Supporting Information

Exploring the shape influence on melting temperature, enthalpy and solubility of organic drug nano-crystals by a thermodynamic model

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A further verification of the model was performed by considering two other small organic drugs (nifedipine and griseofulvin, both of them belonging to the Amidon class II: low water solubility and good permeability) whose characteristics are reported in Table S1 and Table S2, respectively.

Table S1. Nifedipine physico-chemical parameters. *UCS* indicates the diameter of the unit cell imagined as a sphere, M_w is the molecular weight, γ_∞^{sl}, γ_∞^{lv} and γ_∞^{sv} are, respectively, the solid-liquid, liquid-vapor and solid-vapor surface energy referring to a plane surface (infinite curvature radius), δ_0 is the Tolman's length, ρ_s and ρ_l are, respectively, the solid and the liquid densities, $T_{m\infty}$ and $\Delta H_{m\infty}$ are, respectively, the melting temperature and enthalpy of the infinitely large crystal, ΔC_P is the difference between the liquid and the solid specific heat at constant pressure, V_m is the molar volume, while C_s is the solubility in water (37°C).

Formula	$C_{17}H_{18}N_2O_6$	Ref
UCS(nm)	1.47	S_R-1
M_w(-)	346.34	-
γ_∞^{sl}(J/m^2)	0.0064	46
γ_∞^{lv}(J/m^2)	0.0461	46
γ_∞^{sv}(J/m^2)	0.0525	46
ρ_s(kg/m^3)	1375.5	46
ρ_l(kg/m^3)	1272.3	46
$T_{m\infty}$(°C)	172.8	46
$\Delta H_{m\infty}$(J/kg)	107500	46
ΔC_P(J/kg°C)	486	46
V_m(m^3/mole)	272*10^{-6}	46
C_s(μg/cm^3) - 37°C	20	S_R-2

Table S2. Griseofulvin physico-chemical parameters. *UCS* indicates the diameter of the unit cell imagined as a sphere, M_w is the molecular weight, γ_∞^{sl}, γ_∞^{lv} and γ_∞^{sv} are, respectively, the solid-liquid, liquid-vapor and solid-vapor surface energy referring to a plane surface (infinite curvature radius), δ_0 is the Tolman's length, ρ_s and ρ_l are, respectively, the solid and the liquid densities, $T_{m\infty}$ and $\Delta H_{m\infty}$ are, respectively, the melting temperature and enthalpy of the infinitely large crystal, ΔC_P is the difference between the liquid and the solid specific heat at constant pressure, V_m is the molar volume, while C_s is the solubility in water (37°C).

Formula	$C_{17}H_{17}ClO_6$	Ref
UCS(nm)	1.45	S_R-3
M_w(-)	352.77	-
γ_∞^{sl} (J/m^2)	0.0097	46
γ_∞^{lv} (J/m^2)	0.0525	46
γ_∞^{sv} (J/m^2)	0.0622	46
ρ_s(kg/m^3)	1494.7	46
ρ_l(kg/m^3)	1383.1	46
$T_{m\infty}$(°C)	220.9	46
$\Delta H_{m\infty}$(J/kg)	124400	46
ΔC_P(J/kg°C)	511	46
V_m(m^3/mole)	255*10^{-6}	46
C_s(μg/cm^3) - 37°C	11.9 ± 0.5	S_R-4

Figures S1-S4 show that a satisfactory agreement between the thermodynamic model and MD predictions was achieved also for nifedipine and griseofulvine.

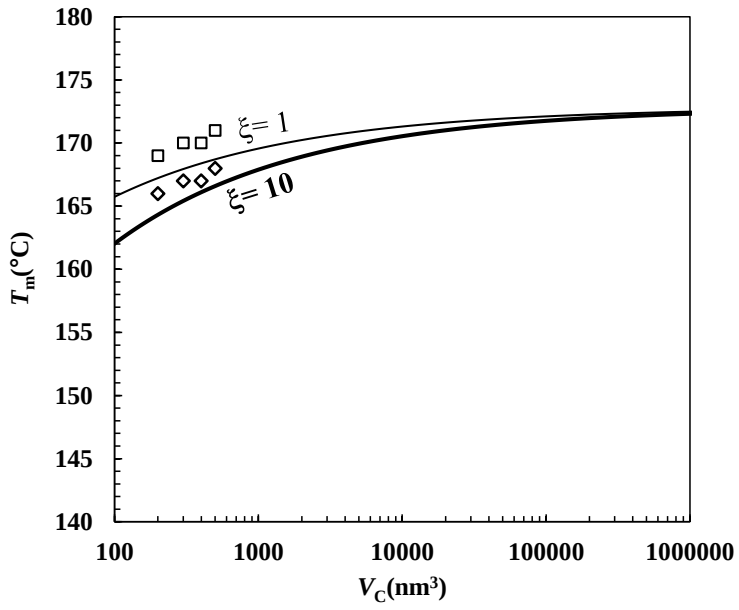

Figure S1. Nifedipine. Comparison between the melting temperature T_m decrease according to the thermodynamic model (Eqs. (9) and (10); solid lines) and to the molecular dynamics approach (symbols). The simulations were performed assuming Nifedipine nano-crystals in the form of parallelepipeds characterized by a square base (β = 1), two different values of the shape factor (ξ = 1, 10) and the nano-crystals mass fraction X_{nc} = 1.

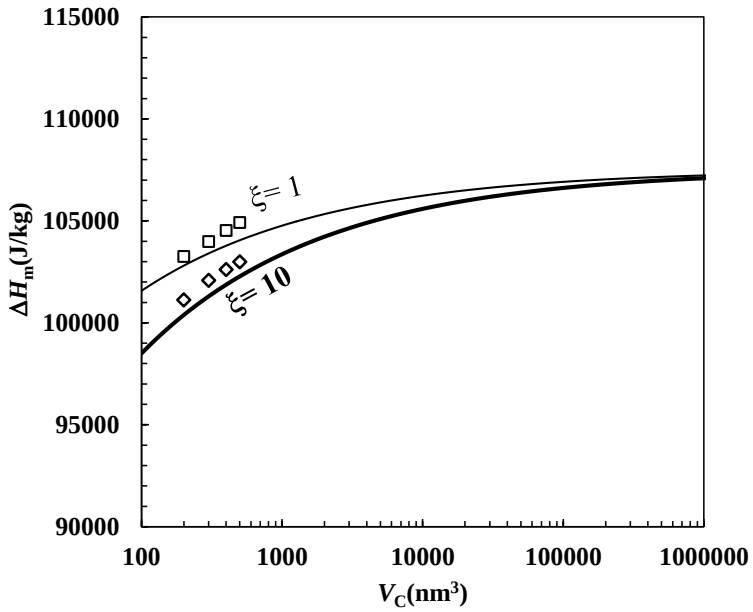

Figure S2. Nifedipine. Comparison between the melting enthalpy ΔH_m decrease according to the thermodynamic model (Eqs. (9) and (10); solid lines) and to the molecular dynamics approach (symbols). The simulations were performed assuming Nifedipine nano-crystals in the form of parallelepipeds characterized by a square base (β = 1), two different values of the shape factor (ξ = 1, 10) and the nano-crystals mass fraction X_{nc} = 1.

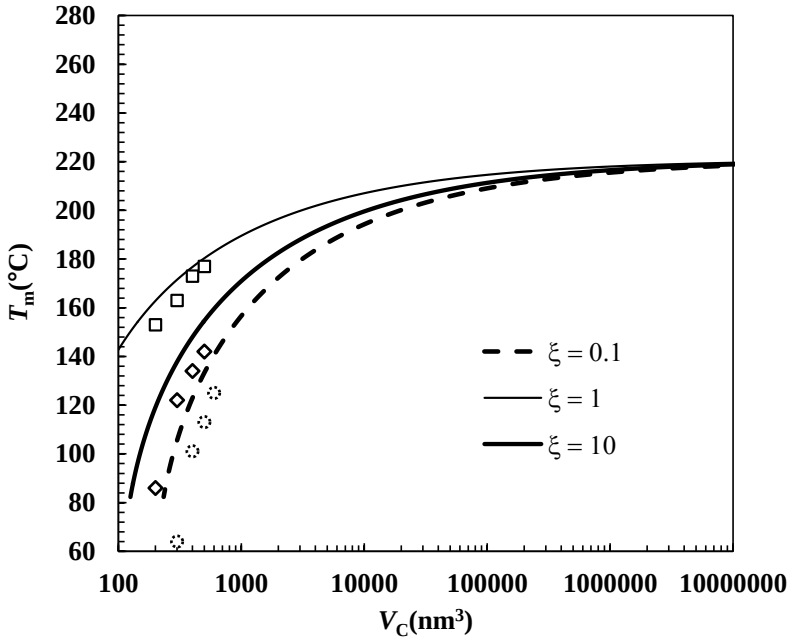

Figure S3. Griseofluvin. Comparison between the melting temperature T_m decrease according to the thermodynamic model (Eqs. (9) and (10); solid lines) and to the molecular dynamics approach (symbols). The simulations were performed assuming Griseofulvin nano-crystals in the form of parallelepipeds characterized by a square base (β = 1), three different values of the shape factor (ξ = 0.1, 1, 10) and the nano-crystals mass fraction X_{nc} = 1.

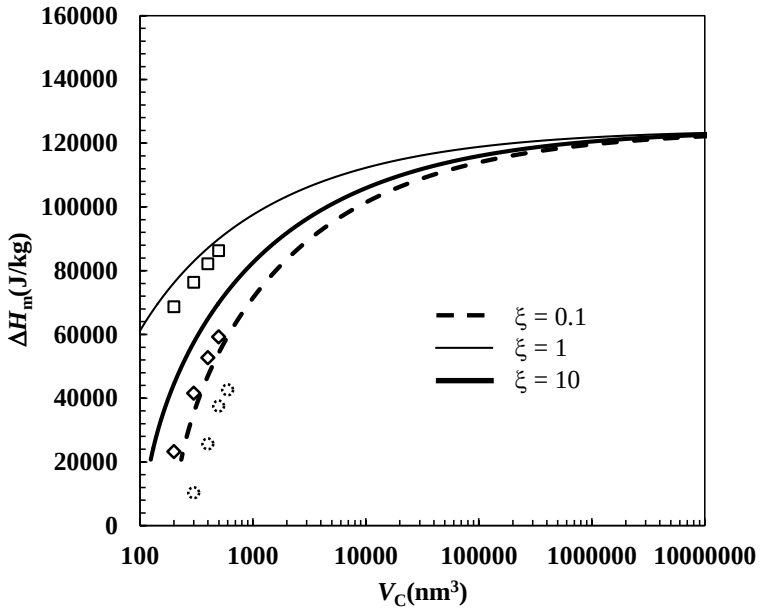

Figure S4. Griseofluvin. Comparison between the melting enthalpy ΔH_m decrease according to the thermodynamic model (Eqs. (9) and (10); solid lines) and to the molecular dynamics approach (symbols). The simulations were performed assuming Griseofulvin nano-crystals in the form of parallelepipeds characterized by a square base ($\beta = 1$), three different values of the shape factor (ξ = 0.1, 1, 10) and the nano-crystals mass fraction $X_{nc} = 1$.

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