Macedonian pharmaceutical bulletin, 69 (Suppl 1) 59 - 60 (2023)
Online ISSN 1857 - 8969
DOI: 10.33320/maced.pharm.bull.2023.69.03.029
Short communication

Drug-Polymer Miscibility and Interaction Study as a Preliminary Step in Amorphous Solid Dispersion Development: Comparison of Theoretical and Experimental Data

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Introduction

One of the most common techniques to enhance the bioavailability of poorly water-soluble drugs is the use of amorphous solid dispersions (ASDs) by means of hot melt extrusion (HME). However, the challenge is optimal selection of polymer excipient. Several approaches to selecting the polymer for ASD formulation are described, but few are useful for screening of HME systems (Forster et al., 2001). Therefore, our work aimed to select polymers for ASD formulations of three poor-water soluble APIs through the calculation of Hansen solubility parameters (HSP), to study experimentally drug-polymer miscibility and interactions, and to check the applicability of the theoretical data by comparison to experimental results.

Materials and methods

Flutamide (FLT), naproxen (NPX), and probenecid (PRC) supplied by Kemprotec Limited (UK) were used as model APIs. Based on the calculation of HSP (HSPiP software, 5th edition) three functional polymers were selected – Eudragit EPO (EPO), Kollidon VA64 (VA64), and Soluplus (SOL). Experimental drug-polymer miscibility was determined by measuring melting enthalpy (ΔHm) of preliminary milled drug-polymer physical mixtures (PMs) at 90, 80, 70, and 60 % w/w drug concentrations and linearly extrapolating 'API concentration vs ΔHm' plot to zero enthalpy (i.e., zero-enthalpy extrapolation (Z-EE) method). DSC was performed with TA Q20, 10 °/min heating rate from 20 °C up to 20 ° above the API endset melting point, and nitrogen as a purge gas. Drug-polymer interactions in solid dispersions (SDs) obtained in DSC cell were studied by FT-IR (Perkin Elmer Spectrum 100 FT-IR Spectrometer) using KBr disks. All experimental determinations were performed in triplicate.

Results and discussion

HSP calculation was based on the molecular structure namely their molecular functional group contribution to the dispersive (δ_d), polar (δ_p), and hydrogen-bonding (δ_h) forces. Several methodologies including Yamamoto-molecular break (Y-MB) and Van Krevelen (VK) methods, were considering (Table 1). In general, the closer HSP of the components, the more miscible they are, however, the criterion for HSP evaluation also varies (Greenhalgh et al., 1999; Van Krevelen and te Nijenhuis, 2009).

Comparison of theoretical miscibility data with Z-EE results (Table 2.), revealed no correlation between the order in which the polymers could be arranged and the percentages obtained. For example, by Hoftyzer and Van Krevelen approach $\Delta\delta_T$ for NPX and VA64 is 6.14 which falls into an ambiguous area between being likely miscible ($\Delta\delta_T \leq 5.0$) and likely immiscible ($\Delta\delta_T \geq 10.0$), whereas by the Z-EE method this polymer is ranked 2nd for NPX with high enough solubility percentage of 62.08 %. On the other hand, none of the theoretical methods resulted in prediction of immiscibility, which obviously would have been in contradiction with experimental data. Interestingly, the Bagley's evaluation approach was the only one which produced data predicting highly likely miscibility for all drug-polymer systems (Fig 1).

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Table 1. HSP for the selected drugs and polymers

API / polymer	$\delta_d, \delta_p, \delta_h, \delta_v$ $[MPa^{0.5}]$		
	Y-MB	VK	Average
FLT	17.8, 11.2, 5.8, 21.0	18.2, 6.4, 5.6, 19.3	18.0, 8.8, 5.7, 20.2
NPX	19.7, 4.0, 10.2, 20.1	19.7, 3.0, 8.2, 19.9	19.7, 3.5, 9.2, 22.0
PRC	17.8, 11.6, 8.7, 21.2	18.5, 4.5, 9.4, 19.0	18.2, 8.1, 9.1, 20.1
EPO	16.6, 3.7, 5.6, 16.9	16.2, 5.4, 8.5, 17.1	16.4, 4.5, 7.1, 17.0
VA64	18.4, 8.6, 8.2, 20.3	17.6, 10.2, 9.2, 20.4	18.0, 9.4, 8.7, 20.3
SOL	17.9, 6.9, 7.1, 19.2	16.9, 8.4, 8.4, 18.9	17.4, 7.6, 7.7, 19.0

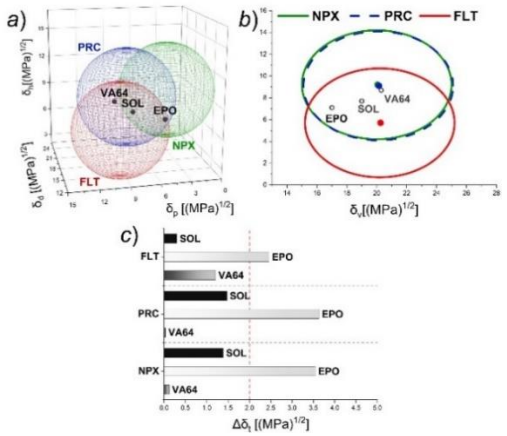

Fig. 1. Evaluation of the drug-polymer miscibility using averaged HSP: a) three-dimensional approach authored by Hoftyzer and Van Krevelen (likely miscibility if $\Delta\delta_T = \left[(\delta_{d1} - \delta_{d2})^2 + (\delta_{p1} - \delta_{p2})^2 + (\delta_{h1} - \delta_{h2})^2\right]^{0,5} \leq 5.0$); b) two-dimensional Bagley's plot ($[(\delta_{v1} - \delta_{v2})^2 + (\delta_{h1} - \delta_{h2})^2]^{0,5} \leq 5.0$, where is $\delta_v = (\delta_d^2 + \delta_p^2)^{0,5}$); c) bar graph according to Greenhalgh ($(\Delta\delta_{T1} - \Delta\delta_{T2}) \leq 2.0$)

Table 2. Drug-polymer miscibility (%) by Z-EE method

APIs	Polymers		
	EPO	VA64	SOL
FLT	40.67	25.94	16.19
NPX	65.32	62.08	41.05
PRC	65.50	55.73	29.18

FT-IR study revealed significant deviations in the spectra of FLT-VA64 and NPX-EPO 70 % SDs from those of pure components, which could be attributed to the intermolecular bonding between N-H and C=O, and O-H and C=O groups, respectively (Fig. 2). A possible explanation of this fact from the side of HSP might lay in the very close polar solubility parameters (considering averaged HSP). Although if so, there should be evidence of such interactions in PRC-SOL SD spectrum as well, but nothing significant was observed. In turn, this might be caused by another copolymer structure of SOL (graft vs block) and large molecular weight hindering its potential interactions.

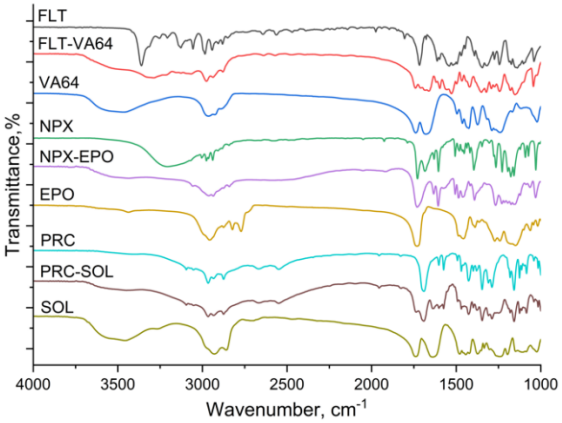

Fig. 2. FT-IR spectra of the APIs, polymers, and SDs

Conclusion

Theoretically selected polymers were found to be all appropriate in terms of their experimental miscibility with the model drugs, however, arranging them according to HSP values does not correlate with the solubility percentage obtained by the DSC method. Drug-polymer interactions revealed for two of the model drugs might not only contribute to the miscibility but also additionally stabilize the ASDs after cooling. The finding of this study will be further used to investigate processing condition effect on the drug amorphization in the SDs.

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