The step-wise dissolution method: An efficient DSC-based protocol for API–polymer solubility determination

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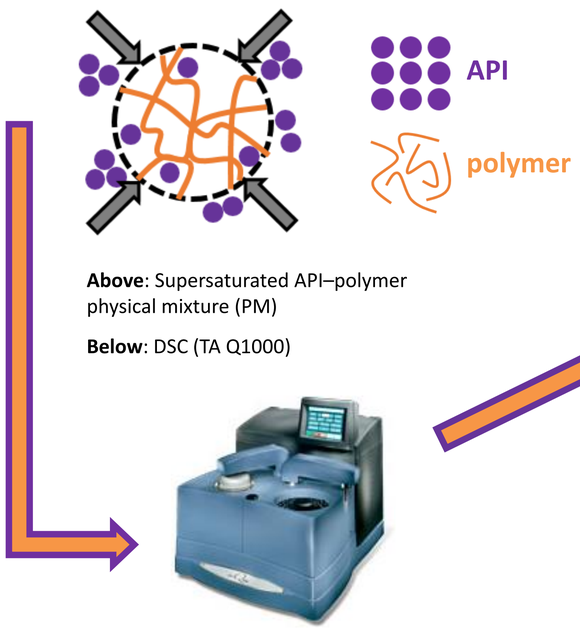
The step-wise dissolution (S-WD) method



Above: Supersaturated API–polymer physical mixture (PM)

Below: DSC (TA Q1000)

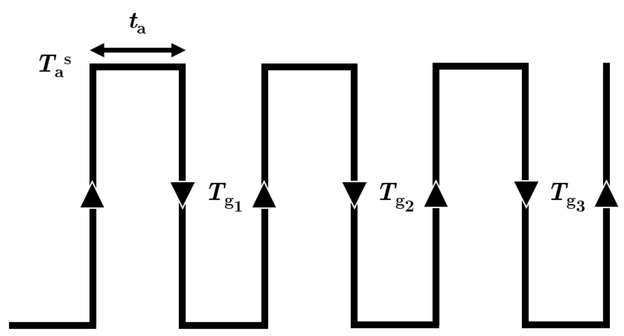


Figure 1a. The mechanism for the ATI experiment. The superscript "s" stands for "starting" (i.e., T_a^s is the starting temperature of annealing). The subscripts "1", "2", and "3" denote the T_g value obtained after the first, second, and third time of annealing (t_a) cycle, respectively.

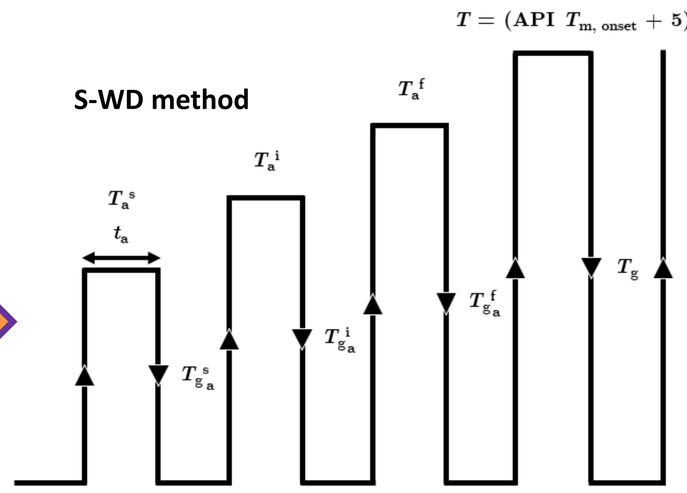
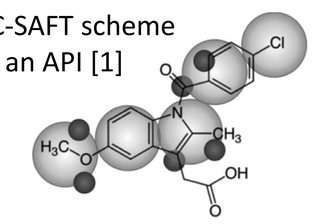


Figure 1b. The mechanism for the S-WD method. The superscripts "s", "i", and "f" stand for "starting", "intermediate", and "final", respectively.

SLE curve modeling (PC-SAFT EOS)

PC-SAFT scheme of an API [1]



The perturbed chain-statistical associating fluid theory (PC-SAFT) equation of state (EOS) was employed to purely predict (and later using experimental SLE data) the API activity coefficient (γ_{API}^{L}) in the presence of a polymer.

$$x_{API}^{L} = \frac{1}{\gamma_{API}^{L}} \exp\left[-\frac{\Delta_{fus}H}{RT}\left(1-\frac{T_{m,\,onset}}{T}\right)-\frac{1}{RT}\int_{T}^{T_{m,\,onset}}\Delta_{fus}C_p\,dT+\frac{1}{R}\int_{T}^{T_{m,\,onset}}\frac{\Delta_{fus}C_p}{T}\,dT\right]$$

The PC-SAFT EOS and the Gordon–Taylor equation were used to purely predict the API–polymer solid-liquid equilibrium (SLE) curve and glass-transition temperature (T_g) line, respectively.

The S-WD method was employed to obtain the experimental API–polymer solubility dataset (and T_g values). The DSC-based values were compared to the purely-predicted T–C phase diagram. The SLE curve was remodeled using the PC-SAFT EOS, and the T_g line was recalculated via the Kwei equation.

T–C phase diagram

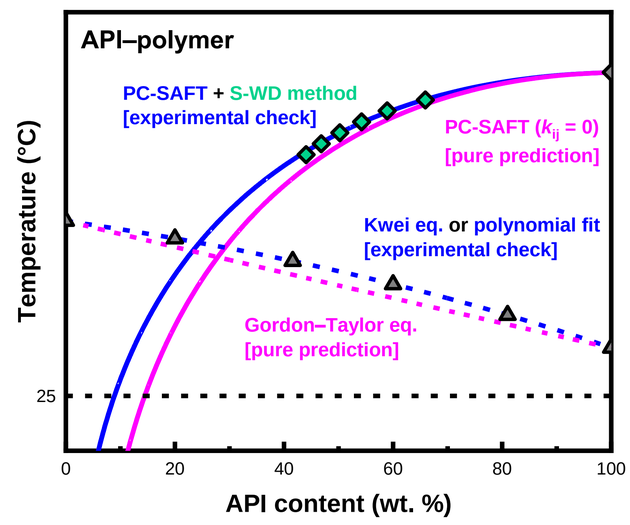
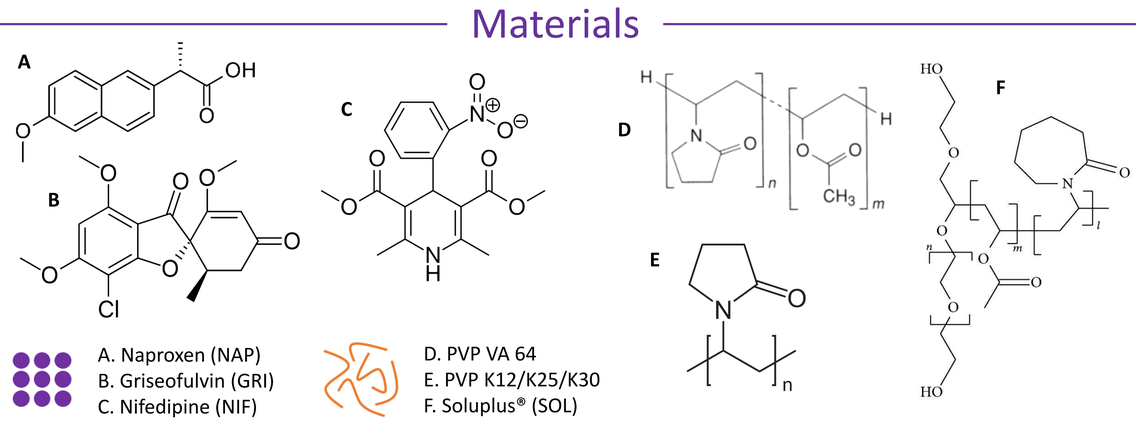


Figure 2. A constructed temperature–composition (T–C) phase diagram for an API–polymer binary system.

Materials



A. Naproxen (NAP)
B. Griseofulvin (GRI)
C. Nifedipine (NIF)

D. PVP VA 64
E. PVP K12/K25/K30
F. Soluplus® (SOL)

API–polymer compatibility screening

The API–polymer compatibility for **fifteen** binary systems was purely predicted and experimentally measured, and the results were compared.

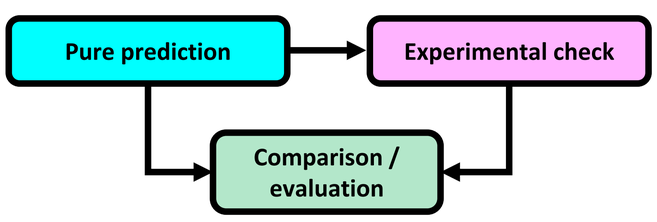
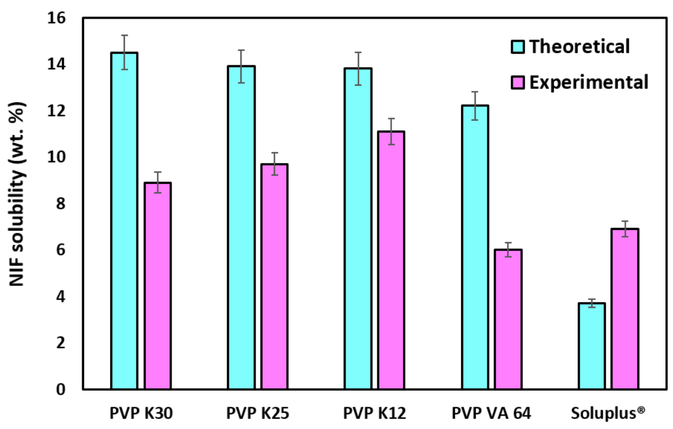


Table 1. A comparison between the theoretical- ("Theo.") and experimental-based ("Exp.") predicted API solubility in each of the polymers at T = 25 °C in addition to the optimized ("Opt.") kij and AARD values.

Polymer	Case type	$w_{API,\,sol}$ (wt. %): Theo.	$w_{API,\,sol}$ (wt. %): Exp.	Opt. k_{ij}	No. of exp. values	AARD (%)
NAP–polymer						
PVP K25	II	40.9	41.6	–0.003	5	0.1789
PVP K30	II	40.7	40.5	0.001	6	0.1368
PVP K12	I	41.0	34.5	0.022	6	1.8688
PVP VA 64	I	30.1	29.7	0.001	6	0.7375
SOL	I	46.3	8.2	0.059	4	1.3036
NIF–polymer						
PVP K30	II	13.8	11.1	0.004	3	0.9832
PVP K25	II	13.9	9.7	0.006	5	2.0072
PVP K12	I	14.5	8.9	0.008	6	0.9006
PVP VA 64	I	3.7	6.9	–0.007	5	2.3110
SOL	I	12.2	6.0	0.008	6	2.5396
GRI–polymer						
PVP K12	I	0.1	0.3	–0.008	3	3.5254
SOL	III	0.1	0.3	–0.010	2	4.8141
PVP K25	II	0.1	0.2	–0.008	2	3.0743
PVP VA 64	I	0.1	0.1	–0.002	3	5.6309
PVP K30	II	0.1	0.1	–0.001	2	5.4533

Right: **Figure 3**. Theoretical vs. experimental NIF solubility at T = 25 °C for each of the polymers.



Three distinct API–polymer case types were identified based on the physicochemical properties of the pure components.

Case I: API $T_{m,\,onset}$ ≠ polymer T_g
Case II: API $T_{m,\,onset}$ ≈ polymer T_g
Case III: API T_g ≈ polymer T_g

Summary and outlook

The S-WD method was successfully employed to rapidly acquire SLE data for fourteen of the fifteen investigated API–polymer combinations. A satisfactory agreement was found between the purely-predicted SLE curve (via the PC-SAFT EOS) and the experimental API solubility values for the majority of the binary systems. An important output of this work was the identification of three distinct API–polymer case types that can facilitate a rational and reliable approach to API solubility determination in a polymer. These promising results may find application in the expeditious compatibility screening of various polymeric candidates with expensive anticancer compounds.

Reference: 1. Prudic, A.; Ji, Y.; Sadowski, G. Thermodynamic Phase Behavior of API/Polymer Solid Dispersions. *Mol. Pharm.* **2014**, 11 (7), 2294-2304.