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Ibuprofen Degree of Polymerization and Phase Behaviour of Ibuprofen-Nicotinamide Mixtures

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Abstract

Recently we showed that the ibuprofen dimer formation can cause the incomplete cocrystalization of ibuprofen and nicotinamide in course of hot melt extrusion process. Here, we extend our analysis to investigate the effect of ibuprofen degree of polymerization on ibuprofen and nicotinamide phase behaviour. We used extended Flory–Huggins model combined with molecular dynamics employing a refined version of consistent valence forcefield developed from ab initio energy surfaces. Results suggest that increasing the ibuprofen degree of polymerization systematically: (1) decreases the lower and upper critical mixture temperatures and (2) moves the critical point of mixture toward higher fraction of nicotinamide, $x_{NCTA} \rightarrow\approx 0.83$. High fraction of nicotinamide is not desirable as it is added as coformer and not the active pharmaceutical ingredient (ibuprofen). Therefore, the ibuprofen polymerization should be avoided, and to do so, it is needed to keep the operating temperature of mixture well below the ibuprofen melting temperature i.e. 353.15K.

Data availability: The associated data of this paper can be found under Downloads page at: https://sites.google.com/view/makhansary, using tag ID = CoCryM.dPly.

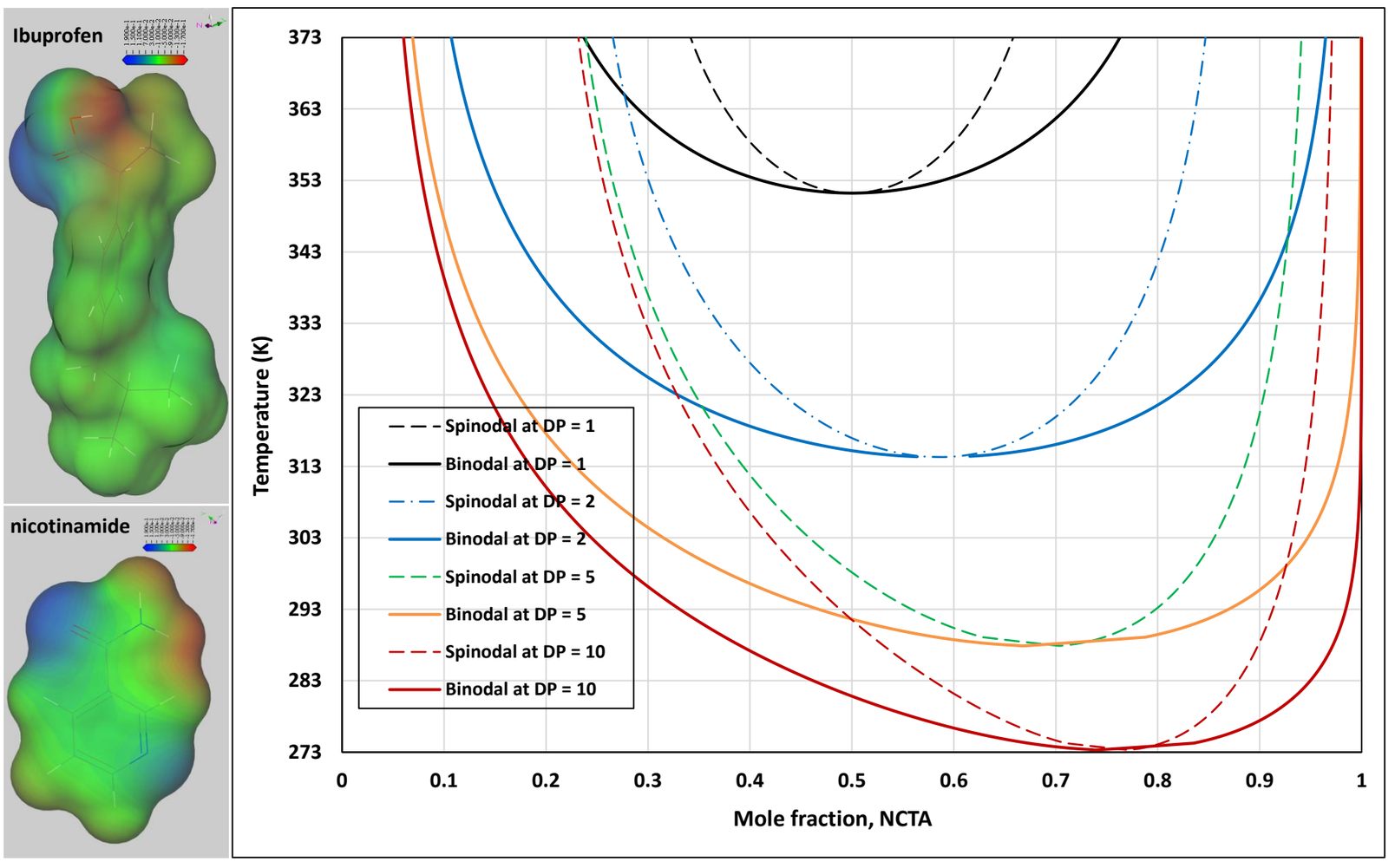
Concluding remarks

In case of no ibuprofen polymerization, the mixture has a lower critical solution temperature of around 350 K and an upper critical solution temperature of ≈ 215 K. Once allowing ibuprofen polymerization, both lower critical solution temperature and upper critical solution temperature drop systematically. For temperatures between lower critical solution temperature and upper critical solution temperature, the mixture remains unchanged and shows no tendency in changing its thermodynamic behaviour in absence of external fluctuations/excitations. Also, the plate point, i.e., critical point where binodal and spinodal boundaries meet, systematically moves toward higher nicotinamide concentrations as the degree of ibuprofen polymerization increases.

Methods

The molecular structure of ibuprofen and nicotinamide were retrieved from National Institute of Standards and Technology Reference Database Number 69 (https://webbook.nist.gov/chemistry). The molecules were optimized using the DMol^3 density functional theory package. We employed the Generalized Gradient Approximations with Perdew-Becke-Ernzerhof functional including implicit solvent as described by COnductor-like Screening MOdel. To control the convergence behaviour for enhanced self-consistent field calculations, thermal smearing was also applied including double numerical basis including d-polarization function level of theory. The convergence tolerances are energy: 2.0×10^{-5} kcal/mol, force: 10^{-3} kcal/mol/Å, max iterations: 10^4, displacement: 10^{-5} Å. The thermodynamic properties were extracted following Hirano's formulation.

Presenting phase diagram in terms of temperature-composition is of great interest of formulation scientists as it may provide estimation of stability. It can be easily understood from such phase diagrams if the mixture is stable or may experience phase separation due to composition or temperature variations. From temperature-composition phase diagrams, the mixtures could be expected to be thermodynamically stable above the binodal curve where mixtures form one phase. In region surrounded by binodal and spinodal boundaries, the compounds are partially miscible and mixtures are metastable and two phases of polymer-rich and drug-rich coexist. The boundary between stable and metastable regions is known as binodal curve, which represents the local thermodynamic equilibrium. Below the equilibrium composition of the two components i.e., within binodal boundary, the free energy of mixing is less than zero and phase separation is thermodynamically not favourable. The boundary between metastable and unstable regions is known as the spinodal boundary. Increasing mixture temperature to cross binodal, mixture either enter directly into unstable region though lower critical solution temperature point or it enters the metastable region i.e., the region between binodal and spinodal curves. In metastable region, the second derivative of free energy is positive the mixture tends to remain unchanged and resists against small composition fluctuations. In this case, a phase separation cannot be expected unless some nucleus for nucleation appears.



Notes

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