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► **To cite this version:**

Nicolas Couvrat, Morgane Sanselme, Manon Poupard, Céline Bensakoun, Simon Drouin, et al.. Solid-State Overview of R-Baclofen: Relative Stability of Forms A, B and C and Characterization of a New Heterosolvate. *Journal of Pharmaceutical Sciences*, 2021, 110 (10), pp.3465-3471. 10.1016/j.xphs.2021.06.018 . hal-03261061

HAL Id: hal-03261061

<https://hal.science/hal-03261061>

Submitted on 16 Oct 2023

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Solid-State Overview of R-Baclofen: Relative Stability of Forms A, B and C and Characterization of a New Heterosolvate

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KEYWORDS: arbaclofen/ R-baclofen, polymorphs, solvate(s), Solid-state stability, Phase diagram(s), Crystallization, Desolvation

ABBREVIATIONS

XRPD: X-Ray Powder Diffraction

DSC: Differential Scanning Calorimetry

TGA: Thermogravimetric Analysis

MS: Mass Spectrometry

DMF: Dimethylformamide

Mp: Melting Point

HEM: High Energy Milling

ABSTRACT

A new polymorphic form (Form C) of enantiopure Baclofen was isolated and characterized. Crystal structures of R-Baclofen Form A and Form C were resolved from powder diffraction data, and cell parameters by profile matching for Form B. The relative stability of these three forms is proposed based on structural data, thermal analyses and solvent-mediated conversions. The experiments highlight the stability order $A < C < B$ at 25 °C (A is the most stable form), whereas above 180°C it would likely be: $C < A < B$ (C being the stable modification). Moreover, a new heterosolvate of the molecule is observed in N,N-DMF/water mixture. This heterosolvate offers a new pathway to isolate pure R-Baclofen Form B provided the lactam impurity does not exceed 3%. Upon mechanical stress Form B tends to evolve to Form C.

INTRODUCTION

Precise knowledge of thermodynamic stability and relationships between different solid phases of an API is a prerequisite to envisage its marketing as a solid form^{1,2}. In case of polymorphism, the identification of the phase stability is indeed a critical parameter. This relative stability is sometimes difficult to characterize, as polymorphs can be concomitant³ with close free energies or phase transitions can be prevented (for compounds with low solubility values⁴ or with high activation energies). In an industrial perspective, specific and robust pathways to isolate either one polymorph or another should be developed⁵. Moreover, the solid-state landscape is often complicated by the presence of hydrates and solvates^{6,7,8,9}. In addition to the thermodynamic stability, it is also important to know the behavior of the different solid phases upon various stresses such as: mechanical and humidity stresses^{10,11,12}. Indeed, the chemical and structural purity¹³ can be jeopardized in case of repetitive stimulations.

Baclofen is a pharmaceutical active ingredient originally produced as a myorelaxant¹⁴, which recently gain interests to prevent alcoholic addiction¹⁵. Nevertheless, the latter usage is still under debate as high dosages should be required to possess efficient action¹⁶. One pathway to limit the dosage without

lowering the activity would result in a 'chiral switch' towards the main active enantiomer: R-Baclofen or Arbaclofen (figure 1a).

By contrast to racemic Baclofen¹⁷, few data about enantiopure Baclofen solid state are reported in the literature. Chang *et al* have reported in 1981 the crystal structures of S and R-Baclofen¹⁸ but they actually considered enantiopure Baclofen hydrochloride and corrected this initial mistake in another publication in 1982¹⁹. In addition to this hydrochloride, the crystal structures of enantiopure Baclofen hydrogen maleate was resolved by Gendron and co-workers²⁰.

The main description of R-Baclofen (as a free aminoacid) solid state deals with a patent from Sumitomo chemical company²¹. This patent details the existence of two crystal forms of R-Baclofen (described as polymorphs): i) Crystal B (the lower melting polymorph, Mp at circa 185°C) which is produced at the end of synthesis process (principally by neutralization of R-Baclofen Hydrochloride with an inorganic base in an aqueous solution) and ii) Crystal A (the higher melting polymorph, Mp at circa 200°C), which is claimed in this patent and described as a polymorph of better stability than Crystal B. Whereas Form A is clearly claimed in this patent, Form B is considered as anticipated in previous papers (detailing R-Baclofen synthesis)^{22,23}.

In this publication, we present the full characterization of a third polymorph: namely Form C. The relative stability of every polymorph will be discussed based on structural and thermal data, as well as pathways to isolate either one polymorph or another. In addition to these anhydrous forms, we also present a new heterosolvate of the molecule with N,N-DMF and water, which offers interesting pathway to recycle the product into a desired polymorphic form. The resilience of Form B to various stresses will be investigated.

MATERIALS AND METHODS

Starting Materials

R-Baclofen was supplied by Seqens company (Porcheville-France) with a chemical purity greater than 98%. Crude R-Baclofen was recrystallized in order to isolate the different polymorphs with the best possible structural purity:

Pure Form A was isolated in Seqens facilities by recrystallization from the hydrochloride salt (10 kg in acid medium) followed by a salting out (with NH₄OH addition, 0.97 equivalent) at temperatures lower than 25°C in presence of n-Butanol as co-solvent (1.5 vol, total volume water+HCl+NH₄OH= 8.25).

Pure Form B was isolated by recrystallization from the sodium salt (circa 1.7g in basic medium) followed by a salting out (with aqueous HCl addition, 4.5 equivalent) at temperatures comprised between 25°C and 45°C in presence of n-Butanol as co-solvent (0.6 vol, total volume water+NaOH+HCl = 12.2).

Pure Form C was isolated by recrystallization from the sodium salt (circa 1.7g in basic medium) followed by a salting out (with aqueous HCl addition, 4.5 equivalent) at temperatures comprised between 25°C and 45°C without any co-solvent (total volume water+NaOH+HCl = 12.2).

Every polymorph isolated by these processes displays a content of lactam impurity <0.05%.

R-Baclofen main impurity (lactam²⁴, see figure 1b) was also supplied by Seqens company with a chemical purity greater than 95%.

X-Ray Diffractometry

X-ray Powder Diffraction

XRPD analyses were performed at room temperature using a D8 Discover diffractometer (Bruker analytic X-ray Systems, Germany) with Bragg-Brentano geometry. The instrument is equipped with a copper anticathode (40 kV, 40 mA, K α radiation ($\lambda = 1.5418 \text{ \AA}$)), and a Lynx Eye linear detectorTM. The diffraction patterns were recorded with a scan rate of 0.04° (2 θ) in the angular range of 3-30° (2 θ), with a counting time of 0.5s per step. Data treatment was performed using Bruker Eva Software release 2018 V. 4.3.0.1.

Crystal structure determination

Data for the crystal structure resolutions were carried out on Bruker diffractometer D8 Discover equipped with a copper source ($\lambda=1.5418\text{\AA}$), divergence slit of 0.1mm (primary optics), and a K β filter (Ni). The detector is a Lynx Eye, with the aperture slit set to 1 mm. Each measurement was performed from 5° up to 90° in 2 theta, with a step size of 0.02°; and an exposure of 1sec per step. The recording pattern was allowed to auto-increment for 10 cycles. The software Biovia - Material studio²⁵ (Dassault System) was used all along the resolution steps, using different programs of the Reflex module. The same protocol was used for the three different sets of data. The cell parameters (based on 20 up to 25 peaks) were determined using the X-Cell program²⁶. The profile parameters and the cell parameters were refined using Pawley refinement²⁷. For each compound, the space group was determined from systematic absence. A molecular model of the compound was implemented in simulated annealing procedure using Powder Solve program²⁸ (15 cycles of 100000 steps, standard parameters) with 4

torsion angles free to rotate. Finally, the best solution of this previous step was used to carry out a Rietveld refinement²⁹ to achieve the crystal structure determination.

Thermal Analysis

Differential Scanning Calorimetry

DSC measurements were performed on a Netzsch DSC 214 Polyma apparatus in aluminum pans with pierced lids. DSC runs were performed with circa 5mg of solid sample and using a heating rate $5 \text{ K}\cdot\text{min}^{-1}$. The atmosphere of the analyses was regulated by a nitrogen flux ($40\text{mL}\cdot\text{min}^{-1}$). The calibration of the DSC in temperature and enthalpy was performed using analytical standards (adamantane, indium, tin, bismuth and zinc). Netzsch Proteus Software V. 7.1.0. was used for data Processing.

Thermogravimetry Analysis

TGA was performed (coupled with DSC measurements) on a Netzsch STA449C apparatus. Approximately 4-5 mg of the sample was used. The samples were heated at a constant heating rate of $5 \text{ K}\cdot\text{min}^{-1}$. The samples were purged with a stream of flowing helium throughout the experiment at $40\text{mL}\cdot\text{min}^{-1}$. Netzsch Proteus Software V. 6.1.0. was used for data Processing.

Mass Spectrometry

MS analyses were performed concomitantly to TGA-DSC analyses with a Mass Spectrometer Netzsch MS 403C Aeolos coupled with the STA449C. The device used a quadrupole QMA200 (measurements all along temperature ranges from 0 to 100 m/Z). The temperature was fixed at 290°C (issue STA 449C, transfer line and analysis chamber).

High Energy Milling

Millings were performed using a planetary mill Fritsch P7. Circa 1g of powder were placed in 80 mL jars in zirconium dioxide, using three ZrO_2 balls of 10 mm \varnothing . In our experiments, the milling couple was fixed at (400, -400) rpm. 99 cycles of milling of 5-minute duration were applied, followed by 5-minute breaks. The effective milling duration was 8.25 hours.

Jet Milling

Jet milling experiments were performed using a Glen Mills device model 00 Jet-O-Mizer, employing compressed nitrogen at 6 bars. Circa 1g of powder sample were fed into the vortex along an engineered tangent circle and accelerates. Recovery of powder sample after micronization (circa 80% yield) was achieved using a cyclone link to an aspirator and a collector bowl.

RESULTS

Structural and thermal characterization of R-Baclofen polymorphic forms.

Every polymorph (A, B and C) can be clearly characterized by its XRPD pattern (figure 2). The thermal behavior of every form was investigated by DSC and thermogravimetric analyses. So far, neither solid-solid transition, nor any thermal phenomenon was recorded prior to the melting/degradation of the samples. A similar thermal degradation occurs upon melting for each polymorph: the departure of one water molecule is recorded due to the formation of the lactam impurity (see figures S1 and S2, supplementary information). These data were confirmed by Temperature Resolved -XRPD, which did not reveal any conversion from one polymorph towards another upon heating (see figure S3, supplementary information).

The melting/degradation phenomenon of the three forms lays within 185°C and 200°C in DSC (heating rate= 5K/min). Form B is the lowest melting polymorph (Onset= 185.4°C), Form A melts at circa 195°C (onset temperature) and Form C has the highest melting point (close to 199°C), see figure 3.

Due to limited solubilities of these forms in most of the usual solvents, no single crystal was obtained. Nevertheless, crystal structure determination by X-Ray Powder Diffraction and Rietveld refinement attempts were carried out. The determination of the profile parameters, cell parameters, and space group was achieved using the program X-Cell. The 20 (up to 25) first peaks were manually selected. The best solution was not the correct one, as the proposed space group was a non-chiral one (the same applied to the three polymorphs). Therefore, the solution with the highest reliability exhibiting a chiral space group was retained. Profile matching refinements led to the following cell parameters and space groups (see Table 1).

A detailed presentation of Forms A and C structure is displayed in SI structural data. The final reliability values after Rietveld refinement of Form B were not satisfying, then only cell parameters are presented in this study.

On the relative stability of R-Baclofen anhydrous forms

According to literature²¹, Form B exhibits a monotropic relationship with Form A. However, Form C was not considered previously and, based on our data, the situation seems to be more ambiguous. Indeed, a first ranking may be established based on the thermal behavior (see figure 3). Since no solid-solid transition takes place upon heating, a classification of the melting/chemical degradation temperature can be performed: 'melting' temperature Form C > 'melting' temperature Form A > 'melting' temperature Form B. Since chemical degradation takes place upon fusion, comparing endotherms enthalpies would be rather meaningless.

By considering crystallographic data, we can classify the polymorphs according to the density rule³⁰. Then at room temperature, Form B ($d = 1.42 \text{ g.cm}^{-3}$) would be more stable than Form A ($d = 1.40 \text{ g.cm}^{-3}$) which would be also more stable than Form C ($d = 1.36 \text{ g.cm}^{-3}$). Nevertheless, it is well-known that this rule suffers from several counter examples, and the differences between couples of forms are 0.06 at their maximum preventing any robust conclusion. As conformations and packings are substantially different, any solid-solid transition path between polymorphic forms should go through a destructive – reconstructive process probably associated with a high activation energy. As a matter of fact, any combination of solid- solid transition has never been observed even after annealing.

Solvent-mediated transformation was thus envisaged to establish a reliable ranking. To ensure water solubility and try to cross-seed suspensions, we assumed that a partial salting in/salting out process may actually take place during the slurring, which could accelerate the solvent-mediated transformation.

It was then decided to perform double-seeding experiments with salting in/salting out process: 100 mg of R-Baclofen were dissolved at room temperature in an equimolar amount of NaOH 0.1M (R-Baclofen forms under these conditions the sodium salt). This preparation was repeated three times. The three solutions were seeded with different solid mixtures: Form A + Form B; Form A + Form C and Form B+ Form C. The seeds remained in suspension in every case. An equimolar amount of HCl 0.1M was poured into the three suspensions. The latter were let under stirring for 24 hours to let the crystallization of R-Baclofen occur. The three suspensions were then filtrated,

and the solids were analyzed by XRPD (figure S4, supplementary information). According to these analyses, the final situations were as followed: Sample 1: Mixture of Form A + Form C (initially A+B); Sample 2: Mixture of Form A + Form C (initially A+C); Sample 3: Form C (initially B+C). Based on above data, it seems that Form B is likely to be metastable compared to Forms A and C at room temperature. Moreover, since its melting/chemical degradation takes place below that of Forms A and C, Form B is probably a monotropic form under room pressure.

Nevertheless, salting in/salting out processes may display kinetic effects which lead to risk of recrystallization of metastable forms, preventing thus an efficient evolution towards thermodynamic equilibrium. To avoid those possible side-effects and to clarify the stability difference between Forms A and C, additional “true” cross-seeding experiments were performed. 500 mg of R-Baclofen were added to 3 mL of water and an equimolar amount of NaOH 0.1M was poured leading to a clear solution (formation of the sodium salt). A mixture comprising 100 mg of Form A and 100 mg of Form C was added to the solution and the resulting suspension was stirred for 72 hours at room temperature. The kinetics of polymorphic interconversion were thus accelerated by the continuous exchange with the relatively high amount of solvated molecules. After filtration, an XRPD analysis revealed the presence of structurally pure Form A (see figure S5, supplementary information), in accordance with the density rule. Despite a rather poor soluble character and close melting points, Forms A and C cannot be considered as concomitant or isoenergetic forms^{3, 31}. Since Form C was highlighted as the highest melting polymorph (see figure 3), they seem to be related by an enantiotropic relationship, Form A being likely stable at room temperature and Form C being likely stable at high temperature, but the transition temperature would be difficult to determine experimentally. Moreover, except density, all recorded data seem to underline the metastable character of Form B compared to the two other polymorphs in the range: room temperature to fusion. Then, the data gives the energetic order $A < C < B$ at 25 °C (A is the most stable form), whereas above 180°C it would likely be $C < A < B$ (C stable modification).

Above any consideration of crystalline phase conversion, it seems that the initial crystallization (from the salting out) would be the decisive step to isolate either Form B or Form A or Form C. Indeed, once R-Baclofen crystallizes, it would be difficult to convert, by slurring, one form into another in a reasonable period of time (without redissolving a significant part of the material by salt formation).

Characterization of a heterosolvate of R-Baclofen with DMF and water

During a solvent screen of R-Baclofen, a solid phase was isolated after filtration of suspension in mixture between N,N-DMF and water. This original crystalline phase (arbitrarily labelled Phase D, see figure 2) was actually proven to be a heterosolvate of N,N-DMF and water, as depicted by TGA-DSC-MS analysis (figure 4).

The desolvation occurred above 80°C (DSC data) and was linked to the concomitant departure of both N,N-DMF and water (see figure 4). After thermal desolvation, the resulting anhydrous phase exhibits a complex endothermic phenomenon (melting/chemical degradation) above 150°C. Based on the mass losses recorded, the stoichiometry of this heterosolvate would likely be: (R-Baclofen)₂/ Water/ N,N-DMF.

Several experiments with different amounts between N,N-DMF and water led to isolate this crystalline phase. The same mass loss was every time recorded by TGA (data not shown), leading to conclude on the heterosolvate nature of phase D (and disproves the possibility of a mixed solvate)³². Moreover, Phase D was never isolated from the pure solvents alone (N,N-DMF and water).

A Temperature Resolved-XRPD experiment performed on Phase D confirmed a transition towards defective Form B between 91°C and 111°C (under static conditions, see figures S6 and S7, supplementary information).

Isolating R-Baclofen Form B by means of desolvation of Phase D and impact of its lactam content on the final form

Starting from Phase D, the solid was soaked in pure water in order to observe a putative evolution towards a new crystalline phase. At room temperature (circa 25°C), whether the initial Phase D was prepared from Form A or B or C, Form B was always isolated after stirring in pure water. This observation confirmed that, at this temperature, Phase D exhibits a non-congruent solubility in water³³, which finally results in Form B aqueous suspension.

In order to confirm this behavior, the isothermal section at 20°C of the ternary system R-Baclofen/ Water/ N,N-DMF was experimentally investigated by preparing suspensions at different compositions and analyses of the solids in suspension by XRPD. Figure 5 displays the experimental ternary section determined from these analyses, which confirms that the heterosolvate exhibits an extended stability domain with an overall poor solubility.

The same experiment was conducted in cold water at 5°C, using In Situ XRD monitoring of phase conversion was performed in the InSituX[®] prototype³⁴. By contrast to the behavior observed at room temperature no evolution was

noticed within 24 hours of continuous stirring at 5°C: phase D remains in suspension (see figure S8, supplementary information).

The impact of the main impurity of R-Baclofen (lactam) was also investigated in order to determine the final form obtained after complete desolvation. A large amount of Phase D was prepared (indifferently from the starting batch: Form B or Form C). Then, the same desolvation process was applied but with different mixtures between Phase D and its lactam. After filtration, the solid was analyzed by XRPD. The different mixtures prepared, and the results obtained by XRPD are collected in table 2. According to these experiments, pure Form B was isolated by desolvation in water up to 3% of lactam impurity. However, at high impurity contents (5% and 10%) pure Form A was isolated from desolvation of Phase D.

This desolvation pathway in water at RT appears more reproducible (to isolate pure metastable Form B) than the one described in experimental section. However, this selective process is strongly impacted by the impurity content.

Impact of mechanical stress on R-Baclofen

On the one hand, structurally pure R-Baclofen Form B was milled using HEM (see materials and methods) under dry conditions. On the other hand, structurally pure R-Baclofen Form B was jet milled under 6 bars of pressure. The solid isolated after circa 8 hours of effective milling, and the solid micronized at 6 bars were both proven to exhibit a mixture between Form B and Form C (figure S9, supplementary material). Form C would thus likely be the steady state of anhydrous R-Baclofen upon mechanical constraints. Even though a polymorphic transition induced by HEM is not a rare phenomenon^{10,35,36,37}, it is less frequent to observe a solid-solid transition by a simple jet-milling. Indeed, the latter process generally preserves the initial crystal structure^{38,39}. Thus the new polymorph described in the present paper (Form C) should also be taken into consideration due to its dynamic stability under mechanical stress.

CONCLUSION

Depending on the initial crystallization conditions, three different polymorphs of R-Baclofen (Forms A, B and C) could be isolated. The crystal structure of forms A and C (achieved from XRPD data), and the cell parameters

determination in Form B case, revealed a putative conformational polymorphism and probably the necessity of a full destructive/reconstructive process to transit from one form to another. Based on: i) these structural data, ii) their close melting points and iii) the overall poor solubility of Baclofen in most solvents, these interconversions are pretty slow. Experiments highlighted a probable enantiotropic relationship between Forms A and C, Form A being the stable form at room temperature. By contrast, Form B is likely to be metastable at any temperature compared to forms A or C under normal pressure. To avoid a recrystallization procedure implying salting in /salting out protocol, a new pathway to structurally pure Form B was found by using the crystallization of a new hetero solvate (DMF and water) followed by soaking in pure water at room temperature. This process is robust provided the amount of lactam remains low. This study also highlights that Form B cannot stand much mechanical stress and partially transforms in Form C even by implementing a simple jet-milling.

AUTHOR CONTRIBUTIONS

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ACKNOWLEDGEMENTS

PCAS Porcheville (Seqens Group) is acknowledged for its financial support of the present study.

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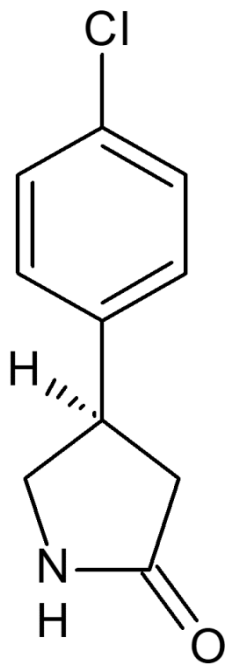
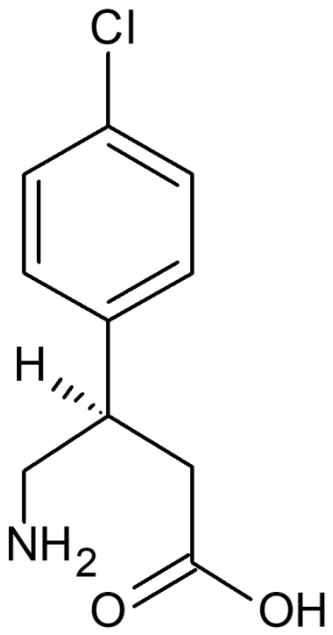


Figure 1. Developed formulae of a) R-Baclofen and b) R-baclofen lactam

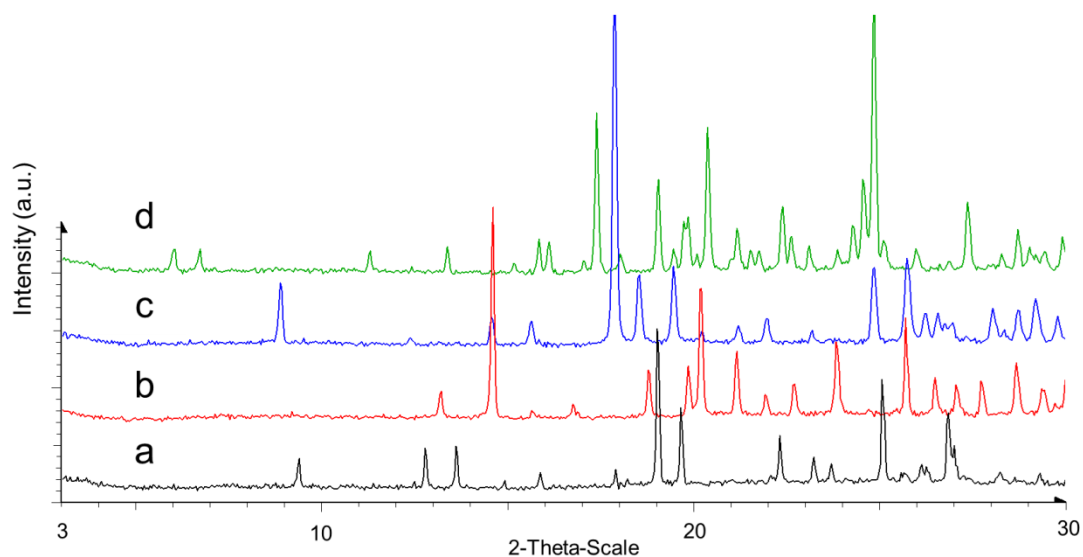


Figure 2: Comparison between XRPD patterns of R-baclofen solid phases: a) Form A, b) Form B, c) Form C and d) new phase isolated in DMF/water (Phase D).

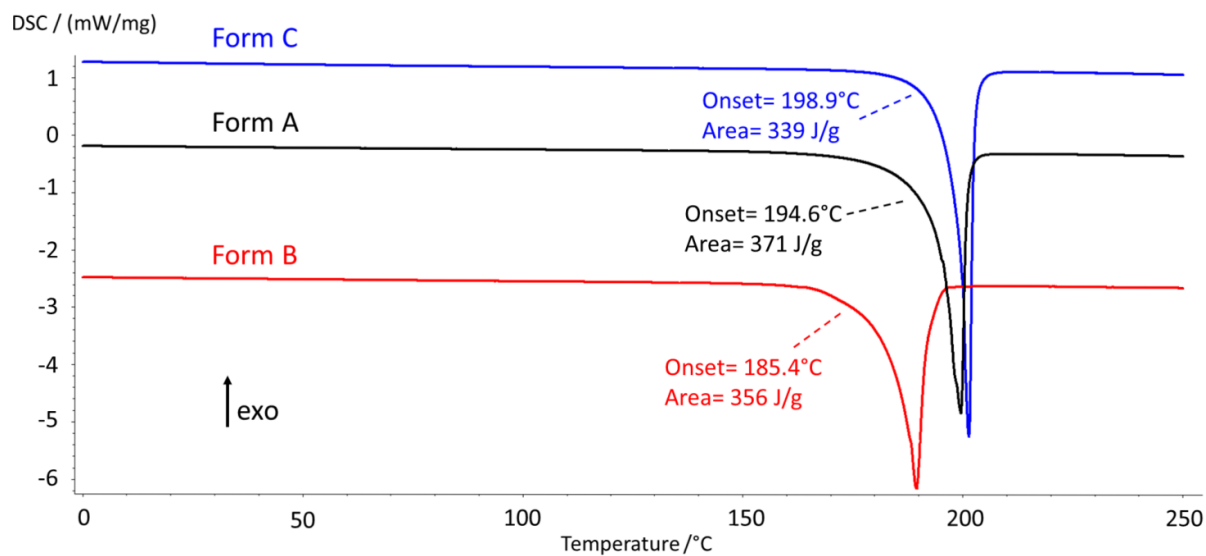


Figure 3: Comparison between DSC scans (heating rate= 5K.min⁻¹) of R-Baclofen polymorphs. Note that the endothermic phenomena observed results from a combination between melting and concomitant water departure/lactam formation.

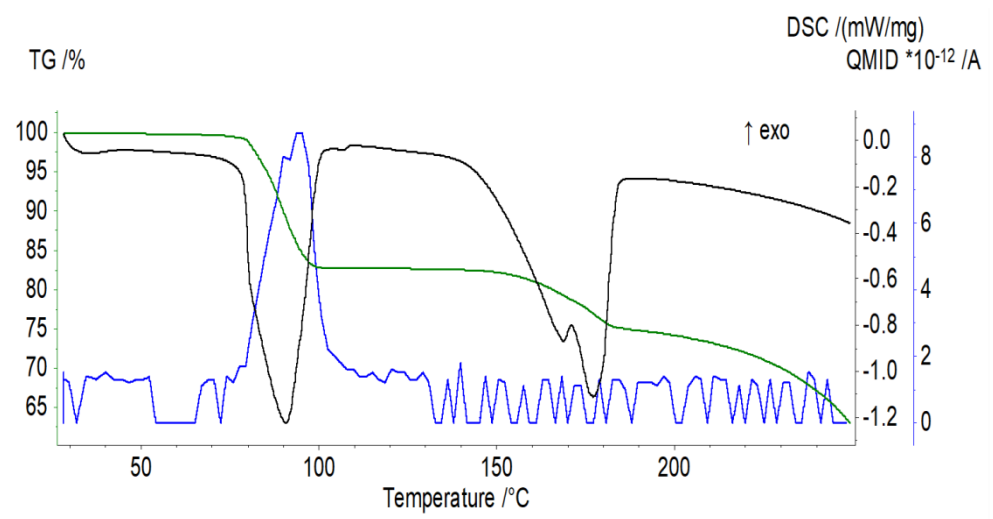
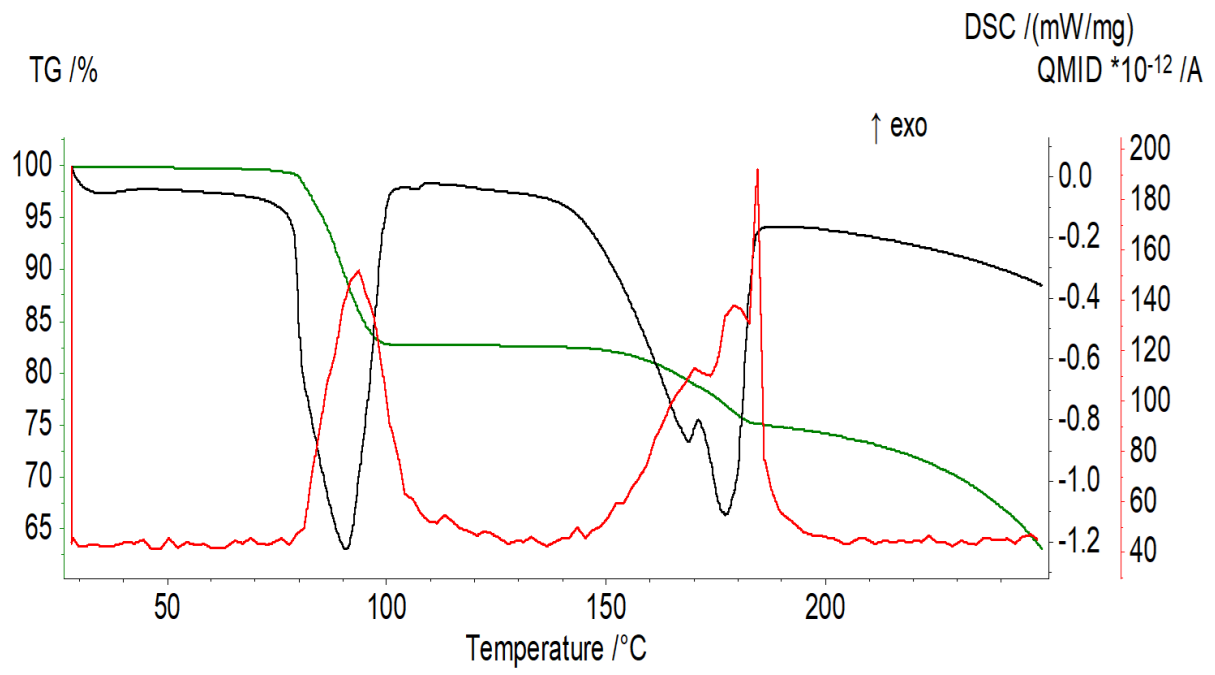
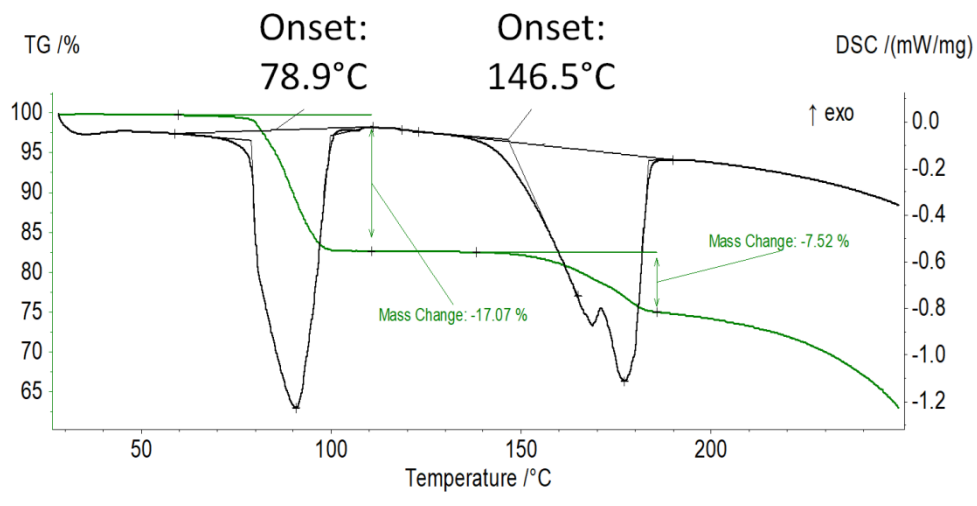


Figure 4: TGA-DSC-MS curves of R-Baclofen Phase D (heating rate= 5K/min): a) TGA-DSC curves with mass losses, b) mass spectrometry curve (QMID) for $m/z= 18$ (molecular peak of water, in red) recorded concomitantly to the TGA-DSC analysis and c) Mass spectrometry curve (QMID) for $m/z= 73$ (molecular peak of N,N-DMF in blue) recorded concomitantly to the TGA-DSC analysis

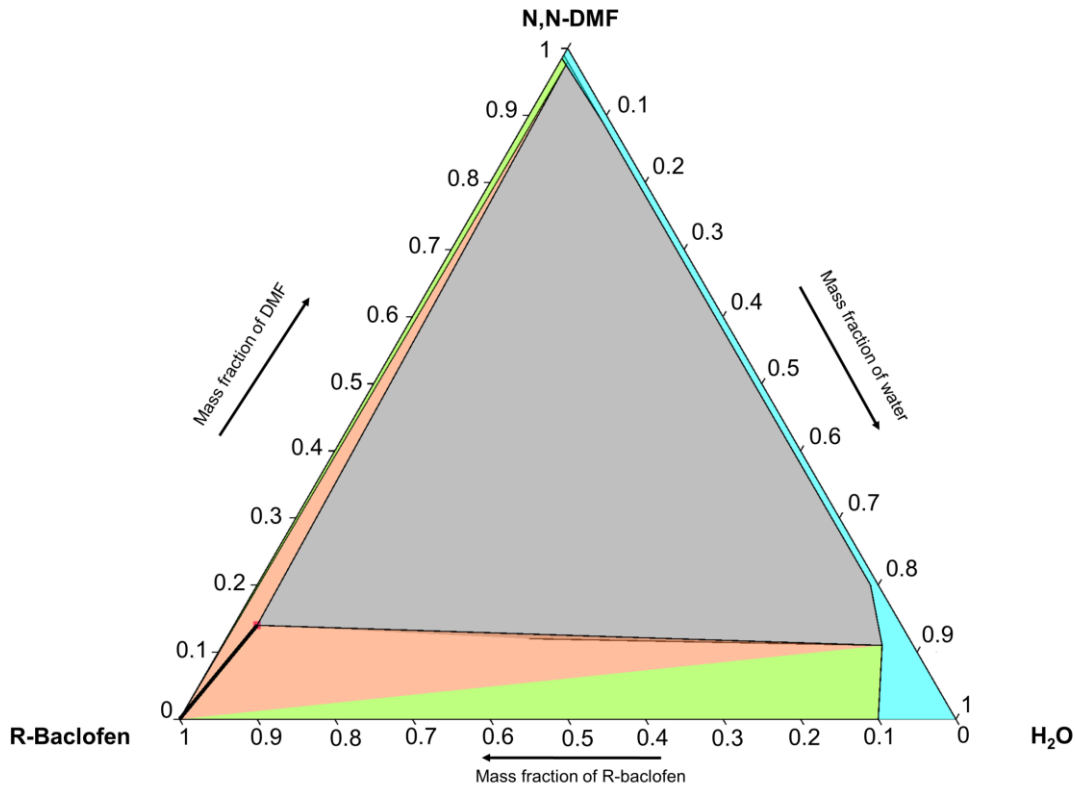


Figure 5: Experimental ternary section at 20°C between R-Baclofen, water and DMF (expressed in mass fraction): Blue domain: under saturated solution, Grey domain: Phase D + saturated solution, Green domains: R-Baclofen Phase B + saturated solution, Pink domains: R-Baclofen Form B + Phase D + polysaturated solution

Table 1: Lattice parameters for the three polymorphic forms of R-Baclofen and final refinement Rwp / Rp values

	Form A	Form B	Form C
CSD reference code	CCDC2038419	-	CCDC2038417
Crystal system	Orthorhombic		
Space group	$P2_12_12$ (n°18)	$P2_12_12_1$ (n°19)	$P2_12_12_1$ (n°19)
Lattice parameters (in Å)	$a=18.937(3)$	$a=24.318(5)$	$a=19.884(1)$
	$b=7.667(1)$	$b=5.831(1)$	$b=7.623(1)$
	$c=6.943(1)$	$c=7.006(1)$	$c=6.844(1)$
Density at RT (in g.cm ⁻³)	1.40	1.42	1.36
2θ range	5 to 90	5 to 60	7 to 90
Number of peaks	1028	-	1086
Number of peaks refined	514	-	543
Final Rietveld Rwp	7.67%	6.56%*	5.91%
Final Rietveld Rp	5.80%	4.96%*	4.56%

*values obtained after Pawley refinement

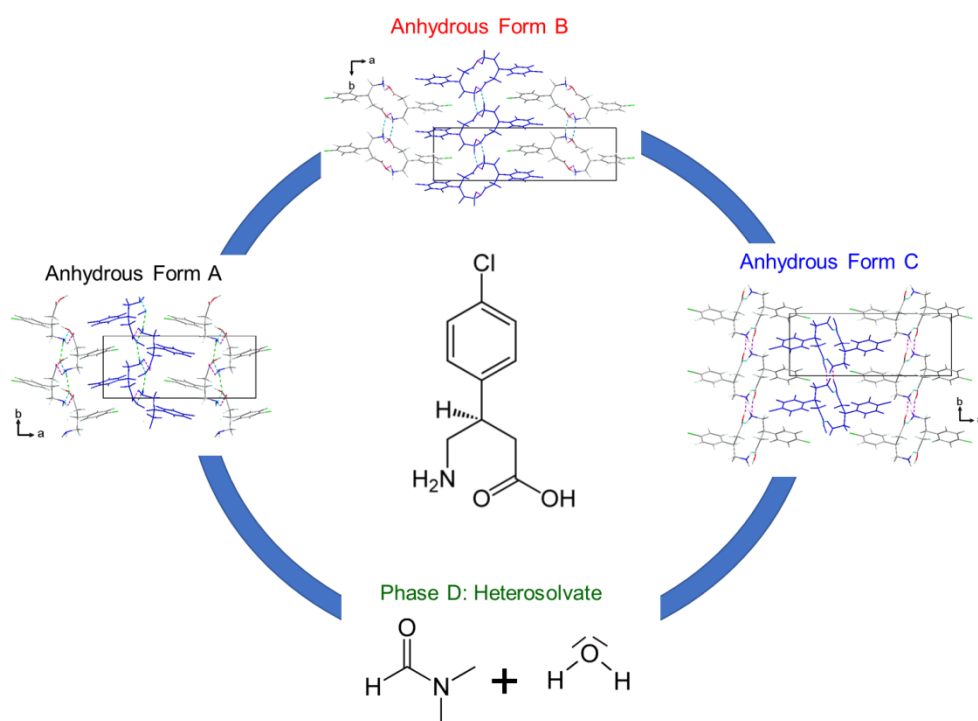
Table 2: Results of desolvation experiments with increasing lactam content

% in mass of Phase D	% in mass of Lactam	Final solid form by XRPD
99.5%	0.5%	Form B
99.4%	0.6%	Form B
99.3%	0.7%	Form B
99.2%	0.8%	Form B
99.1%	0.9%	Form B
99%	1%	Form B
97%	3%	Form B
95%	5%	Form A
90%	10%	Form A

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Graphical Abstract



Highlights

- A new polymorph (Form C) of R-Baclofen was isolated and characterized.
- The relative stability of every R-Baclofen polymorph was established.
- Crystal structures of Forms A and C were solved from Powder-XRPD measurements.
- A new heterosolvate of R-Baclofen with N,N-DMF and water was isolated and characterized. It presents a non-congruent solubility in water at 25°C leading to metastable Form B.
- Mechanical treatments on R-baclofen seems to lead to Form C as steady-state.