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Structure and Thermodynamical Properties of Metformin Salicylate

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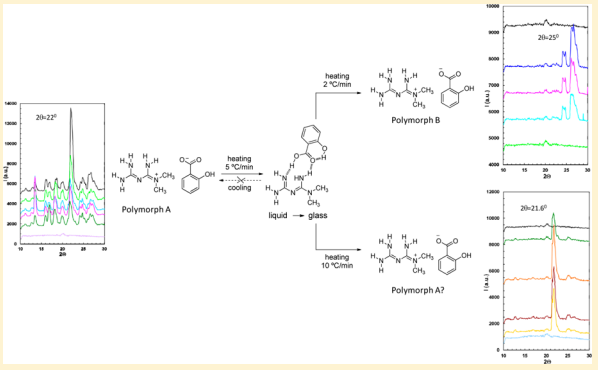
Supporting Information

ABSTRACT: The behavior under thermal conditions of the cocrystal formed by metformin and salicylic acid was studied by DSC, crystallography (single-crystal), and powder diffraction (WAXS). Metformin salicylate crystallizes in space group $P2_1/c$, with the salicylate anion showing a planar structure, stabilized by strong intramolecular hydrogen bonds. The more flexible metformin cations link through the oxygen atoms of salicylate, forming a dense hydrogen-bonding network. The compound exists initially as a salt, metformin salicylate, but after melting and cooling, it is transformed into a glass form that crystallizes and melts again, showing different behaviors depending on the heating rate.



INTRODUCTION

There is a great interest in salts or cocrystals formed by two APIs (active pharmaceutical ingredients) or drugs.[1−4] In some cases, these salts have low melting points (below 100 °C) belonging to the ionic liquids class.[5,6] After screening a wide range of Brønsted acid and base mixtures by nuclear magnetic resonance (NMR) and differential scanning calorimetry (DSC),[7] the unusual behavior showed by metformin salicylate (Figure 1) in DSC led us to analyze it in depth. Metformin[9] is an oral antidiabetic drug of the biguanide family. It is the first-line drug of choice for the treatment of type 2 diabetes mellitus,[10] in particular, in overweight and obese people. On the other hand, salicylic acid is an antipyretic and analgesic drug that is being used for the treatment of acne and other skin diseases. Note that the charges in the guanidinium cation and in the carboxylate anion are delocalized. In addition, as a complication for this study, metformin hydrochloride presents polymorphism.[8]

EXPERIMENTAL SECTION

Materials and Methods. All chemicals were purchased from commercial suppliers and used without further purification. Elemental analysis was determined with a LECO Elemental Analyzer CHNS-932. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 300 spectrometer operating at 300.13 and 75.47 MHz respectively, in DMSO-d_6 as solvent. Chemical shifts are reported in parts per million on the δ scale. In the case of multiplets, the signals are reported as intervals. Signals were abbreviated as s, singlet; d, doublet; and m, multiplet. Coupling constants are expressed in hertz.

Synthesis of Metformin Salicylate. A methanol solution (20 mL) of sodium salicylate puriss. p.a. > 99.5% (485 mg, 3.03 mmol) and metformin hydrochloride 97% (500 mg, 3.03 mmol) was stirred for 12 h at room temperature. After removing the solvent under reduced pressure, 2-propanol (20 mL) was added to the reaction crude. The solid part (sodium chloride) was filtered off. A part of this solution was concentrated under reduced pressure (40 °C, 200 mbar). The resulting white solid was studied by DSC. The rest of the solution was slowly evaporated at room temperature (21 °C), yielding suitable crystals for X-ray diffraction experiments. mp: 148 °C (Gallenkamp capillary melting point apparatus). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.66 (dd, J = 7.5, 1.9 Hz, 1H, CH_{ar}), 7.14 [m, 3H, (2 NH + 1 CH_{ar})], 6.87 [m, 4H, (4NH)], 6.61 [m, 3H, (2 CH_{ar} + 1 OH)], 2.93 (s, 6H, 2 CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.2 (C═O), 163.1 (C−OH), 159.5 (C═N), 160.0 (C═N), 131.8 (CH_{ar}), 130.3 (CH_{ar}), 120.7 (C_{ar}), 116.4 (CH_{ar}), 37.8 ppm ($2CH_3$). Analysis calculated for $C_{11}H_{17}N_5O_3$: C, 49.43; H, 6.41; N, 26.20. Found: C, 49.37; H, 6.68; N, 25.99. Both ^{1}H NMR and elemental analysis corresponds to a 1:1 stoichiometry.

DSC. The thermal properties of metformin salicylate were investigated by DSC using a METTLER TA 4000/DSC30 differential scanning calorimeter, calibrated with indium (T_m = 156.6 °C, ΔH_m = 28.45 kJ·kg^{-1}) and zinc (T_m = 419.47 °C, ΔH_m = 108.37 kJ·kg^{-1}).[11−16] The experiments were carried out in a nitrogen atmosphere with a flow rate of 25 mL·min^{-1}, using approximately 10 mg of sample sealed in aluminum pans. Original samples of metformin salicylate were heated from 5 to 180 °C at a rate of 5 °C·min^{-1}, first heating, and then were cooled down at 2, 5, and 10 °C·min^{-1} to 0 °C. Subsequently, each sample was heated to 180 °C at different rates of 2, 5, and 10 °C·min^{-1}, second heating. Melting and crystallization temperatures, T_m and T_c

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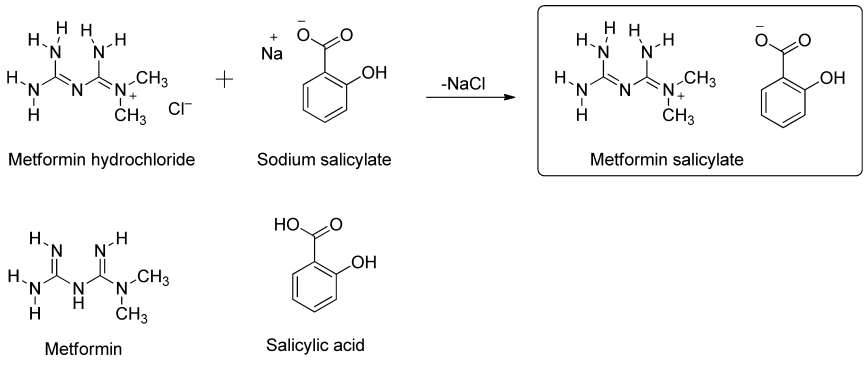

Figure 1. Structure of metformin salicylate, precursor salts, and neutral species.

Table 1. Crystal Data and Structure Refinement

metformin salicylate			
empirical formula	C11 H17 N5 O3	calculated density (Mg/m^3)	1.390
formula weight	267.30	μ (mm^{-1})	0.870
temp (K)	122.5(8)	F(000)	568
wavelength (Å)	1.54180	cryst size (mm)	0.175 × 0.108 × 0.028
cryst syst	monoclinic	reflns collected/unique	4863/2390 [R(int) = 0.0244]
space group	$P2_1/c$	completeness to θ = 68.00	99.1%
a (Å), α (deg)	15.271(5), 90	data/restraints/params	2390/0/199
b (Å), β (deg)	6.002(5), 119.72(2)	goodness-of-fit on F^2	1.050
c (Å), γ (deg)	16.050(4), 90	final R indices [$I > 2\sigma(I)$]	R1 = 0.0561, wR2 = 0.1526
V (Å^3)	1277.5(12)	R indices (all data)	R1 = 0.0761, wR2 = 0.1742
Z	4		

Table 2. Hydrogen Bonds for Metformin Salicylate (Å, deg)

D−H···A (Å)	D−H (Å)	H···A (Å)	D···A (Å)	D−H···A (deg)	symmetry[a]
N(2)−H(2B)···O(1)	0.99(5)	2.04(5)	3.004(5)	164(4)	0
N(2)−H(2A)···O(2)	0.86(7)	2.24(6)	3.047(5)	157(5)	1
N(4)−H(4B)···O(2)	0.92(6)	2.56(5)	3.462(5)	168(5)	2

[a]Symmetry transformations used to generate equivalent atoms: (0) x, y, z; (1) $-x + 1, -y, -z - 1$; (2) $x, +y - 1, +z$.

were determined as the maximum and minimum of the endothermic and exothermic transitions, respectively. The extrapolated peak onset temperatures, T_{mo} and T_{co}, were also considered. The apparent enthalpy of the transition, ΔH_i, was determined as the area under the curve. Glass transition temperature, T_g, values were determined at the midpoint of the corresponding change in the specific heat of the baseline in the thermograms. Heating and cooling cycles have been repeated four times with new samples, ensuring reproducibility. Temperature and enthalpy standard deviations were ±0.4 °C and ±3 J·g^{-1}, respectively.

WAXS. Wide-angle X-ray scattering (WAXS) measurements were conducted at the A2 beamline of the HASYLAB synchrotron facility (DESY, Hamburg). The experiments were performed with monochromatic X-rays of 0.15 nm in wavelength using a germanium single crystal as the dispersing element. The scattering was detected with a linear Gabriel detector, and the scattering angle of the WAXS pattern was calibrated with a PET standard. The methodology used in the crystallization and melting experiments of the samples was similar to that described for the calorimetric experiments. Measurements were performed with acquisition times between 30 and 150 s, depending on the heating rate.

Crystal Structure Determination. Suitable crystals for X-ray diffraction experiments were obtained by slow evaporation of 2-propanol at room temperature. Data were collected at 123 K to achieve better intensity and resolution using CuK/α, l = 1.54184 Å. A total of 4863 ($-18 \le h \le 18$, $-7 \le k \le 4$, $-16 \le l \le 19$) reflections were collected for it with 2390 independent reflections. Data collection was made using the program CrysAllis CCD.[17] Semiempirical absorption correction[18] was applied to the intensity data. The crystal structure was solved by direct methods, using the program Sir92.[19] Anisotropic least-squares refinement was carried out with SHELXL-97.[20] Refinement was made in the space group $P2_1/c$. Further details of the X-ray structural analysis are given in Table 1. Hydrogen bonds are listed in Table 2. Geometrical calculations were made with PARST97[21,22] and PLATON,[23,24] and molecular graphics with ORTEP-3[25] and MERCURY for Windows.[26] The crystals were checked at room temperature, giving the same unit cell and symmetry at both temperatures within the expected ranges of thermal volume contraction. The structure was deposited and has the following code number: CCDC 883514.

RESULTS AND DISCUSSION

Single-Crystal Structure. The molecular structure of metformin salicylate is represented in Figure 2. The single-crystal X-ray data for this compound are listed in Table 1. The hydrogen-bonding geometry is reported in Table 2.

The crystal packing of metformin salicylate shows infinite layers in zigzag that are parallel to the bc plane, as shown in Figures 3 and 4, formed by N−H···O hydrogen bonds.

Layers are formed by tetramers (Figure 5) in which the molecules are connected by N(2)−H(2B)···O(1) and N(2)−H(2A)···O(2) hydrogen bonds. Each tetramer is interacting with four tetramers by N(4)···O(1) hydrogen bonds forming the layer within the bc plane. The N(4)−H(4B)···O(1) hydrogen bonds are shown in Figure 6.

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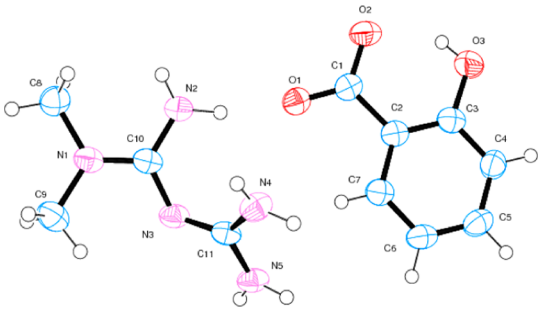

Figure 2. Crystal structure of metformin salicylate at 123 K (ORTEP).

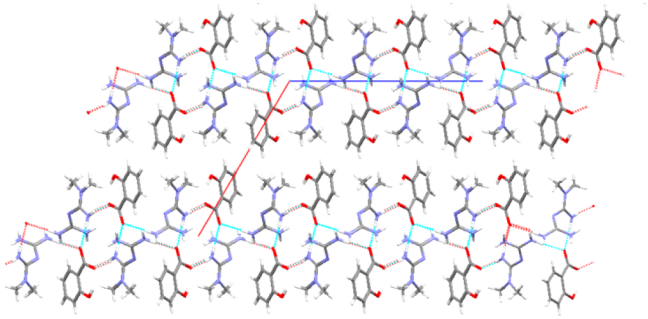

Figure 3. Crystal packing of metformin salicylate. Parallel layers within *bc* plane. View along *b* axis.

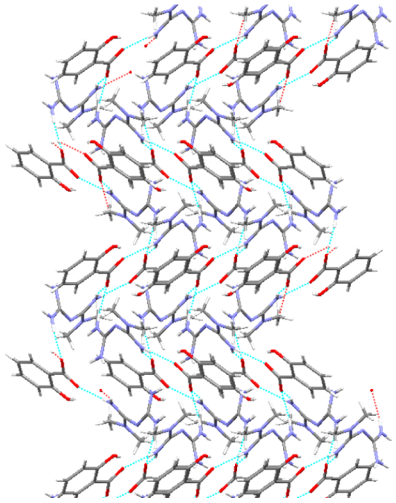

Figure 4. Layer within *bc* plane. View along *a* axis.

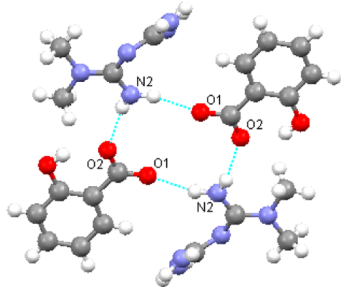

Figure 5. Tetramer formed by N(2)−H(2B)···O(1) and N(2)−H(2A)···O(2) hydrogen bonds. View along *c* axis.

The metformin cation can exist in three tautomeric structures a, b, and c, all of them fully delocalized (Figure 7). This could be related to a possible desmotropy of metformin salicylate.[27] The X-ray structure corresponds to tautomer c. All reported metformin salts and related compounds, such as biguanide hydrochloride salt, also belong to tautomer c.[8,28−31]

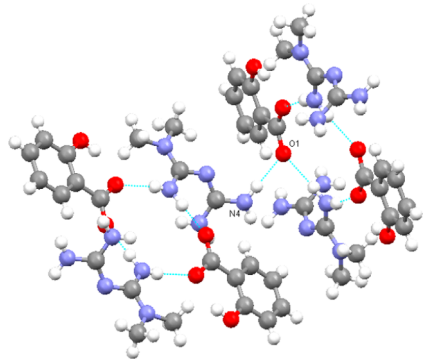

Figure 6. N(4)−H(4B)···O(1) hydrogen bond network present in metformin salicylate.

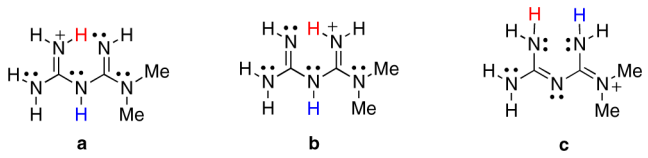

Figure 7. Tautomerism of the metformin cation.

DSC. When an original sample of metformin salicylate is heated at 5 °C·min^{-1}, an endothermic transition is found with a maximum at 147.5−147.8 °C and an enthalpy of 102.6−103.4 J·g^{-1}. During its subsequent cooling at 10 °C·min^{-1}, no crystallization-associated exothermic process was observed in any case, but a small variation in specific heat at 25.1−25.8 °C can be assigned to a glass transition (Figure 8).

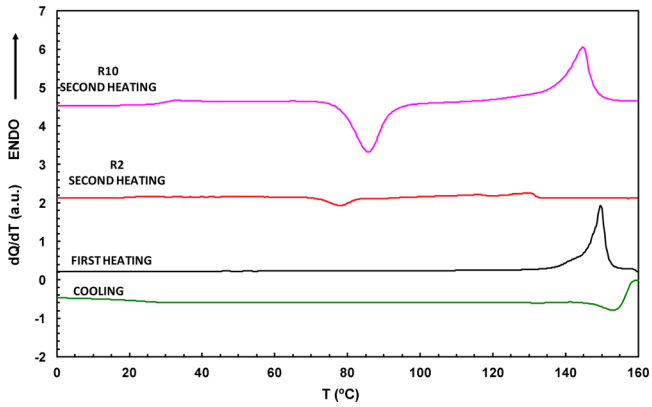

Figure 8. Metformin salicylate DSC traces at 2, 5, and 10 °C·min^{-1} heating rates. From bottom to top: cooling (green); first heating at 5 °C·min^{-1} (black); second heating R2 at 2 °C·min^{-1} (red), second heating R10 at 10 °C·min^{-1} (pink).

The high-temperature exothermic change at 157 °C observed at cooling is attributed to the initial thermal effect of the cooling process and not to the crystallization process. Changing the cooling rate to 2 and 5 °C·min^{-1} after the first heating cycle did not affect the DSC thermogram, not showing any crystallization exotherm during the cooling process. Table 3 compiles the temperatures and enthalpies for the first heating cycle and for the

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Table 3. DSC Measurements of Metformin Salicylate at 2, 5, and 10 °C·min^{-1} Heating Rates

S[a]	first heating			cooling	second heating						
	T_m (°C)	T_{mo} (°C)	ΔH_m (J·g^{-1})	T_g (°C)	T_g (°C)	T_c (°C)	T_{co} (°C)	ΔH_c (J·g^{-1})	T_m (°C)	T_{mo} (°C)	ΔH_m (J·g^{-1})
R10	147.7	140.3	102.9	25.1	28.3	86.7	77.1	76.0	142.8	129.6	80.9
R5	147.5	140.6	102.6	25.5	25.9	79.8	70.6	66.4	140.1	128.4	70.6
R2	147.8	140.4	103.4	25.8	18.8	78.0	69.2	41.9	115.6–129.1	110.1	79.1

[a]Sample R2 (2 °C·min^{-1}), sample R5 (5 °C·min^{-1}), sample R10 (10 °C·min^{-1}).

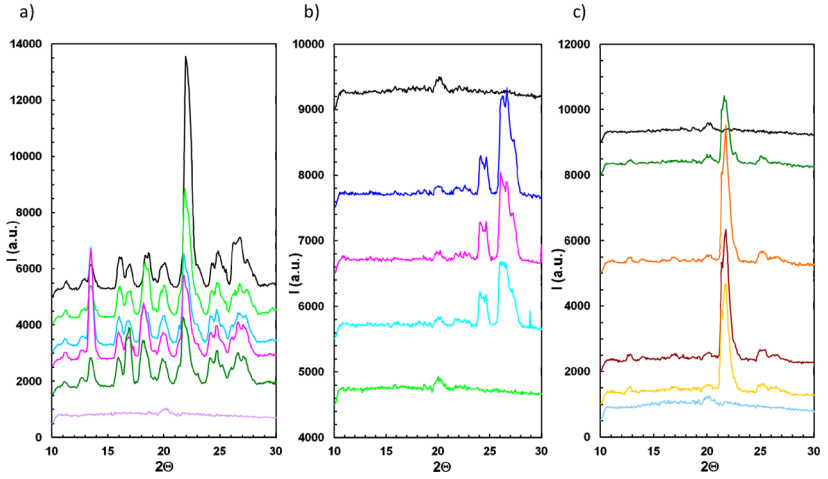

Figure 9. WAXS of metformin salicylate: (a) initial sample at 5, (b) 2, and (c) 10 °C·min^{-1}. XRPD: 2θ zone between 10 and 30°. Heating temperatures from top to bottom: 30, 80, 100, 120, 140, 150 (only in (c)), and 160 °C (only in (a)).

cooling cycle previous to the second heating cycle at different temperatures.

During the heating at 10 °C·min^{-1} (sample R10) immediately after the cooling, a glass transition is observed, followed by an exothermic transition associated with the cold crystallization of the system with an exothermic peak located at 86.7 °C and followed by the melting at 142.8 °C of the crystals generated during heating (Figure 8).

The aforementioned cold crystallization process is very dependent on the heating rate employed. When the heating rate is lower (samples R5 and R2), the cold crystallization exotherm shifts to lower temperature (79.8 and 78.0 °C, respectively), as the melting endotherm that splits into a double endotherm (115.6 and 129.1 °C) when the heating rate is 2 °C·min^{-1} (Table 3).

WAXS. Taking into account the pK_a's of salicylic acid (2.97)[32] and metformin (12.4),[33,34] the compound must be a salt in solution and probably in the solid state. Figure 9 shows the wide-angle X-ray pattern evolution. The DSC recordings shown in Figure 8 are in accordance with these WAXS patterns at heating rates of 5, 2, and 10 °C·min^{-1}.

Mercury (CCDC) software[35,36] was used to generate a predicted powder pattern from the single crystal using a full width at half-maximum (fwhm) 2θ = 0.5 (Figure 10), which was compared with the observed WAXS patterns (Figure 9a, top).

Taking into account the broadening of the WAXS spectrum, no extra peaks were found, verifying that the crystal grown in solution for single-crystal analysis is the same as the ones used for the DSC/WAXS experiments (polymorph A). The phenomena observed in the DSC and WAXS experiments are summarized in Figure 11.

At 5 °C·min^{-1}, the first diffraction peak (2θ = 13.5°) appears and a dominant diffraction peak can be observed at 2θ = 22° (polymorph A). At the same heating rate in the DSC

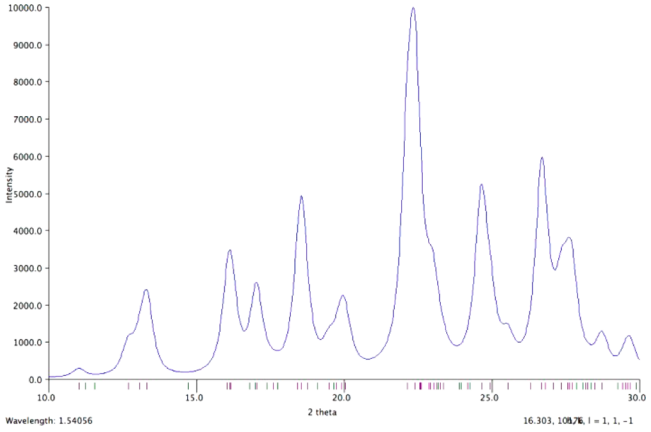

Figure 10. Predicted powder pattern from the single-crystal metformin salicylate using a full width at half-maximum (fwhm) 2θ = 0.5.

thermogram, the metformin salicylate crystal melts at 147.7 °C, transforming it into a liquid, probably no longer a salt, but a hydrogen-bonded complex, "liquid" in Figure 11. Upon cooling, a glass transition is observed and the compound does not rearrange to the starting metformin salicylate salt (polymorph A) but transforms into a solid hydrogen-bonded complex, "glass" in Figure 11. Neither the liquid nor the glass diffracts, which is the reason why we assumed that they are no longer salts, but noncrystalline complexes. On heating, the behavior of the glass differs depending on the heating rate. At the 2 °C·min^{-1} rate, the glass crystallizes, but the crystal obtained, as shown by the WAXS pattern, is another polymorph we have named B. With a faster heating, 10 °C·min^{-1}, the glass also crystallizes probably to polymorph A, although the WAXS spectrum is not identical, it may be because the equilibrium was not reached. Polymorphs A and B are comparable to polymorphs A (stable) and B

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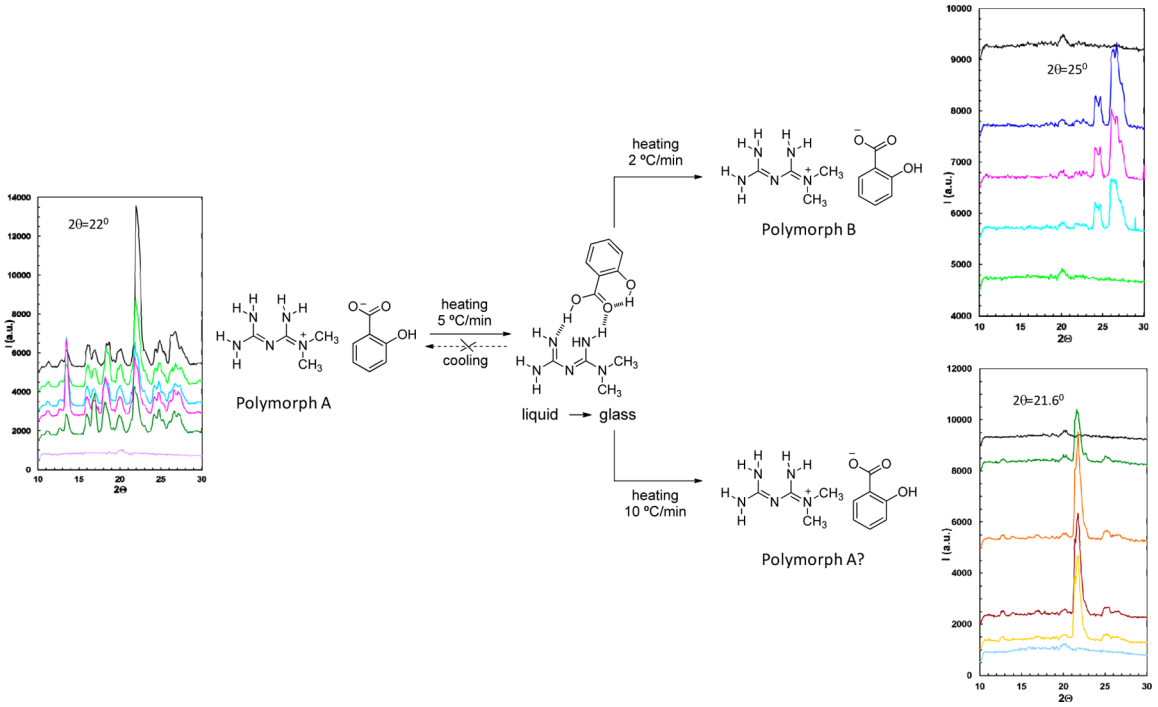

Figure 11. Metformin salicylate structural changes.

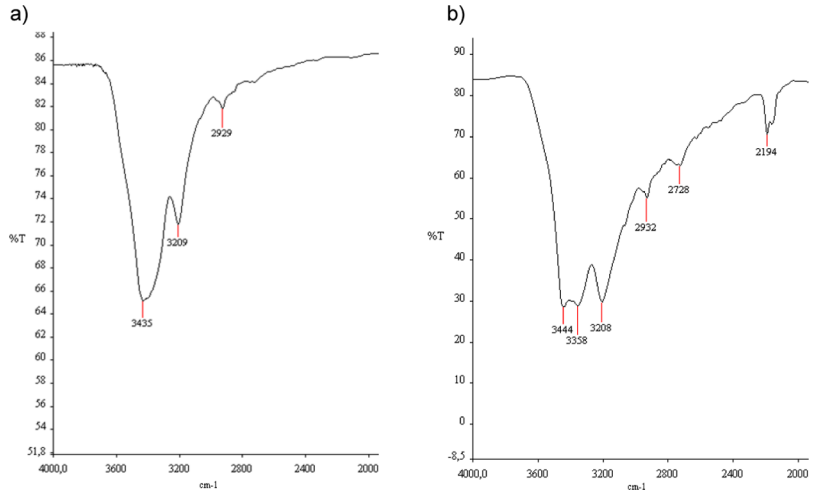

Figure 12. Metformin salicylate IR (4000−2000 cm^{-1}): (a) starting compound, (b) after heating/cooling cycle.

(metastable) in metformin hydrochloride, the transformation conditions being different.[8]

Spectroscopic data from IR experiments support the structure of the liquid/glass states. IR experiments from metformin salicylate before and after the heating/cooling cycle were performed (Figure 12). The broadening of the O−H stretching bands due to the stronger hydrogen-bonded hydroxyl group complex and the peaks shifting suggested a noncharged complex.

As observed in DSC, the WAXS patterns turned out to be very dependent on the heating rate employed (2, 5, or 10 °C·min^{-1}). Heating at 2 °C·min^{-1} gave two main diffraction peaks at 2θ = 25° and 27°, the last one being the predominant. This could correspond to a more compacted crystal rearrangement compared to the original metformin salicylate salt. When the heating rate is 10 °C·min^{-1}, one main diffraction peak is observed at 2θ = 21.6° and could be mimicking a similar 3D rearrangement to the starting metformin salicylate salt.

CONCLUSIONS

The great interest in the properties of compounds resulting from mixing two drugs or their APIs prompted us to study the case of the antidiabetic metformin and the analgesic salicylic acid. This combination could be used, modifying the pharmacokinetics of each component to treat dermatological illnesses. We have characterized by single-crystal X-ray diffraction the structure of metformin salicylate, formed by infinite zigzag layers parallel to the *bc* plane, holding together by N−H···O hydrogen bonds. The evolution of metformin salicylate under heating was studied by DSC and WAXS.

ASSOCIATED CONTENT

Supporting Information

Crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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