Compatibility Screening of Drug-Polymer Blends Using Computational Modelling

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Abstract Summary

- Many drugs present solubility challenges which adversely affect bioavailability
- Drug-polymer solid dispersions can improve solubility by maintaining the drug in an amorphous state
- This study investigated computational modelling for use in pre-formulation studies of drug-PVP solid dispersions
- Computational modelling was able to provide insight to temperature dependence of miscibility and to calculate key mixing parameters

Introduction

Compatibility screening is an essential aspect of pre-formulation study [1]. **Miscibility is a key parameter defining physical stability [2].** This work sought to demonstrate how computational modelling may be used in pre-formulation studies to predict drug-polymer miscibility in solid dispersions. This could serve as a preliminary indicator of stability. Interactions in various binary mixtures were studied, with **PVP used as the model polymer screened against poorly water soluble model drugs**. Findings illustrate the merits and limitations of the method in determining miscibility and physicochemical properties, compared to experimental data and established techniques.

Materials and Methods

Software

- Materials Studio (BIOVIA) [3]
- Blends module used for calculations and analysis
- Geometry optimisation in Forcite module
- **COMPASS II force field applied to operations**
- Ultra-fine calculation quality used (10,000,000 energy samples and 100,000 cluster samples with energy bin width of 0.02 kcal/mol)

Structures Studied

- **PVP screened against ibuprofen, carbamazepine and itraconazole**
- Monomer unit and drug structures drawn in Materials Studio before geometry optimisation
- **Degree of polymerisation set to 22 to mimic K-12 PVP**
- Head and tail atoms of PVP monomer unit set as non-contact to simulate full polymer chain

Outputs

- Binding energy distribution
- χ parameter
- Mixing energy
- Free energy of mixing
- Phase diagrams of drug binary mixtures with K-12 PVP

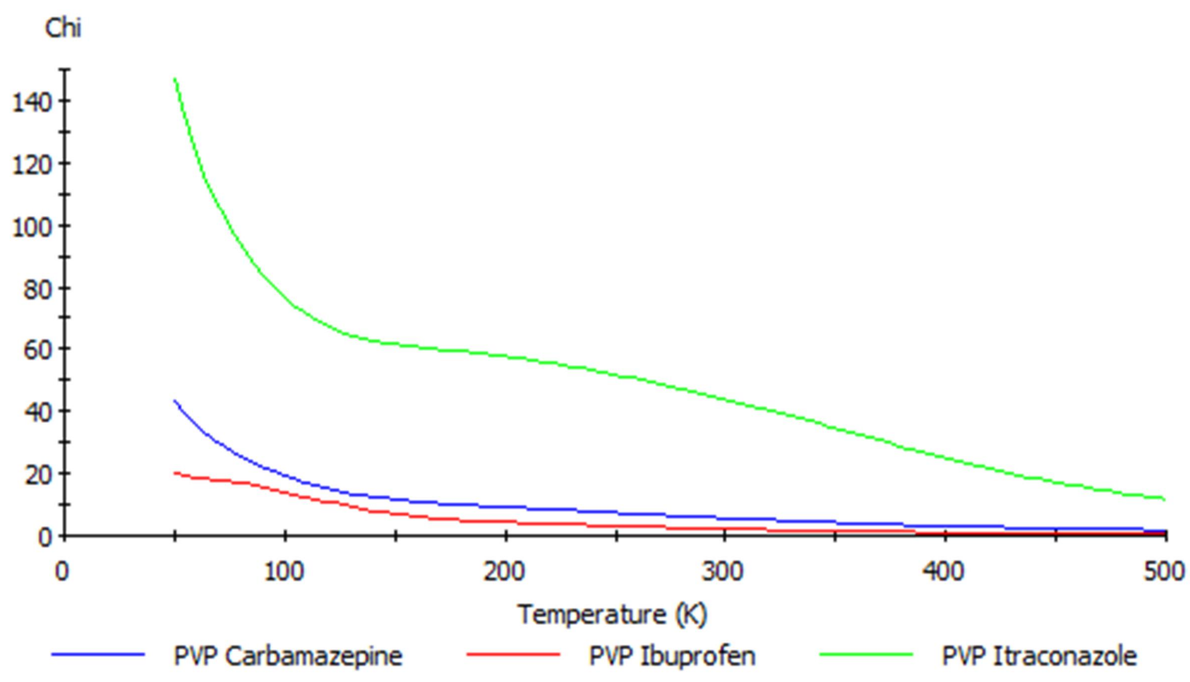
Results and Discussion

Computational modelling showed the model blends would not be stable. **This contradicts experimental findings**. Results may be predictive of long term physical instability. The rate of demixing was not provided, however the **magnitude of the χ parameter may indicate the probability of demixing and crystallisation at a given temperature (Figure 1).** The Blends module was unable to take moisture content into account, or the time-dependence of miscibility.

Ability to vary chain length is a distinct advantage of the software, allowing for study of a very broad range of polymer grades. Information on binary mixtures is provided in a fraction of the time taken to obtain experimental data.

Computational modelling may save time and resources, but **inaccurate results may mislead** when characterising potential formulations. **Results of this study did not correlate well with experimental data.** Computational modelling can be a useful complementary technique when used alongside, rather than in place of, more established techniques such as DSC, optical microscopy, and X-ray diffraction.

Figure 1 – Temperature dependence of χ parameter



Conclusion

Pros:

- ✓ May save time and resources
- ✓ Ability to vary chain length
- ✓ Results may indicate probability of demixing and crystallisation
- ✓ Provides insight to temperature dependence of miscibility
- ✓ Calculates key mixing parameters
- ✓ Merit as a screening tool when used alongside established characterisation techniques

Cons:

- × Rate of mixing could not be established
- × Predictive power for crystallinity is unclear
- × Unable to take moisture content into account
- × Unable to take time-dependence of miscibility into account
- × Not a reliable alternative to experimental study

Next Steps

- This research makes a contribution to the evaluation of potential approaches for studying dug and polymer chemistry
- Future work could investigate the influence of force field selection on the results
- COMPASS II was used in this study, but Materials Studio also offers Dreiding and Universal force fields
- A greater range of drugs could be studied, with differing physicochemical properties

References

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