**Supporting Information**

# Robust bulk preparation and characterization of salt - cocrystal polymorphs of sulfamethazine and saccharine complex

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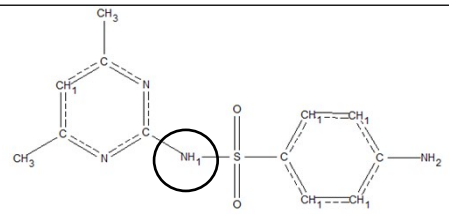
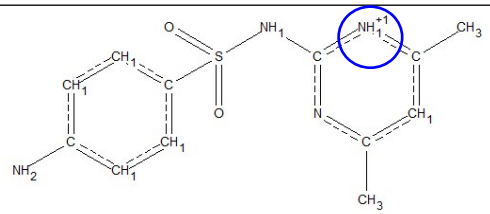
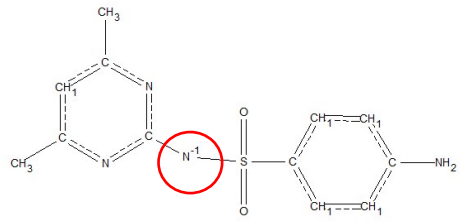
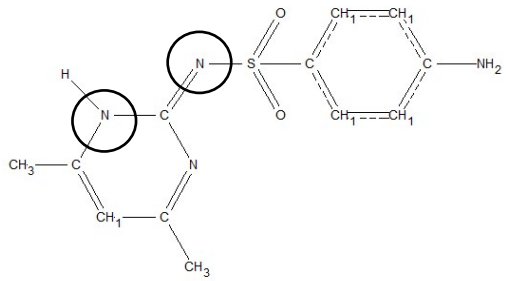
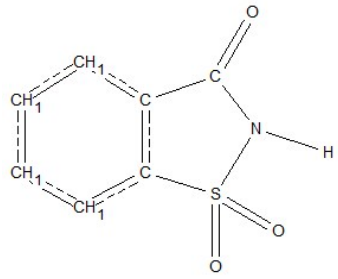
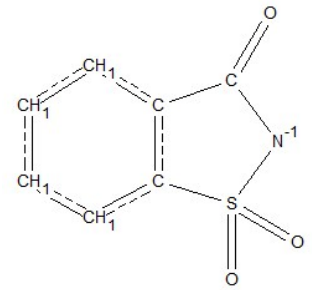
**Table S1.** Crystallographic parameters of sulfamethazine-saccharin complex.

| Solid Form | Salt (Form I) | Cocrystal (Form II) |
|---|---|---|
| Chemical formula | $C_{19}H_{19}N_5O_5S_2$ | |
| Formula weight | 461.51 | |
| Crystal system | Orthorhombic | Monoclinic |
| Space group | Pbca | $P2_1/c$ |
| a/Å | 10.4993(5) | 8.0291(2) |
| b/Å | 16.0117(8) | 17.5002(4) |
| c/Å | 25.1481(12) | 14.6076(3) |
| α/° | 90 | 90 |
| β/° | 90 | 107.827(4) |
| γ/° | 90 | 90 |
| Z | 8 | 4 |
| Z' | 1 | 1 |
| Volume ($Å^3$) | 4227.7(4) | 1953.98(8) |
| wR2 | 0.0877 | 0.1050 |
| $D_{calculated}$ (g $cm^{-3}$) | 1.450 | 1.569 |
| T (K) | 123 | 123 |
| CCDC | 1452828 | 1511452 |

**Table S2.** CSD-refcodes of crystals containing sulfamethazine and/or saccharin (Conquest version 5.39)

| | |
|---|---|
|  Amidine SMT, neutral | AWIJEW, COVXIU, DARGEL, DARNOC<br>EXANAT, EXANEX, EXANIB, EXANOH<br>EXANUN, FEVKUO, GEYSAE, GEYSAE01<br>LESQOR, PAVKUU, RASSUZ, RIWLOY<br>SABDOQ, SLFNMD, SLFNMD02, SLFNMD10<br>SORWEB, SORWIF, VIPXOJ, VUGMIT<br>VUGMOZ, WIHJAA, XEXCAE, XEXCEI<br>YADSAA, YADSEE, YIZQAA, ZOCRAM,<br>ZOCREQ, ZOCRIU, JEPYEL, JEPYIP,<br>JEPYIP01, JEPYOY, JEPYOY01, SEPVAN |
|  Cationic SMT | RILQOU, RILQUA, WIHJAA, XOBCOH,<br>XOBCOH01 |
|  Anionic SMT | DARGAH, DARPAQ, GIFRAO, XOTPON, JUBGUI |

| | |
|---|---|
|  <br>Imidine SMT, neutral | AWIJEW, VAMBIX, EXAMUM, EXAPAV, EXAPEZ, EXAPID, EXAPID01, EXAPUP |
|  <br>(Neutral SAC only) | SCCHRN06 SCCHRN07 YANNEH01 ADECIW BEXVOP ENAHEH HORNEI IHEJEK KIJSAZ LATQOO LOPZAT OTESAI OTESEM SCCHRN SCCHRN01 SCCHRN02 SCCHRN03 SCCHRN04 SCCHRN05 UFERED UNEZAO UNEZAO01 UNEZAO02 VAMBIX VIGFOH VUHFIO VUHFIO01 WUWREM WUWRIQ XOBCUN YANNEH ZIPDIN ZUZBIH ZUZBON YAJFIB YANNEH01 |
|  <br>(SAC anion only) | EWAYIM IKUNEJ OSAHUM01 ADATIJ AGETOW AJOHUC AKEXET BODHAE BODHEI BODHIM BODHOS BOYMEH BUHMEY CABTEF COCRIV COXYIY COXZAR CUXFUW CUXGIL DEXNIE DOHVUS EBEBAQ EGOCEI EKEHOS EKEHUY EKEJAG EKEJIO EMATOC EXOYEV FAGYIW FAGYUI FAGZAP FAGZET FAGZIX FAGZOD FAGZUJ FEYPUW FOCTAU FUDZUA GEHVUL GEHWAS GODHIQ GUQXEV HONBOC HOPJEC HOQKEE HULYAO HULYES HUQTOC HUQVAQ HUQVEU IGALOR IGAYAQ IGAYAQ01 IGAYEU IGAYEU01 IGAYIY ILEDAF KAKGAG KEBKAF KEXVEO KICWEA KUTJAM LEHHUC LEHJAK LEJZEG LEJZEG01 LORBUR LOYCAD MEVQIN MEVQOT MGSACA MGSACA10 MGSACD MGSACD10 MGSACD11 MIPSUA MIRWOA MUCBIV MUKWAQ MUKWEU NAXSUC NAXTAJ NIZCAC NOCKEV NOFYIQ OBIROG OBIROG01 OBIRUM OBIRUM01 OBIRUM02 ODEBAB ODEJUD ODEJUD01 ODEJUD02 ODIHUF OJIZUC OJOBAQ OLOQEL ONUQAQ ONUQEU ONUQIY OQEKIF OQEKOL ORETEL ORETIP ORETOV ORETOV01 OSAHUM PAGBEE PEFZIL PEMPIH PIGSOO PIMDEU01 PIWWUP PULZEC |

| | |
|---|---|
| | QAGBUW QAGCAD QAGCEH QAGCIL QAPMEA QAPMIE QARLAX QAYVAP QAYVET QEKVEI QEKVIM QEKVOS QEKVUY QEKWAF QEKWEJ QEKWIN QEKWOT QEKWUZ QEMLEA QEMLIE QEMLOK QIYPUJ QOGHOK QUGFUU RAFROH RAMZEK RANBEN RANBEN01 REHCIR ROJKOS ROJKUY ROKNOV RUZZOC SELXUC SIJXAM SIJXEQ SOGQEL TAYQOB TAYQUH TUBYUM UDANUJ UMAXOX UMAXUD VAWPAL VAWPEP VAWPIT VAWPOZ VAWPUF VAWPUF01 VAWQAM VAWQEQ VEGLEZ VEGLEZ01 VEQHAB VEQHEF VEQHIJ VEQHOP VEQHOP01 VEQHUV VERPOY VOGRIS VOGRIS01 VOGRIS02 VULVUV VUNNAU VUNNEY WUVKOO WUVKOO01 WUVSIR XABSOJ XOBCOH XOBCOH01 XODQAI XUVHUR XUVJAZ YAHGAP YANMUW YANMUW01 YANNAD YANNIL YOHLIQ YOHLOW YOLYAZ ZECFES ZEYKAR ZEYQAX ZUVWUK ZUVXAR ZUYJIO ZZZFPE ZZZFPI ZZZFPO QEKBAM EWAYIM EYAYOU EZOMAJ EZOMAJ01 FAZHIA FAZHOG IKUNEJ ILEDAF KECJEK OSAHUM01 YAJFEX ZECQOQ ZECQUW |
|   (Both charged and neutral SAC) | FAGYOC FAHBAS FAHBEW FAHBIA FAHBOG FAHCAT FAHCEX QOGHUQ RABBAZ RABBED RUZZUI WOVLEY WOVLEY01 FAZHEW |

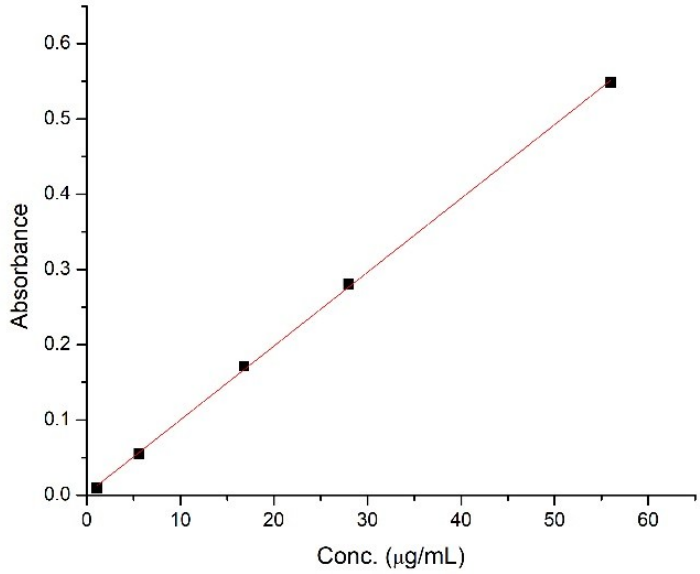



**Figure S1.** Calibration curve of SMT-SAC solution at 245nm. ($y = 0.0098x + 0.0018$, $R^2 = 0.9997$)

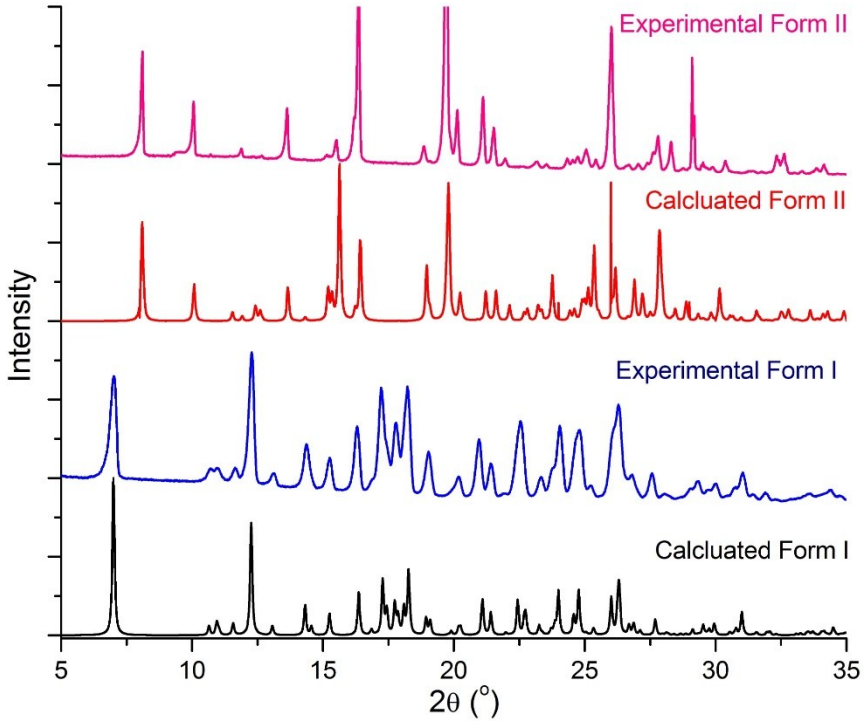



**Figure S2.** PXRD of SMT-SAC Form I (pure acetonitrile) and Form II (acetonitrile: water, 99:1, v/v) prepared by slurry method.

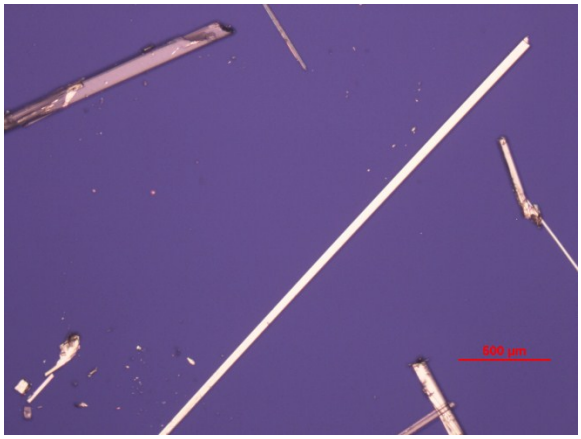



**Figure S3.** Needle morphology of SMT-SAC Form II crystallized from co-solvents of acetonitrile and water (99:1).

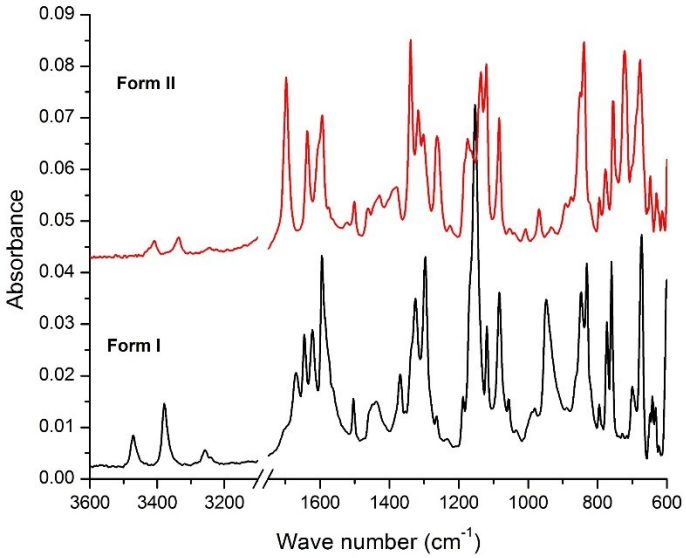



**Figure S4.** IR spectra of SMT-SAC Forms I and II in the ranges of 600−3600 $cm^{-1}$.

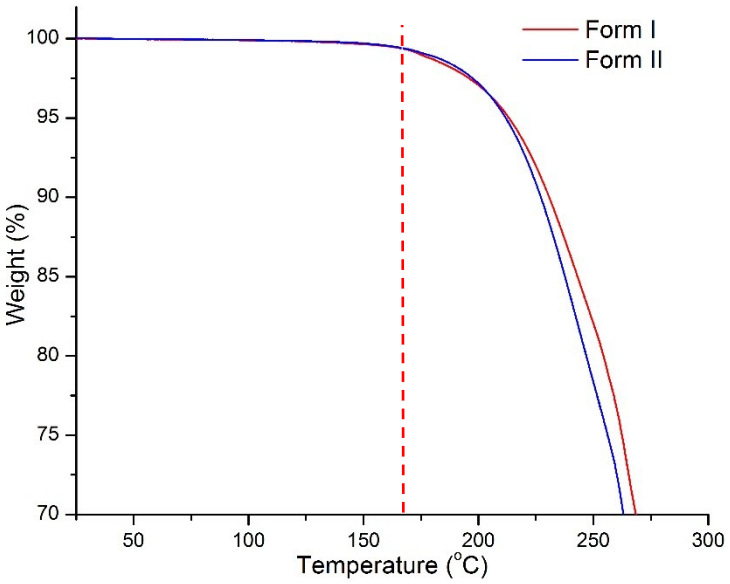



**Figure S5.** TGA traces of SMT-SAC Forms I and II.

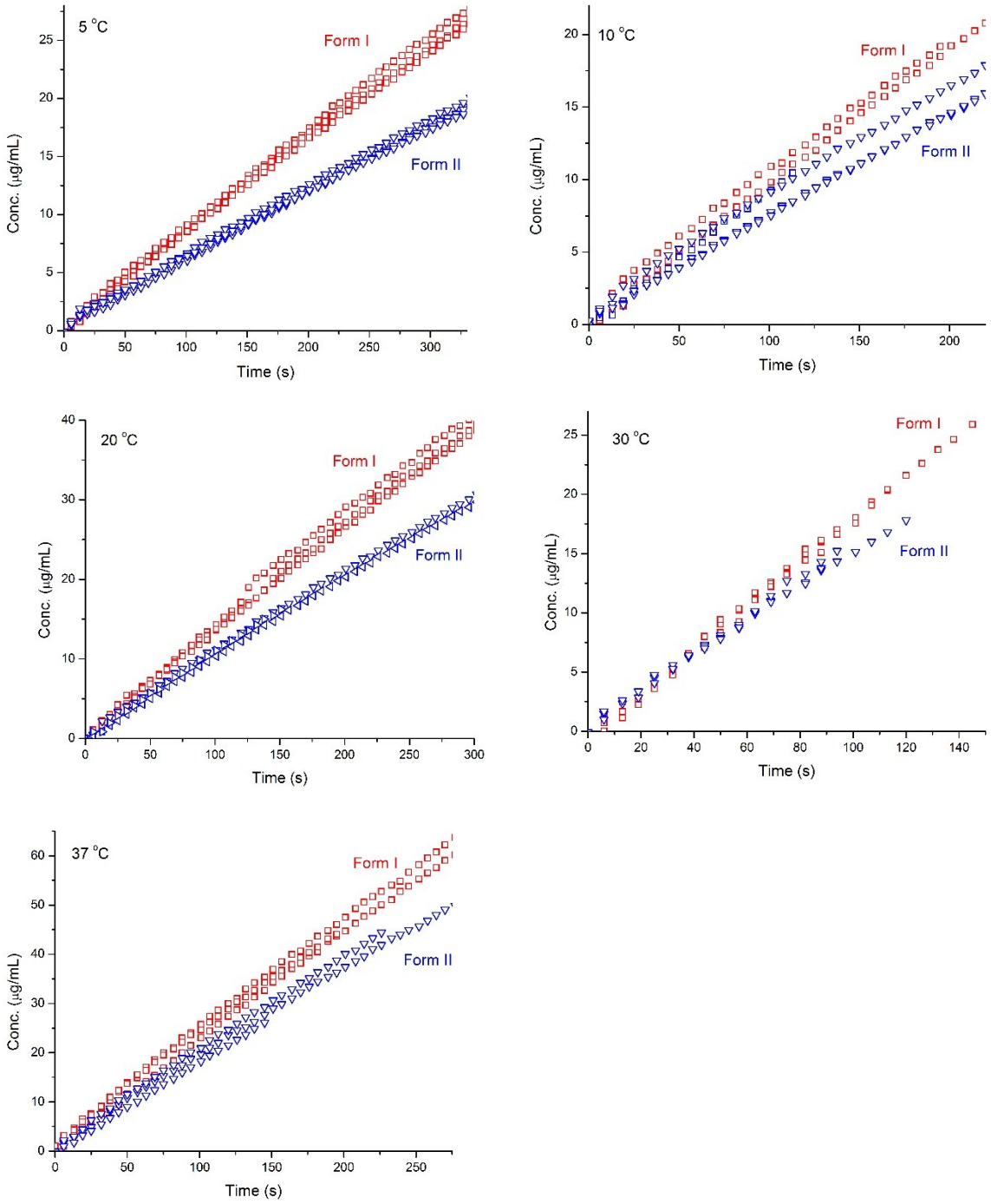



**Figure S6.** IDR of SMT-SAC Forms I and II at different temperatures from 5 to 37 °C in acetonitrile.

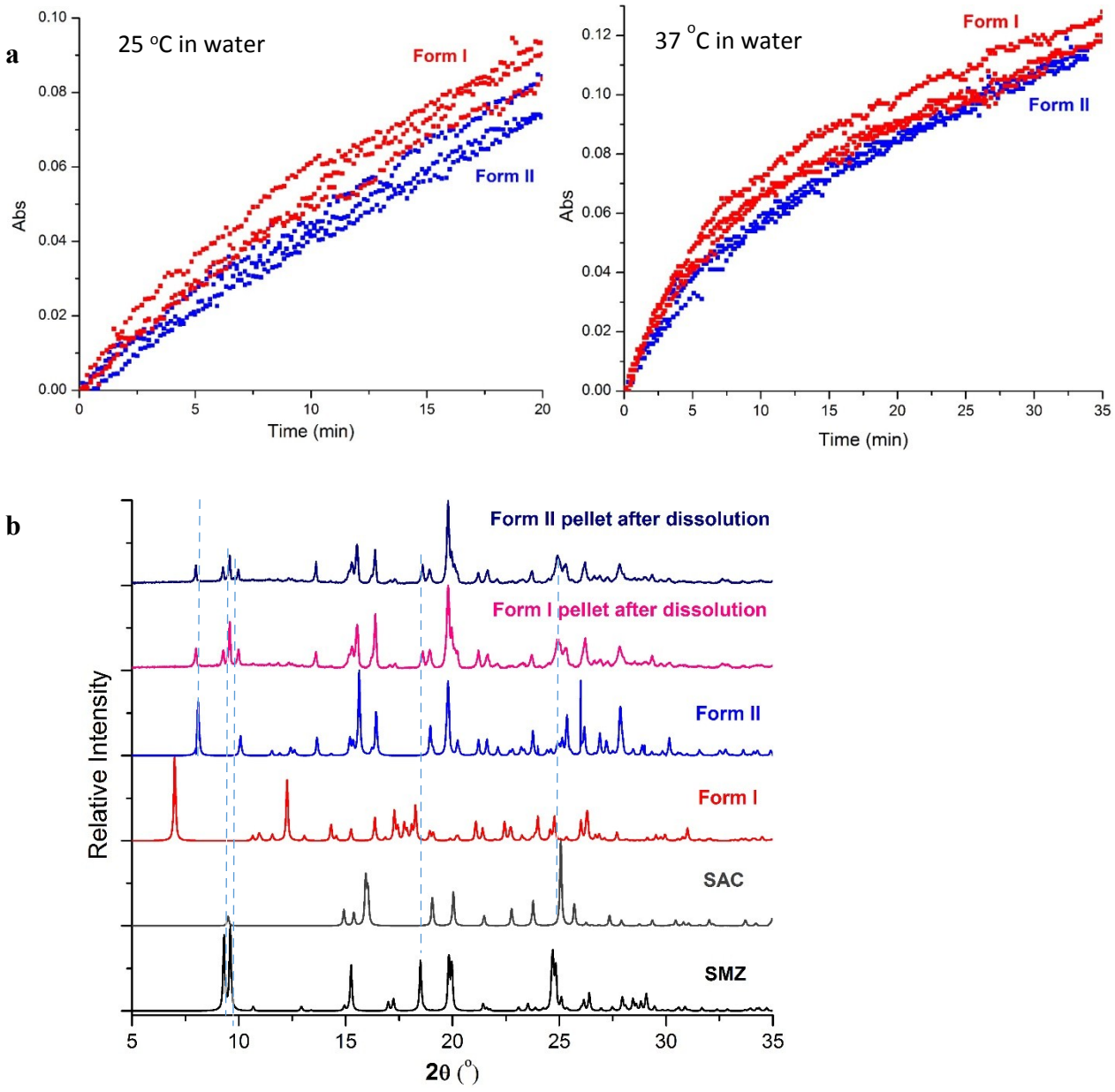



**Figure S7.** a) IDR of SMT-SAC Forms I at 25 and 37 °C in water; b) PXRD patterns of SMT-SAC pellets after IDR experiment in water at 25 °C. The absence of characteristic peaks of Form I indicates complete conversion of Form I to II. The appearance of characteristic peaks of SMZ and SAC indicates partial dissociation of the SMT-SCA complex.

**Method for calculating transition temperature between Forms I and II using DSC data**

The virtual transition temperature ($T_0$) between Form II and Form I was estimated by Yu's method.[1] The following equations 1-8 were used. $\Delta H_{m,I}$, $\Delta H_{m,II}$, $T_{m,I}$, $T_{m,II}$ are heat of fusion of Form I, heat of fusion of Form II, melting point of Form I, melting point of Form II. $C_{P,L}$, $C_{P,II}$ are heat capacity of super-cooled liquid and heat capacity of Form II. Among them, $\frac{(C_{P,L} - C_{P,II})}{\Delta H_{m,II}}$ was usually excess 0.001/K and less than 0.007/K with averaged value near 0.003/K. $\Delta G_0$ $\Delta H_0$ and $\Delta S_0$ are Gibbs free energy, enthalpy and entropy change from form II to Form I at $T_{m,I}$.

$$\Delta H_0 = \Delta H_{m,I} - \Delta H_{m,II} + \int_{T_{m,I}}^{T_{m,II}} (C_{P,L} - C_{P,II})dt$$

***Equation 1***

$$\Delta S_0 = \frac{\Delta H_{m,I}}{T_{m,I}} - \frac{\Delta H_{m,II}}{T_{m,II}} + \int_{T_{m,I}}^{T_{m,II}} \frac{(C_{P,L} - C_{P,II})}{t} dt$$

***Equation 2***

*Since* $\Delta G = \Delta H - T\Delta S$

***Equation 3***

$$\Delta G_0 = \Delta H_{m,II}\left(\frac{T_{m,I}}{T_{m,II}} - 1\right) + (C_{P,L} - C_{P,II})\left[T_{m,II} - T_{m,I} - T_{m,I} ln\left(\frac{T_{m,II}}{T_{m,I}}\right)\right]$$

***Equation 4***

If ΔG is approximately liner in a temperature range ( $\frac{d\Delta G}{dT} = -\Delta S$ ), its value at an arbitrary temperature T below $T_{m,A}$ can be obtained by

$$\Delta G = \Delta G_0 - \Delta S_0 (T - T_{m,I})$$

***Equation 5***

At $T_0$, $\Delta G$ equals zero, we get

$$T_0 = \frac{\Delta H_0}{\Delta S_0}$$

***Equation 6***

$$T_0 = \frac{\Delta H_{m,I} - \Delta H_{m,II} + (C_{P,L} - C_{P,II})(T_{m,II} - T_{m,I})}{\frac{\Delta H_{m,I}}{T_{m,I}} - \frac{\Delta H_{m,II}}{T_{m,II}} + (C_{P,L} - C_{P,II}) ln\left(\frac{T_{m,II}}{T_{m,I}}\right)}$$

***Equation 7***

$$T_0 = \frac{\Delta H_{m,I} - \Delta H_{m,II} + 0.003\Delta H_{m,II}\left(T_{m,II} - T_{m,I}\right)}{\frac{\Delta H_{m,I}}{T_{m,I}} - \frac{\Delta H_{m,II}}{T_{m,II}} + 0.003\Delta H_{m,II} ln\left(\frac{T_{m,II}}{T_{m,I}}\right)}$$

***Equation 8***

From equation 8, To was 477.42 K, which is higher than the melting point of Form II (179.4 K) ΔG as a function of temperature (K) can be calculated using Equation 9 (thick segment in Figure 9).

$\Delta G$(J/mol)= 0.02669*T + 12.7423 ***Equation 9***