**IBUPROFEN DEGREE OF POLYMERIZATION AND PHASE BEHAVIOUR OF IBUPROFEN-** **NICOTINAMIDE MIXTURES**

Milad Asgarpour Khansary,1 Gavin Walker,2 Saeed Shirazian,3

1Confirm Smart Manufacturing, University of Limerick, Limerick, Ireland

2Synthesis & Solid-State Pharmaceutical Centre, University of Limerick, Limerick, Ireland

3Department of Chemical Sciences, University of Limerick, Limerick, Ireland

Key Words: *cocrystalization; thermodynamics; pharmaceuticals; ibuprofen; nicotinamide*

Recently we showed that the ibuprofen dimer formation can cause the incomplete cocrystalization of ibuprofen and nicotinamide [[1](#_ENREF_1)] 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 [[2](#_ENREF_2)] combined with molecular dynamics [[3](#_ENREF_3)] employing a refined version of consistent valence forcefield [[4](#_ENREF_4)] developed from ab initio energy surfaces [[5](#_ENREF_5)]. Results (Fig. 1) 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, *xNCTA*→≈ 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.

Fig. 1. Phase diagram of ibuprofen and nicotinamide mixtures at various ibuprofen degree of polymerizations (DP)

Data available at <https://sites.google.com/view/makhansary/> under *Downloads* using tag = *CoCryM.dPoly* and *CoCryM.dimerRcor*.

[1] M.A. Khansary, G. Walker, S. Shirazian, International Journal of Pharmaceutics (2020) 119992.

[2] M.A. Khansary, M.A. Aroon, S. Shirazian, Environmental Chemistry Letters 18 (2020) 1423-1431.

[3] R.D. Groot, T.J. Madden, The Journal of Chemical Physics 108 (1998) 8713-8724.

[4] H. Heinz, T.-J. Lin, R. Kishore Mishra, F.S. Emami, Langmuir 29 (2013) 1754-1765.

[5] J.R. Maple, U. Dinur, A.T. Hagler, Proceedings of the National Academy of Sciences 85 (1988) 5350.