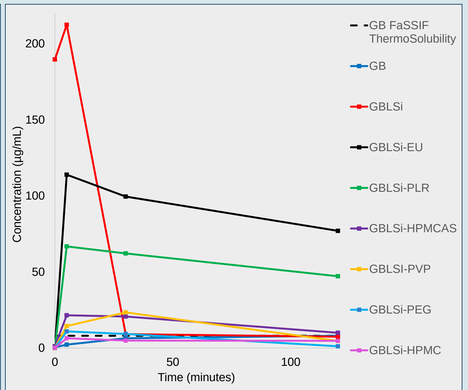


Figure 2. *Dissolution Profiles of glibenclamide and its loaded-silica formulations in FaSSIF, pH 6.5 at 37°C, n=2*

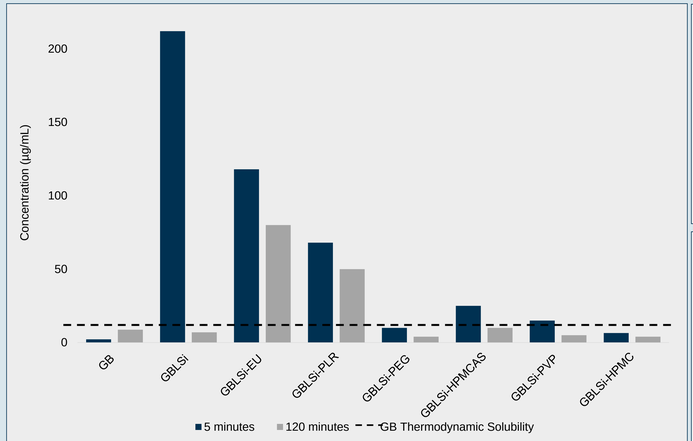


Figure 3. The effect of mesoporous silica and precipitation inhibitors on the 'spring' (5 minutes) and 'parachute' (120 minutes) effect for a range of glibenclamide formulations during dissolution in FaSSIF (pH 6.5) *at 37°C, n=2*

Table. 1. Predicted Rank Order vs. Actual Rank Order

Polymer	Predicted Rank Order	AUC	Actual Rank Order
Eudragit E100	1	10611	1
Pluronic	2	6697	2
PEG	3	745	5
HPMCAS	4	1910	3
PVP	5	1769	4
HPMC	6	573	6

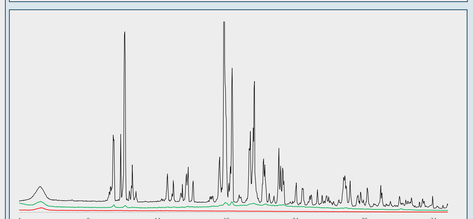


Figure 4. PXRD Patterns of Glibenclamide (black), GBLSi-Eu (red) and GBLSi-HPMCAS (green) in dissolution residues

CONCLUSIONS

- ✓ Developed an novel PI screening protocol utilising the *in silico* software COSMOquick®
- ✓ The PIs selected for the model formulations, based on the *in silico* predictions, showed good correlation with their actual dissolution performance, with the predicted PIs significantly outperforming those commonly used in trial-and-error PI selection
- ✓ The developed protocol has applicability to alternative supersaturable formulations

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References

1) Abramov, YA. *et al.* Rational Co-former or Solvent Selection for Pharmaceutical Co-crystallization or Desolvation. *Journal of Pharmaceutical Sciences.* 2012; **101**(10): 3687-3697

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