Thermodynamic correlation between liquid-liquid phase separation and crystalline solubility of drug-like molecules
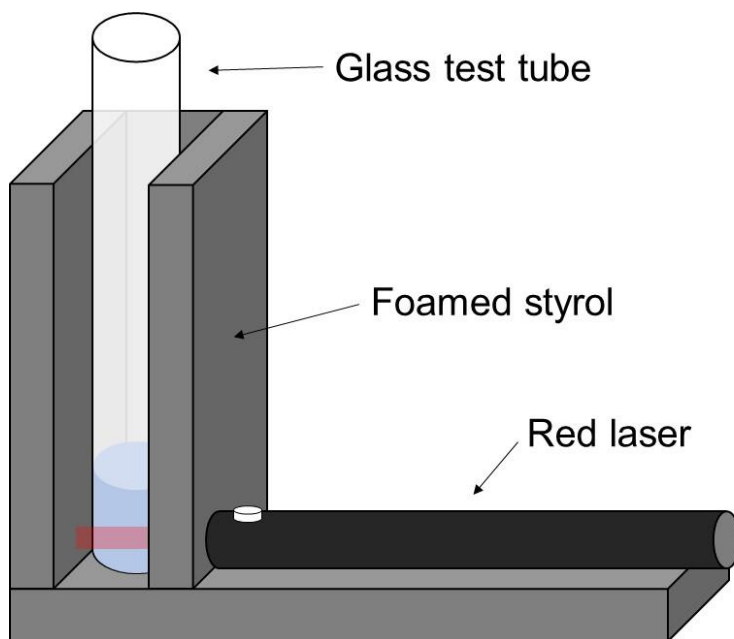
Taiga Uekusa, Tomohiro Watanabe, Daiju Watanabe, Kiyohiko Sugano*

Molecular Pharmaceutics Lab., College of Pharmaceutical Sciences, Ritsumeikan University, 1-1-1, Noji-higashi, Kusatsu, Shiga 525-8577, Japan

* Corresponding author. Tel.: +81-77-561-2773; E-mail address: suganok@fc.ritsumei.ac.jp (K. Sugano).

1. Laser-assisted visual turbidity detection (LAVTD)

The illustration of the LAVTD device is shown in Figure S1.

Figure S1. Illustration of the laser-assisted visual turbidity detection device.

2. Crystallization time of drugs.

The crystallization time for each drug is summarized in Table S1. The examples of PLM observation of crystallization time measurement are summarized in Figure S2.

Table S1. Crystallization time of drugs at 310 K.[1]

Drug	< 3 sec	3 – 10 sec	10 – 30 sec	30 – 60 sec
(S)-(＋)-Naproxen	A+C	A+C	A+C	C
2-Naphthoic-acid	A+C	C	C	C
Acemetacin	C	C	C	C
Benzocaine	C	C	C	C
Bifonazole	A	A	A	A
Bupivacaine	A+C	A+C	A+C	A+C
Carprofen	A	A	A	C
Chlorpromazine	A	A	A	A
Diclofenac [2]	A	A	C	C
Diphenhydramine	A	A	A	A
Dipyridamole	A	A	C	C
Fenofibrate	A	A	A	A
Flufenamic-acid	A	A+C	A+C	A+C
Flumequine	C	C	C	C
Flurbiprofen	A	A	C	C
Furosemide	A+C	A+C	C	C
Glipizide	A	A+C	C	C
Haloperidol	C	C	C	C
Ibuprofen [2]	A	A	A	A
Indomethacin	C	C	C	C
Ketoconazole	A	A	A	A
Ketoprofen	A	A	A	A
Ketotifen	A	A	A	A
Lidocaine	A	A	A	A
Losartan	A	A	A	A
Loxoprofen	A	A	A	A
Meclofenamic-acid	A	A	A	A
Mefenamic-acid	C	C	C	C
Meloxicam	A	A+C	C	C
Niflumic-acid	A+C	A+C	A+C	C
Orphenadrine	A	A	A	A
Papaverine [2]	A	A	A	A
Phenylbutazone	A	A	C	C
Phenytoin	A+C	A+C	C	C
Pramoxine	A	A	A	A
Probenecid	C	C	C	C
Procaine	A	A	A	A

Propafenone [2]	A	A	A	A
Propranolol	A	A	A	A
Quinine	A	A	A	A
Rebamipide	A	A	A	A
Sulfasalazine	A	A	A	C
Sulindac	A	A	A	A
Terbinafine	A	A	A	A
Thioridazine	A	A	A	A
Verapamil	A	A	A	A
Warfarin [2]	A	A	C	C

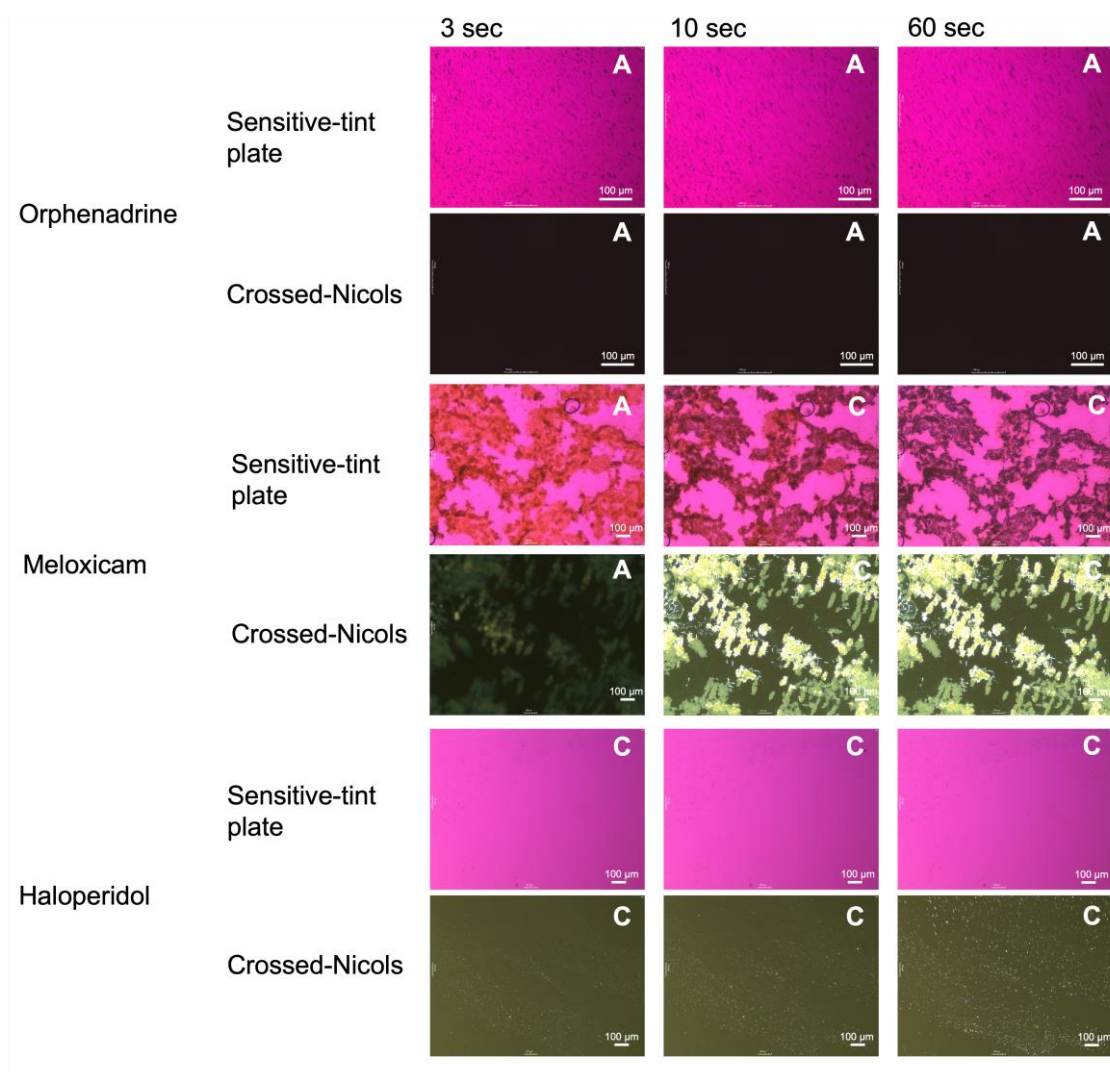[1] A: Amorphous, C: Crystal. [2] Remained amorphous for 10 sec at 298 K.

Figure S2. The examples of PLM observation of crystallization time measurement.

3. The chemical structure of model drugs

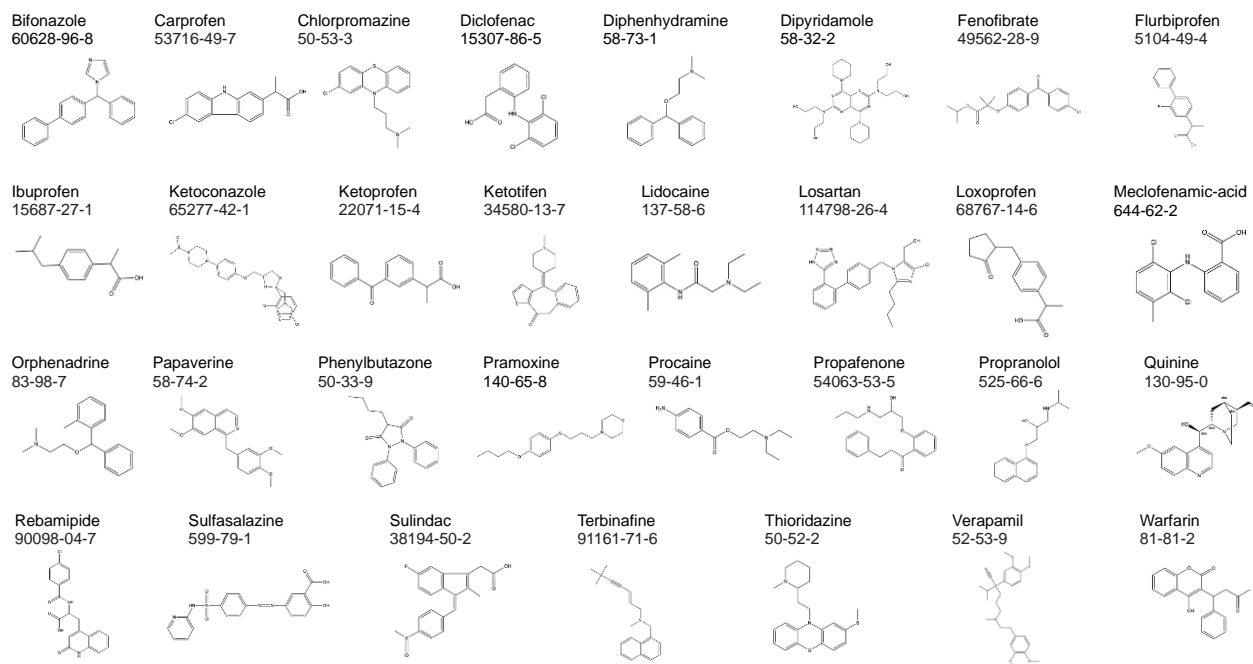The chemical structure and CAS number of model drugs are summarized in Figure S3.

| Bifonazole 60628-96-8 | Carprofen 53716-49-7 | Chlorpromazine 50-53-3 | Diclofenac 15307-86-5 | Diphenhydramine 58-73-1 | Dipyridamole 58-32-2 | Fenofibrate 49562-28-9 | Flurbiprofen 5104-49-4 |

| Ibuprofen 15687-27-1 | Ketoconazole 65277-42-1 | Ketoprofen 22071-15-4 | Ketotifen 34580-13-7 | Lidocaine 137-58-6 | Losartan 114798-26-4 | Loxoprofen 68767-14-6 | Meclofenamic-acid 644-62-2 |

| Orphenadrine 83-98-7 | Papaverine 58-74-2 | Phenylbutazone 50-33-9 | Pramoxine 140-65-8 | Procaine 59-46-1 | Propafenone 54063-53-5 | Propranolol 525-66-6 | Quinine 130-95-0 |

| Rebamipide 90098-04-7 | Sulfasalazine 599-79-1 | Sulindac 38194-50-2 | Terbinafine 91161-71-6 | Thioridazine 50-52-2 | Verapamil 52-53-9 | Warfarin 81-81-2 |

Figure S3. The chemical structure and CAS number of model drugs.

4. The intrinsic solubility (S_0^C) measurement.

The DSC charts of residual particles in the intrinsic solubility measurement are summarized in Figure S4. The DSC chart of the residual particles matched the initial particles except for procaine. In the case of procaine, p-aminobenzoic acid was produced by the decomposition of procaine and precipitated in the test tube. The pH values after reaching the equilibrium of the suspension are summarized in Table S2. The calibration curves of intrinsic solubility measurement are summarized in Figure S5.
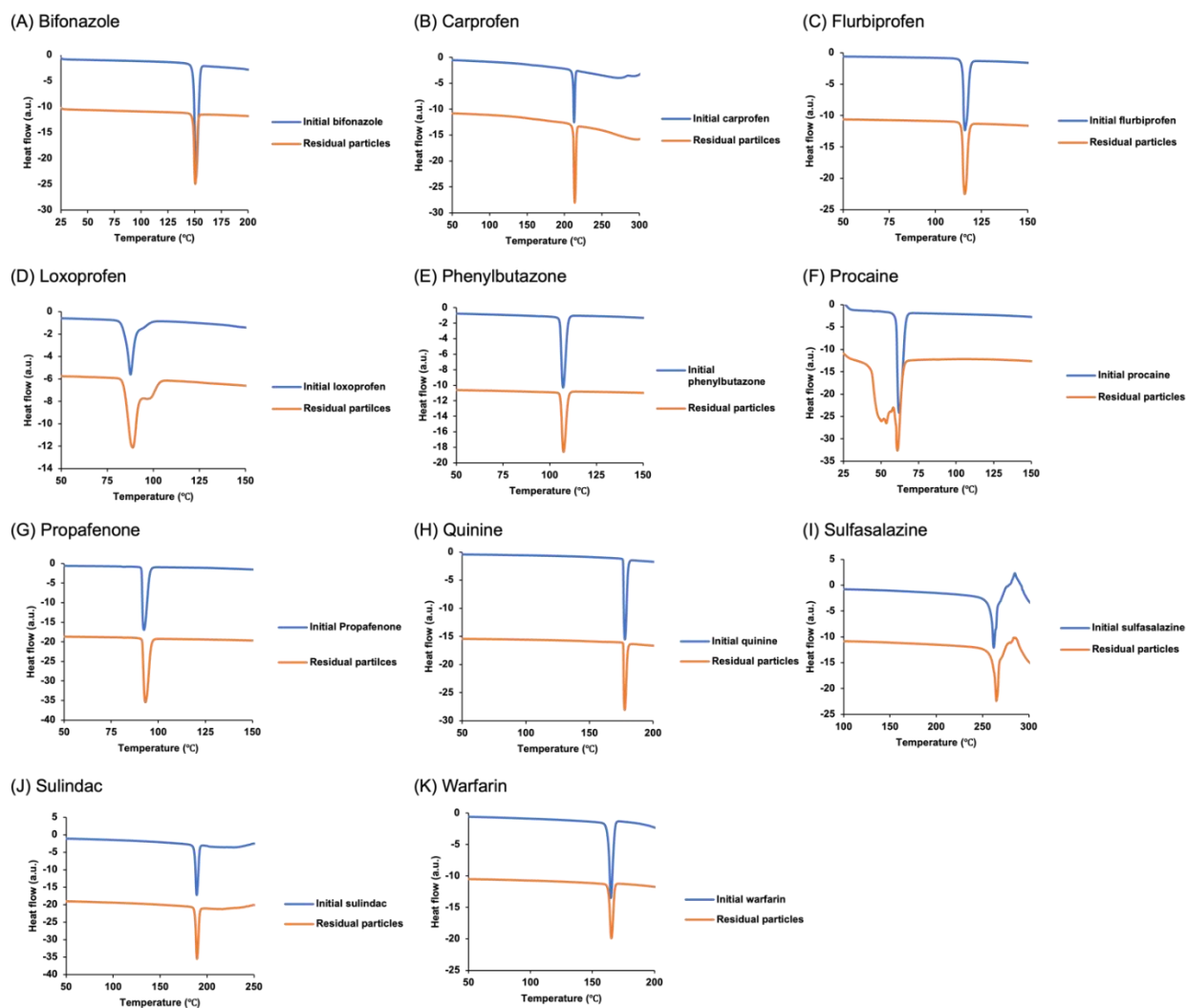
Figure S4. DSC curves of residual particles in intrinsic solubility measurement.

Table S2. The pH value after reaching the equilibrium.

Drug	pH (mean ± S.D.)
Bifonazole	9.0 ± 0.0
Carprofen	1.0 ± 0.0
Flurbiprofen	1.0 ± 0.0
Loxoprofen	1.0 ± 0.0
Phenylbutazone	1.1 ± 0.0
Procaine	11.6 ± 0.0
Propafenone	11.8 ± 0.0
Quinine	11.8 ± 0.0
Sulfasalazine	1.0 ± 0.0
Sulindac	1.0 ± 0.0

Warfarin	1.0 ± 0.0

Bifonazole

y = 0.0726x - 0.004
r² = 0.9996

Absorbance / Concentration (µg/mL)

Carprofen

y = 0.0764x - 0.0011
r² = 1

Absorbance / Concentration (µg/mL)

Flurbiprofen

y = 0.0809x - 0.0049
r² = 0.9987

Absorbance / Concentration (µg/mL)

Loxoprofen

y = 0.0409x - 0.0604
r² = 0.9999

Absorbance / Concentration (µg/mL)

Phenylbutazone

y = 0.1352x - 0.0009
r² = 1

Absorbance / Concentration (µg/mL)

Procaine

y = 40253x + 106568
r² = 0.9998

Area / Concentration (µg/mL)

Propafenone

y = 0.0144x - 0.0009
r² = 0.9987

Absorbance / Concentration (µg/mL)

Quinine

y = 0.016x + 0.0035
r² = 1

Absorbance / Concentration (µg/mL)

Sulfasalazine

y = 0.046x - 0.0003
r² = 0.9994

Absorbance / Concentration (µg/mL)

Sulindac

y = 0.0381x - 0.0013
r² = 1

Absorbance / Concentration (µg/mL)

Warfarin

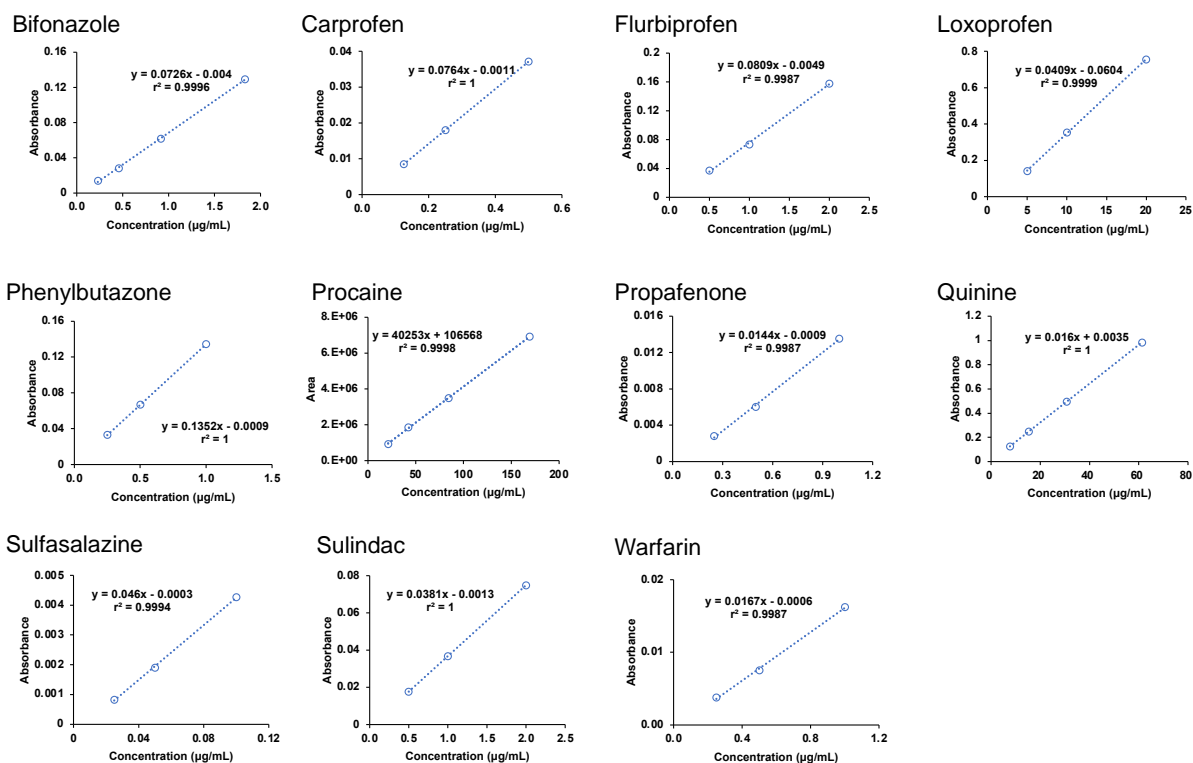y = 0.0167x - 0.0006
r² = 0.9987

Absorbance / Concentration (µg/mL)

Figure S5. Calibration curves of intrinsic solubility measurement.