Supporting Information

A Lection in Humbleness: Crystallization of chiral and zwitterionic APIs Baclofen and Phenibut

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Table S1. *Overview on results obtained by co-crystallization of Baclofen and Phenibut with co-formers tartaric acid and malic acid from solution in solvent water.*

	D-3	L-3	DL-3	D-4	L-4	DL-4
1	**1:D-3 • H_2O** single crystals	**1:D-3 • H_2O** single crystals	**1:DL-3 • H_2O** single crystals	unreliable, phase mixtures	unreliable, phase mixtures	unreliable, phase mixtures
2	**2:D-3 • H_2O**	**2:L-3 • H_2O** single crystals	**2:DL-3** single crystals	Formation of **2 • H_2O**, phase transition after drying	Formation of **2 • H_2O**, phase transition after drying	Formation of **2 • H_2O**, phase transition after drying

Table S2. *Overview on results obtained by milling co-crystallization of Baclofen and Phenibut with co-formers tartaric acid and malic acid under addition of 10 µL methanol at 25 Hz for 30 minutes.*

	D-3	L-3	DL-3	D-4	L-4	DL-4
1	Possible anhydrous form	Possible anhydrous form	Phase mixture of anhydrous forms **1:L-3**, **1:D-3** and **1:DL-3**	YIPLAN, phase mixture	YIPLAN	YIPLAN
2	**2:D-3 • H_2O**	**2:L-3 • H_2O**, phase mixture with possible anhydrous form	**2:DL-3**	Formation of a new co-system	Formation of a new co-system	Formation of a new co-system

Table S3. *Overview on results obtained by co-crystallization of Baclofen and malic acid in solvent mixtures of ethyl acetate / water and aqueous hexafluoropropan-2-ol. No experiment was carried out with Baclofen and DL-malic acid in aqueous hexaflurorpropan-2-ol.*

	D-4	L-4	DL-4
Ethyl acetate	phase mixtures	phase mixtures	phase mixtures
Hexafluoro-2-propanol	**1:D-4 • H_2O** Single crystals after **1 • H_2O** single crystal formation	**1:L-4 • H_2O** after **1 • H_2O** single crystal formation	-

Table S4. *Overview on preparation and results of different Baclofen:tartaric acid compounds. 0.5 mmol of Baclofen (107 mg) and 0.5 mmol of tartaric acid (75 mg) were used if not specified otherwise.*

Compound	Preparation	Result
1:D-3	Crystallization in aqueous solution	Similar to **1:D-3 • H_2O** but with traces of new phases
1:D-3	LAG with 10 µL methanol	Possible anhydrous phase
1:L-3	Crystallization in aqueous solution	Similar to **1:L-3 • H_2O** but with large amounts of new phases
1:L-3	LAG with 10 µL methanol	Possible anhydrous phase
1:DL-3	Crystallization in aqueous solution	Similar to **1:DL-3 • H_2O**
1:DL-3	LAG with 10 µL methanol	Mixture of **1:DL-3 • H_2O**, **1:D-3 • H_2O**, **1:L-3 • H_2O** and possible anhydrous forms

Table S5. *Overview on preparation and results of different Baclofen:malic acid compounds. 0.5 mmol of Baclofen (107 mg) and 0.5 mmol of malic acid (67 mg) were used if not specified otherwise.*

Compound	Preparation	Result
1 • H_2O	Crystallization in aqueous solution with dissolved molecules of 4 present in solution	SCXRD-quality crystals which decompose to **1** after drying
1:D-4	Crystallization in aqueous hexafluoroisopranol solution, only 0.25 mmol of Baclofen (53 mg) and D-malic acid (34 mg) were used	Similar to **1:D-4 • H_2O**
1:D-4	Crystallization in aqueous solution	Phase mixture of **1:D-4 • H_2O**, **1 • H_2O** and YIPLAN
1:D-4	LAG with 10 µL methanol	Similar to YIPLAN but with slight differences in the powder pattern
1:L-4	Crystallization in aqueous hexafluoroisopranol solution, only 0.25 mmol of Baclofen (53 mg) and L-malic acid (34 mg) were used	Similar to **1:D-4 • H_2O**
1:L-4	Crystallization in aqueous solution	Phase mixture of **1:D-4 • H_2O**, **1 • H_2O** and YIPLAN
1:L-4	LAG with 10 µL methanol	Similar to YIPLAN but with slight differences in the powder pattern
1:DL-4	Crystallization in aqueous solution	Phase mixture of **1**, **1 • H_2O**, **1:D-4 • H_2O** and YIPLAN
1:DL-4	LAG with 10 µL methanol	Similar to YIPLAN with slightly higher crystallinity compared to samples with enantiomerically pure 4 molecules

Table S6. *Overview on preparation and results of different Phenibut:tartaric acid compounds. For the preparation of the compounds, 0.5 mmol of Phenibut (90 mg) and 0.5 mmol of tartaric acid (75 mg) were used if not specified otherwise.*

Compound	Preparation	Results
2:D-3	Crystallization in aqueous solution, 0.75 mmol of Phenibut (134 mg) and D-tartaric acid (113 mg) were used	Similar to **2:L-3 • H_2O** with slight amounts of other phases
2:D-3	LAG with 10 µL methanol	Similar to **2:L-3 • H_2O** with amounts of other phases
2:L-3	Crystallization in aqueous solution, 0.75 mmol of Phenibut (134 mg) and D-tartaric acid (113 mg) were used	Similar to **2:L-3 • H_2O** with slight amounts of other phases
2:L-3	LAG with 10 µL methanol	Phase mixture of **2:L-3 • H_2O** and possible anhydrous phase
2:DL-3	Crystallization in aqueous solution	Similar to **2:DL-3**
2:DL-3	LAG with 10 µL methanol	Similar to **2:DL-3**

Table S7. *Overview on preparation and results of different Phenibut:malic acid compounds. For the preparation of the compounds, 0.5 mmol of Phenibut (90 mg) and 0.5 mmol of malic acid (67 mg) were used if not specified otherwise.*

Compound	Preparation	Result
2 • H_2O	Crystallization in aqueous solution with dissolved molecules of **4**	SCXRD-quality crystals which decompose to **2** after drying
2:D-4	Crystallization in aqueous solution	Similar to **2 • H_2O**, phase transition after drying
2:D-4	LAG with 10 µL methanol	Formation of new phases
2:L-4	Crystallization in aqueous solution	Similar to **2 • H_2O**, phase transition after drying
2:L-4	LAG with 10 µL methanol	Formation of new phases
2:DL-4	Crystallization in aqueous solution	Similar to **2 • H_2O**, phase transition after drying
2:DL-4	LAG with 10 µL methanol	Formation of new phases

PXRD and DSC Data Overview

PXRDs of Baclofen:L-tartaric acid hydrate samples are shown in **Figure S1**. Phase transition of Baclofen:L-tartaric acid hydrate occurs quickly after drying of the sample, which can be seen in the differences between the simulated pattern and the recorded pattern of a fresh sample. The pattern recorded after six months for both Baclofen:L-tartaric acid hydrate and Baclofen:D-tartaric acid hydrate share good agreement with the milling, vacuum dried and DSC patterns of said substances.

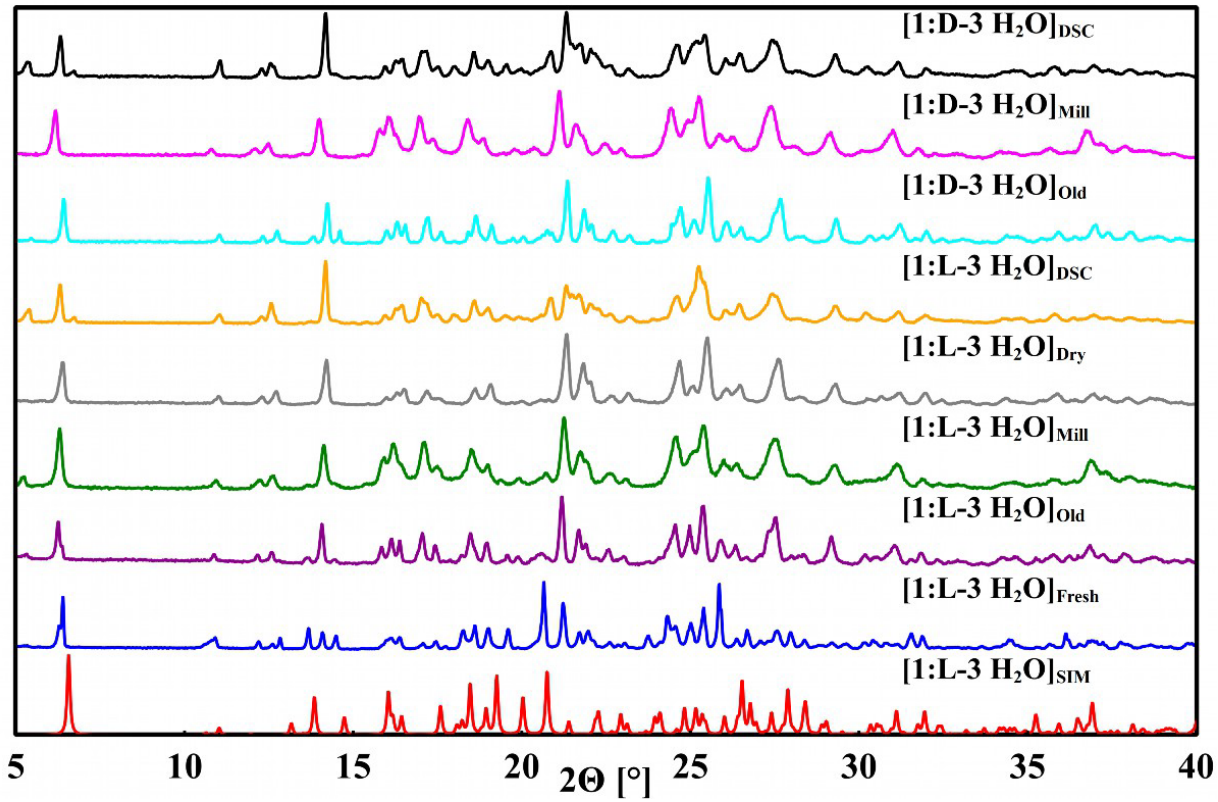

Figure S1. *Recorded powder patterns of Baclofen: tartaric acid systems under different conditions in a range from 5°-40° 2Θ: (blue) a fresh sample of* ***1:L-3 • H2O****, shortly after crystallization, (purple) a sample of the same substance after six months, (green) LAG sample of Baclofen and L-tartaric acid, (grey) a vacuum dried sample of* ***1:L-3 • H2O****,(orange) after heating a fresh sample of* ***1:L-3 • H2O*** *in a DSC chamber to 140 °C and subsequent cooling before melting occurs, (cyan)* ***1:D-3 • H2O*** *after six months, (magenta) LAG sample of Baclofen and D-tartaric, (black) after heating a fresh sample* ***1:D-3 • H2O*** *in a DSC chamber to 140 °C and subsequent cooling before melting occurs. Simulated pattern of* ***1:L-3 • H2O*** *hydrate is shown in red.*

Figure S2 shows that heating of a sample of Baclofen:DL-tartaric acid received by milling crystallization leads to small changes in the powder pattern and a slightly higher resolution of the occurring reflections.

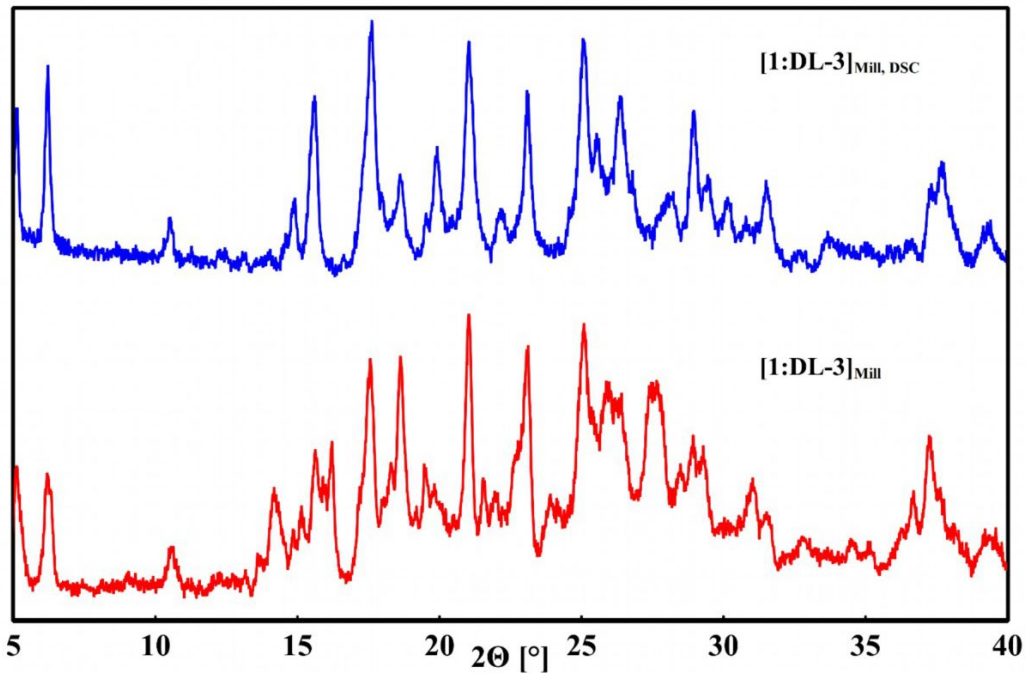

Figure S2. *Recorded powder patterns of Baclofen:DL-tartaric acid under different conditions in a range from 5°-40° 2Θ. Baclofen and DL-tartaric acid sample after a methanol-assisted grinding (red) and the same sample after heating in a DSC chamber to 115 °C and subsequent cooling before melting occurs (blue).*

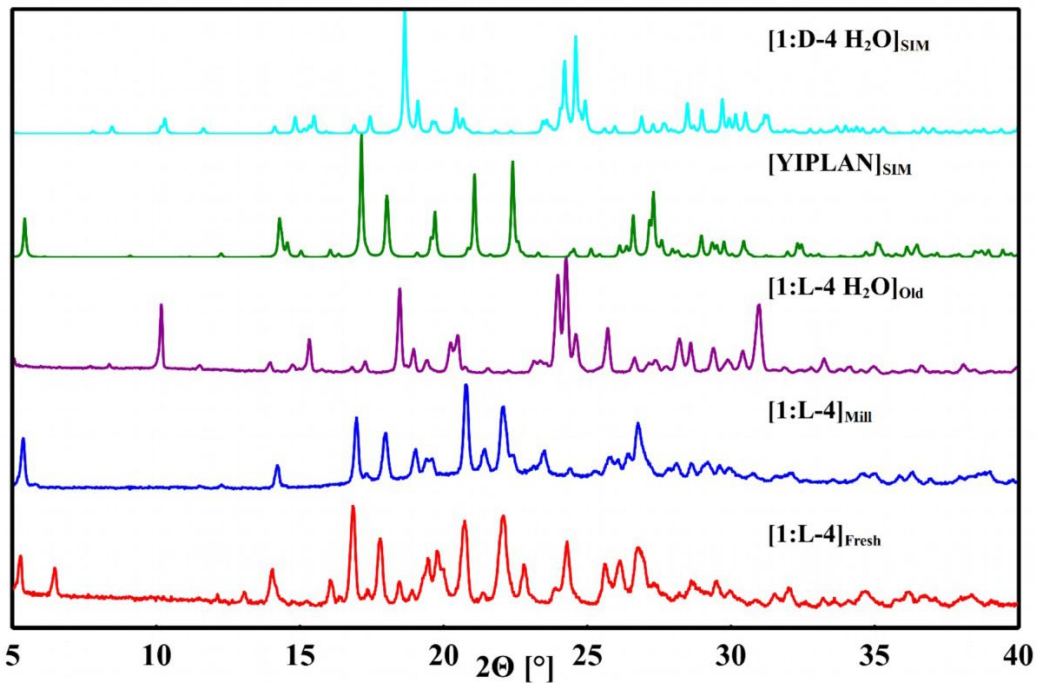

Figure S3. *Recorded powder patterns of Baclofen:malic acid systems in a range from from 5°-40°2Θ: (red) sample of Baclofen and L-malic acid a few days after crystallization occurs; (blue) LAG sample of Baclofen and L-malic acid; (purple)* ***1:L-4 • H2O*** *obtained from hexafluoro-2-propanol solution contaminated with water six months after crystallization occurs; (green) simulated from single crystal data provided by Córdova-Villanueva et al.[50] (Cambridge Crystal Structure Database Ref. Code YIPLAN) and (cyan) simulated pattern of* ***1:D-4 • H2O*** *from collected single crystals data.*

The red pattern in **Figure S3** is in a good agreement with the blue pattern received by milling crystallization of Baclofen and L-malic acid under addition of 10 µL methanol at 25 Hz for 30 minutes as well as the simulated YIPLAN pattern but shows more reflections than both other patterns, which hints at a received phase mixture.

The purple pattern in **Figure S4** shares signals with the simulated patterns of Baclofen hydrate, Baclofen:D-malic acid hydrate and the YIPLAN pattern which leads to the conclusion, that the received phase is made up of a phase mixture of the named substances. The green and the cyan pattern are in good agreement with each other and both are phase mixtures consisting of Baclofen, Baclofen:L-malic acid hydrate and Baclofen hydrate. The pattern of the vacuum dried sample is amorphous, but the signals are in good agreement with the YIPLAN structure.

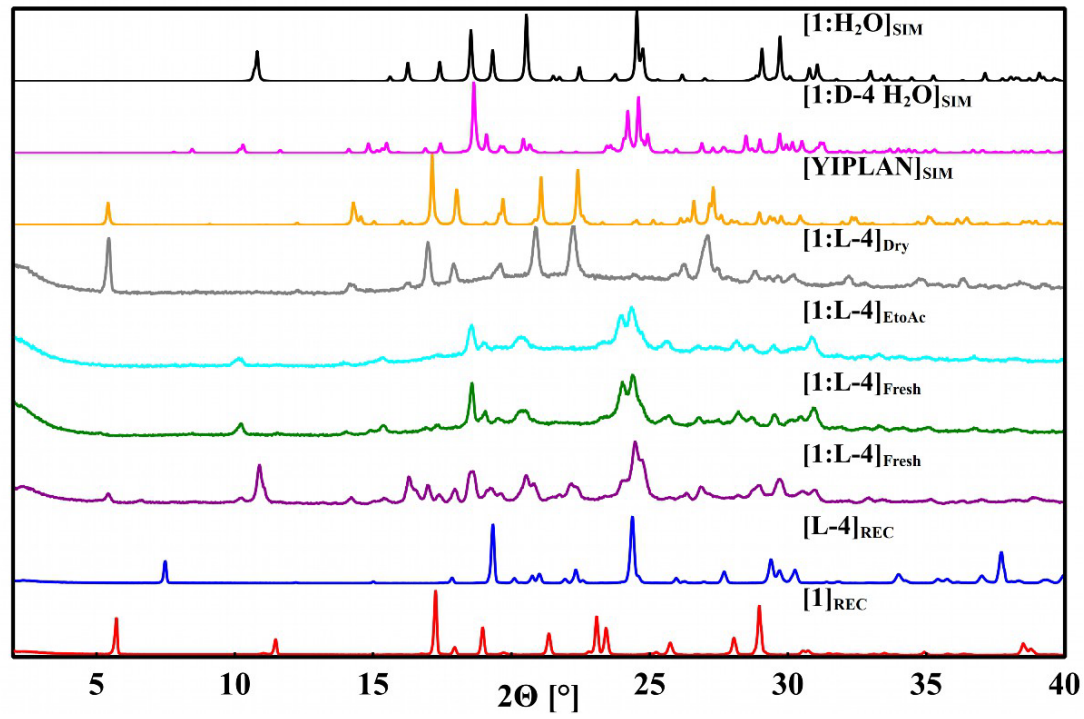

Figure S4. *Overview on some recorded patterns of phase mixtures received by co-crystallization of Baclofen and L-malic acid under different conditions in a range from 2°-40° 2Θ: (red) Baclofen; (blue) L-malic acid; (purple) and (green) both samples of Baclofen and L-malic acid shortly after crystallization occurs; (cyan)* ***1:L-4*** *sample received from a solvent mixture of ethyl acetate and water shortly after crystallization occurs; (grey) a vacuum dried sample of* ***1:L-4****. Simulated powder patterns from single crystal data provided by Córdova-Villanueva et al.[50] (CCDC Ref. Code YIPLAN) (orange), from single crystal data of* ***1:D-4 • H2O*** *(magenta) and from single crystal data of* ***1 • H2O*** *(black) are given for comparison.*

The purple pattern in **Figure S5** shows large similarities to the patterns of Baclofen, Baclofen:D-malic acid hydrate and Baclofen hydrate. The green pattern shows similar signals as the YIPLAN pattern, Baclofen:D-malic acid hydrate and Baclofen hydrate. By comparing the cyan pattern to the recorded Baclofen pattern, it can be seen that heating of Baclofen:D-malic acid hydrate leads to decomposition of the sample to a highly amorphous Baclofen sample.

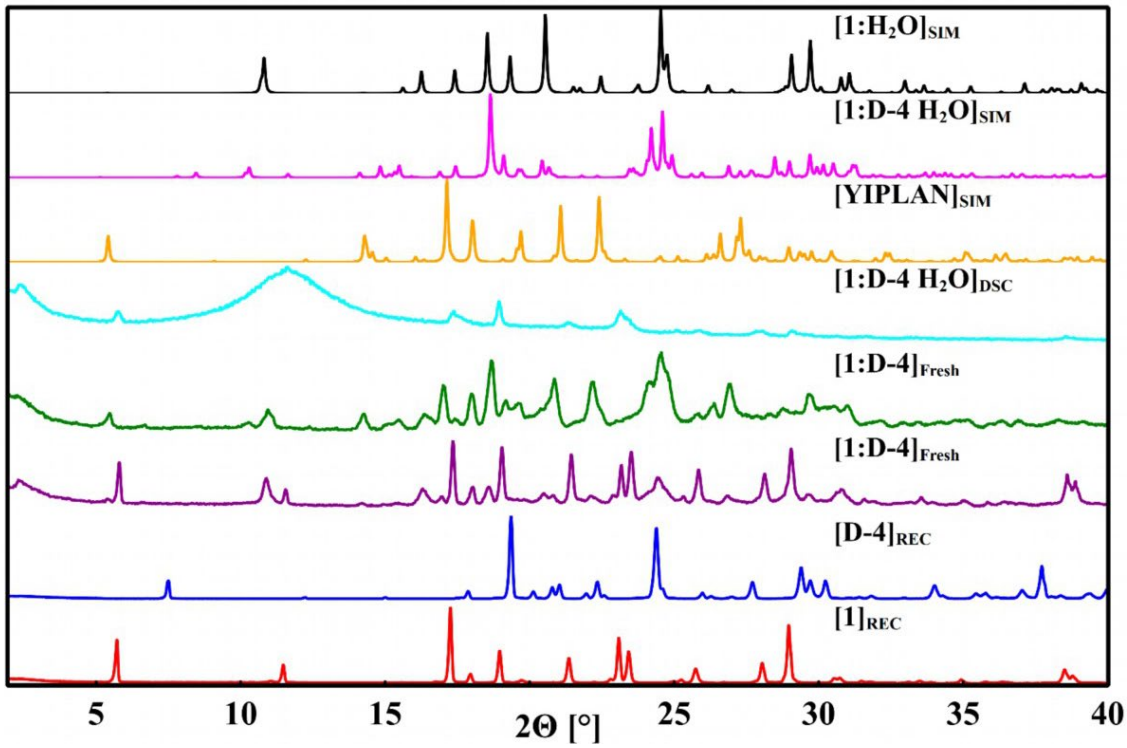

Figure S5. *Recorded patterns of Baclofen:D-malic acid systems under different conditions in a range from 2°-40° 2Θ: Baclofen (red); D-malic acid (blue); different samples of **1:D-4** shortly after crystallization occurs (purple and green); **1:D-4 • H2O** after heating to 130 °C in a DSC chamber and subsequent cooling before melting (cyan);. simulated from single crystal data provided by Córdova-Villanueva et al.[50] (CCDC Ref. Code YIPLAN) (orange);. simulated from single crystal data of **1:D-4 • H2O** (magenta) and of **1 • H2O** (black).*

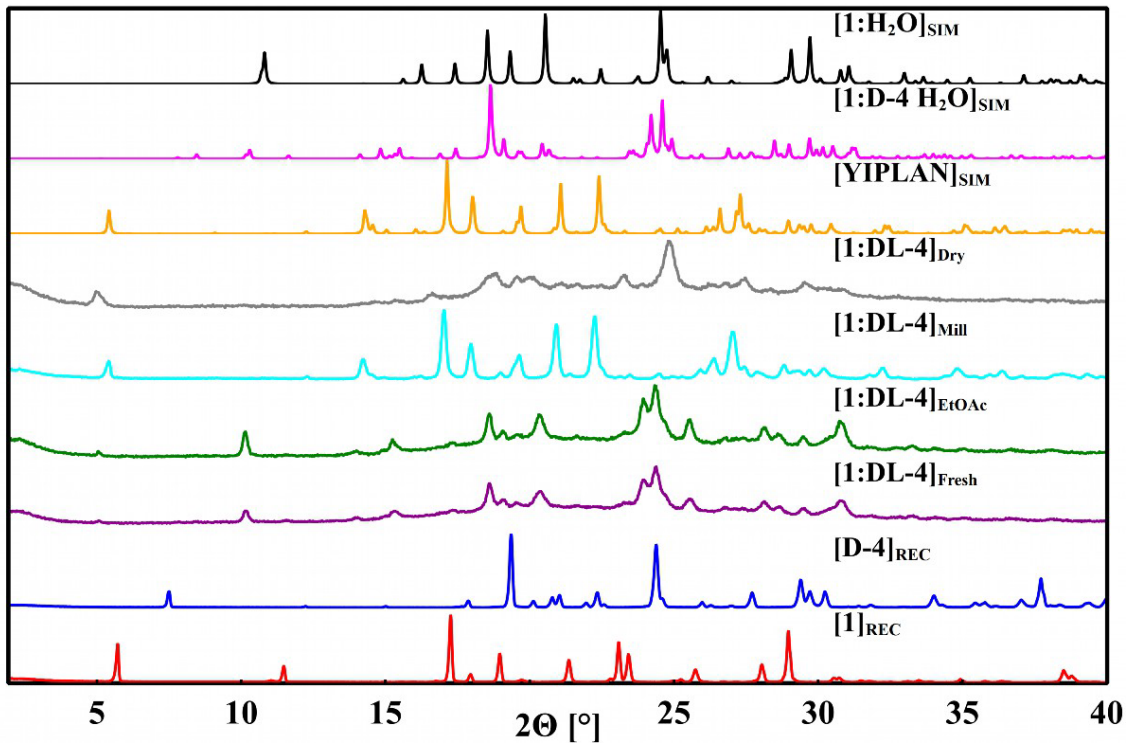

Figure S6. *Recorded powder patterns of systems Baclofen:DL-malic in a range from 2°-40° 2Θ: (red) Baclofen, (blue) D-malic acid; (purple) **1:DL-4** shortly after crystallization, (green) **1:DL-4** from a solvent mixture of ethyl acetate and water; (cyan) LAG sample of Baclofen and DL-malic; (grey) a vacuum dried **1:DL-4**.; (orange) simulated from single crystal data provided by Córdova-Villanueva et al.[45] (CCDC Ref. Code YIPLAN[46]); (magenta) simulated from single crystal data of **1:D-4 • H2O** and (black) simulated from single crystal data of **1 • H2O** .*

Both patterns of Baclofen:DL-malic acid received from aqueous solution presented in **Figure S6** show large similarities to another. Both samples share signals with Baclofen, Baclofen hydrate, Baclofen:D-malic acid hydrate and the YIPLAN pattern, showing that the co-crystallization from solution lead to a phase mixture of named phases. The pattern of Baclofen:DL-malic acid received by milling crystallization is in good agreement with the simulated YIPLAN-pattern, showing that milling crystallization leads to a pure phase. The pattern of the vacuum dried sample shows that this method leads to a new, amorphous phase.

DSC-data in **Figure S7** obtained from the milling products Baclofen:D-malic acid and Baclofen:L-malic acid show the exact same melting signals only distinguishing in different resolutions of the signals recorded.

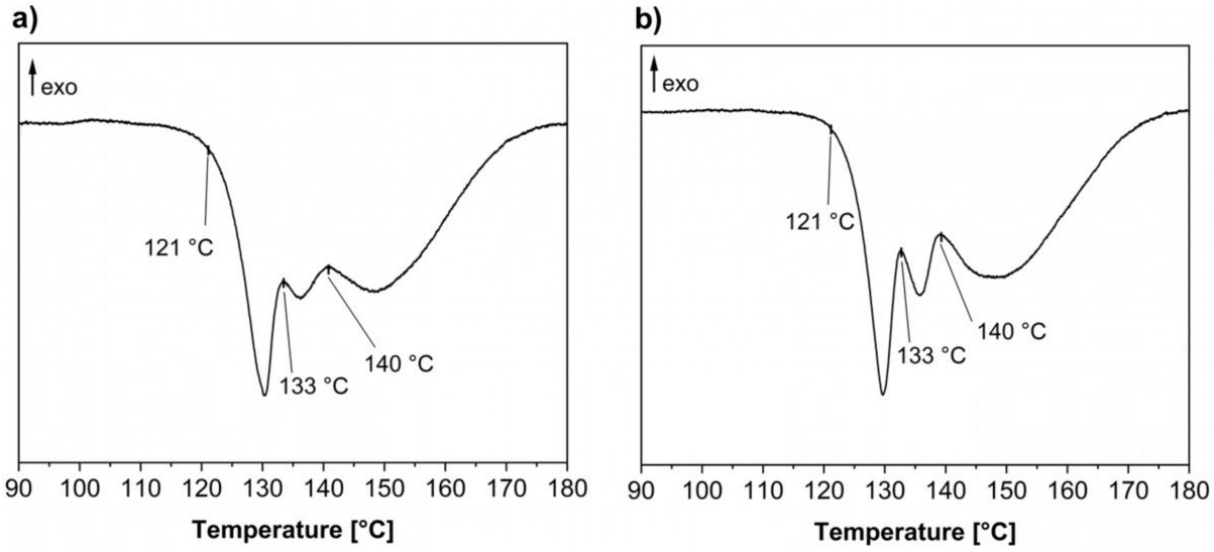

Figure S7. *DSC-data of **1:D-4** (a) and **1:L-4** (b) samples obtained by milling crystallization of Baclofen and D- or L-malic acid under addition of 10 µL methanol at 25 Hz for 30 minutes. DSC was heated at 5 °C min^{-1}, only important temperature ranges are shown for clarity.*

As shown in **Figures S8** and **S9**, the samples produced by crystallization from solution and by milling crystallization are in a good agreement with each other and even with the vacuum dried sample. All samples show strong similarities to the simulated pattern of the Phenibut:L-tartaric acid hydrate, confirming that even by milling crystallization hydrate formation can be observed. It also seems that vacuum drying of the sample does not lead to the formation of an anhydrous system. All three recorded patterns show two signals at about 5.6° 2Θ, which is in contrast to the simulated pattern, leading to the conclusion that phase mixtures were produced with both methods.

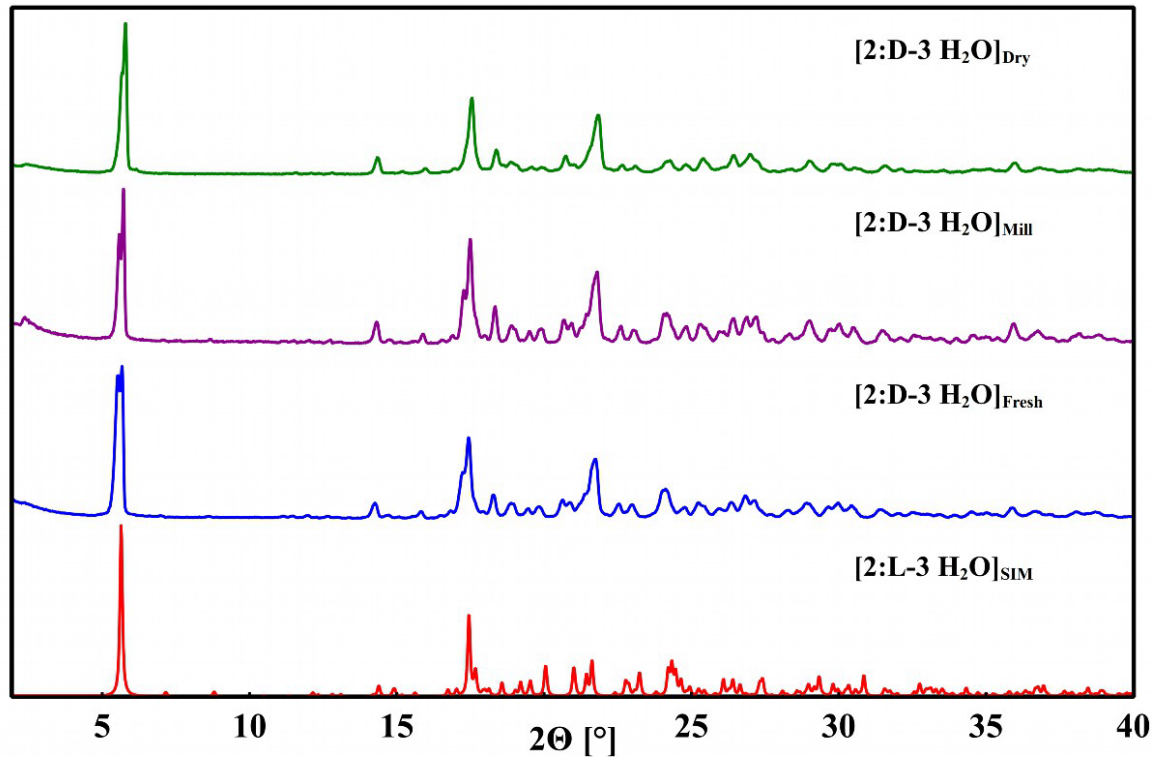

Figure S8. *Recorded powder patterns of Phenibut:tartaric acid systems in a range from 2°-40° 2Θ: (red)* ***2:L-3 • H2O*** *pattern simulated from single crystal data;(blue)* ***2:D-3 • H2O*** *sample shortly after crystallization occurs; (purple) LAG sample of Phenibut and D-tartaric acid; (green) vacuum dried* ***2:D-3 • H2O*** *sample.*

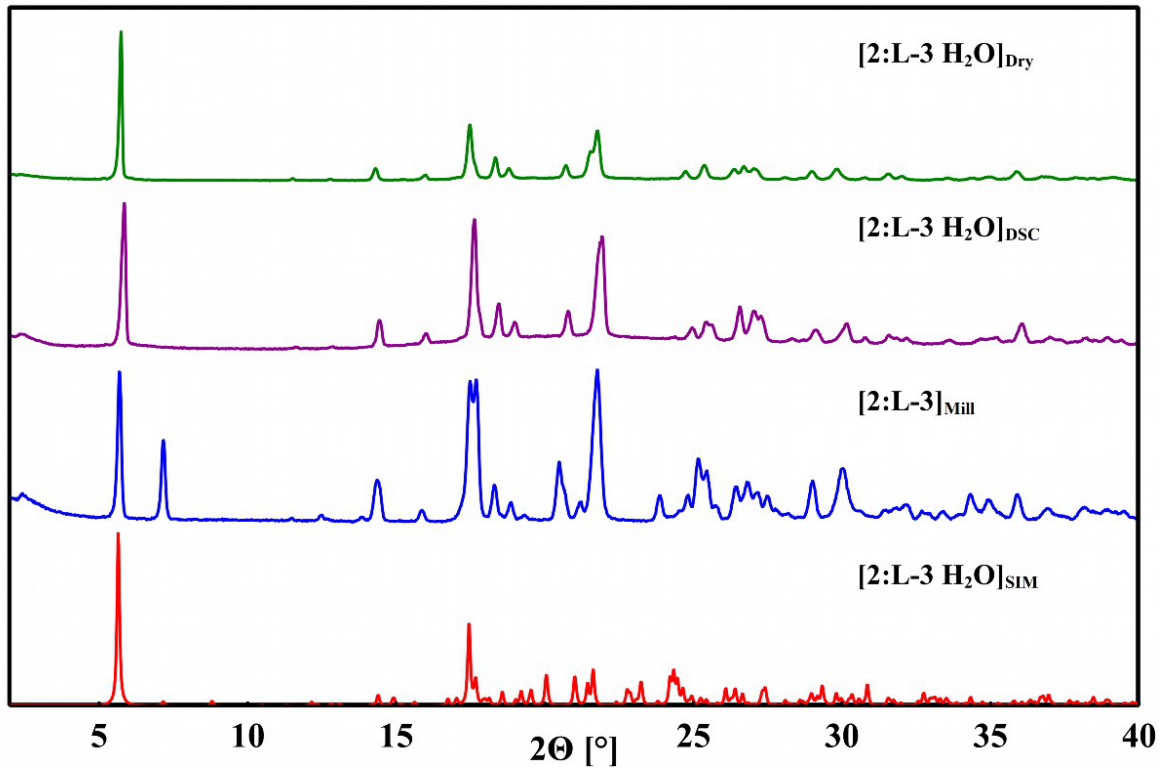

Figure S9. *Further recorded powder patterns of Phenibut:L-tartaric acid systems under different conditions in a range from 2°-40° 2Θ. Simulated pattern from single crystal data of* ***2:L-3 • H2O*** *(red) is compared to an LAG sample of Phenibut and L-tartaric acid (blue),* ***2:L-3 • H2O*** *sample from aqueous solution after heating to 120 °C in a DSC chamber (purple) and a vacuum dried sample of* ***2:L-3 • H2O*** *(green).*

By comparison of the green and the orange pattern in **Figure S10** with the simulated pattern of Phenibut hydrate, it is obvious that in both cases samples of Phenibut hydrate were obtained through co-crystallization from aqueous solution. The purple and the cyan pattern are in good agreement with each other. The purple pattern still has some similarities to the pattern of Phenibut hydrate, showing signals at about 12° and 21.5° which do not occur in the pattern obtained by milling crystallization. The pattern of the vacuum dried sample of Phenibut:L-malic acid shows different signals then all other patterns, showing that vacuum drying lead to a new phase formation. The patter of vacuum dried Phenibut:DL-malic acid is similar to the pattern of pure Phenibut, showing that vacuum drying of this sample leads to decomposition of the Phenibut hydrate obtained from crystallization out of solution.

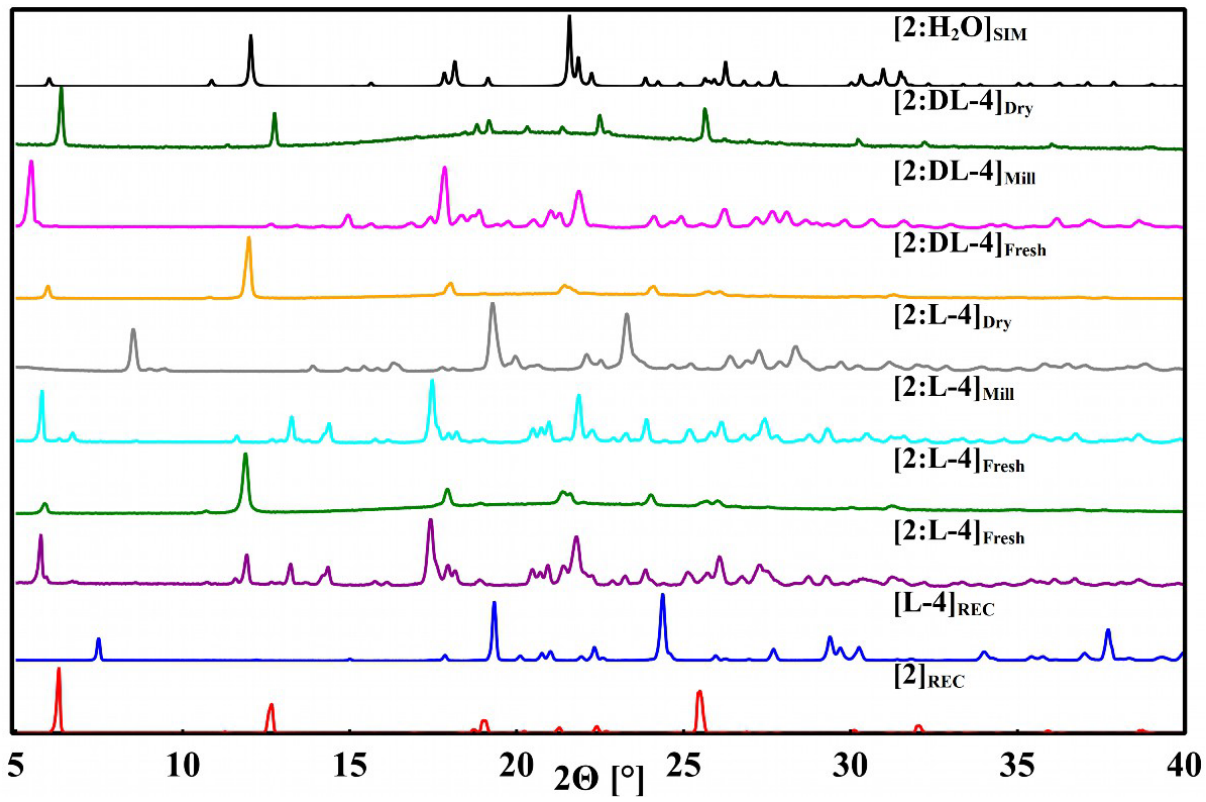

Figure S10. *Recorded powder patterns of Phenibut:malic acid systems under different conditions in a range from 5°-40° 2Θ: (red) Phenibut; (blue) L-malic acid; (purple and green) different samples of* ***2:L-4*** *shortly after crystallization; (cyan) LAG sample of Phenibut and L-malic acid; (grey) a vacuum dried sample of* ***2:L-4****; (orange)* ***2:DL-4*** *shortly after crystallization occurs; (magenta) LAG sample of Phenibut and DL-malic acid; (dark-green) a vacuum dried sample of* ***2:DL-4*** *and (black) simulated pattern from single crystal data of* ***2 • H2O****.*

Infrared Spectroscopy (IR)

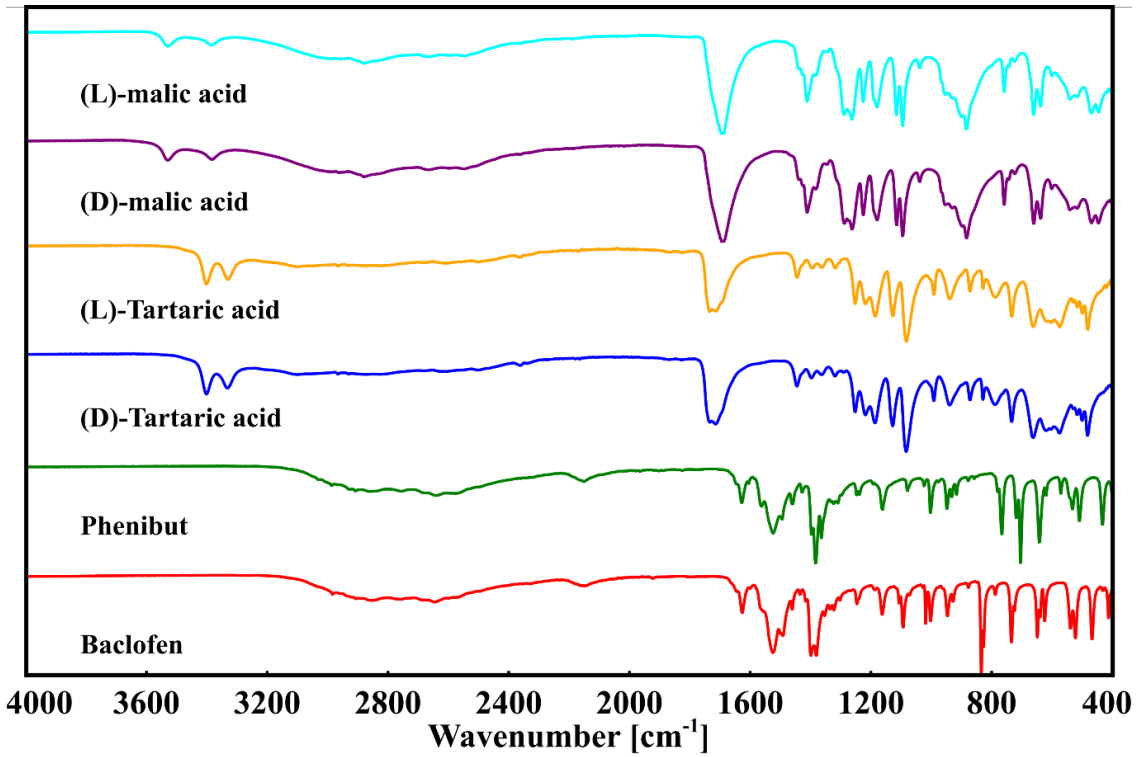

Figure S11. *Recorded IR-spectra of used educts (red) Baclofen, (green) Phenibut, (blue) D-tartaric acid, (orange) L-tartaric acid, (purple) D-malic acid and (cyan) L-malic acid in a range from 4000 cm^{-1} to 400 cm^{-1}.*

Table S8. *Chosen bands corresponding to the carbonyl C=O stretching depicted in* ***Figure S11****.*

Compound	Carbonyl Bands [cm^{-1}]		
1	1646/1625/1602		
2	1646/1627/1607		
D-3	1735/1712		
L-3	1735/1712		
D-4	1696		
L-4	1696		

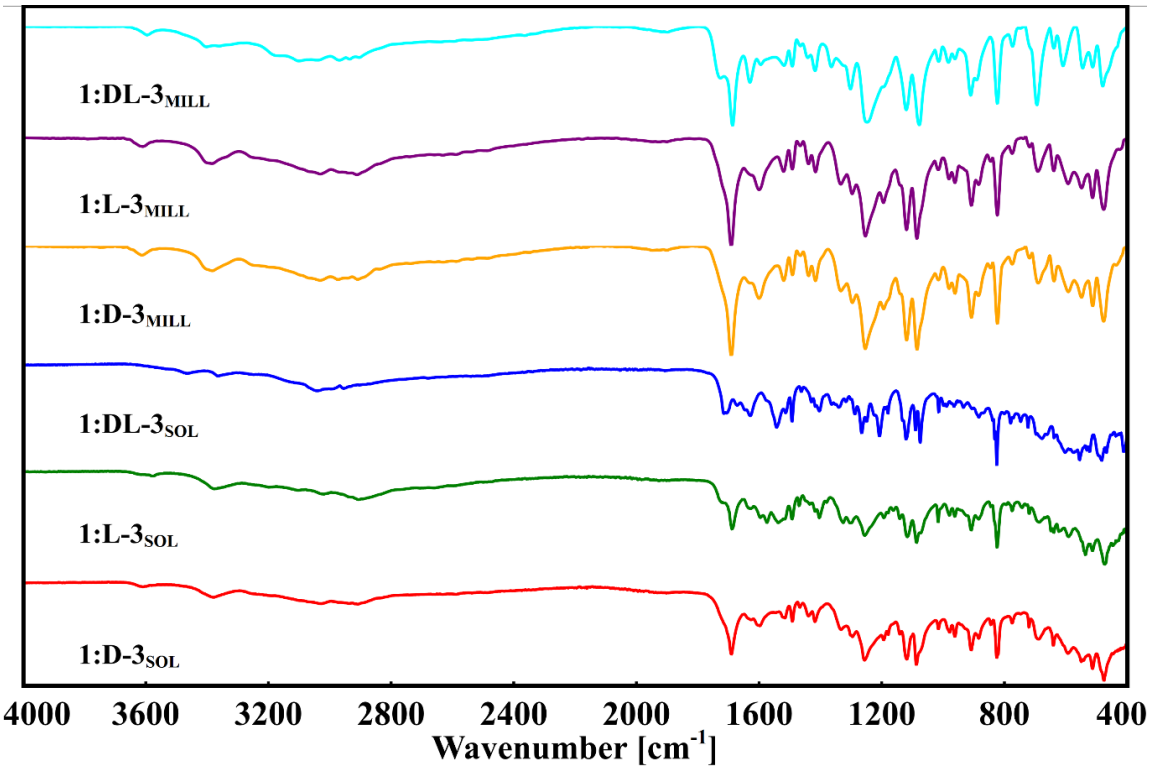

Figure S12. *Recorded IR-spectra of Baclofen:tartaric acid systems under different conditions in a range from 4000 cm^{-1} and 400 cm^{-1}.Samples obtained via crystallization from solution: (red)* ***1:D-3****, (green)* ***1:L-3****, (blue)* ***1:DL-3*** *and samples after methanol-assisted grinding: (orange) Baclofen and D-tartaric acid, (purple) Baclofen and L-tartaric acid, (cyan) Baclofen and DL-tartaric acid.*

Table S9. *Chosen bands corresponding to the carbonyl C=O stretching depicted in* ***Figure S12****.*

Compound	Carbonyl Bands [cm^{-1}]		
1:D-3$_{SOL}$	1723/1691	1626	1599
1:L-3$_{SOL}$	1724/1688	1626	1599
1:DL-3$_{SOL}$	1715/1705	1672	1642/1629
1:D-3$_{MILL}$	1724/1691	1631	1601
1:L-3$_{MILL}$	1723/1691	1631	1601
1:DL-4$_{MILL}$	1727/1687	1630	1595

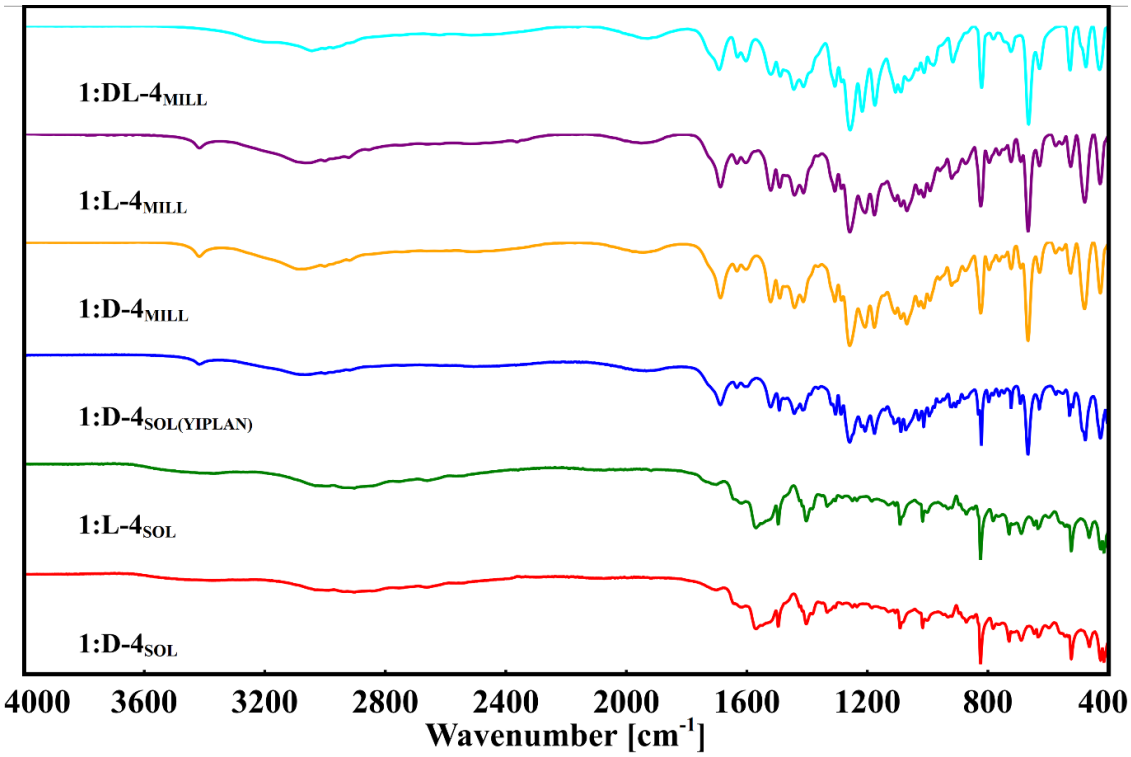

Figure S13. *Recorded IR-spectra of Baclofen:malic acid systems under different conditions in a range from 4000 cm^{-1} and 400 cm^{-1}. Sample s from solution crystallization of **1:D-4 • H_2O** (red), **1:L-4 • H_2O** (green) and of **1:D-4** (blue) which showed similarities to the published YIPLAN structure in its powder pattern. Samples after LAG experiments: (orange) Baclofen and D-malic acid, (purple) Baclofen and L-malic acid, (cyan) Baclofen and DL-malic acid.*

Table S10. *Chosen bands corresponding to the carbonyl C=O stretching depicted in **Figure S13**.*

Compound	Carbonyl Bands [cm^{-1}]		
1:D-4_{SOL}	1706	1646/1617	1599
1:L-4_{SOL}	1706	1646/1623	1599
1:D-$4_{SOL(YIPLAN)}$	1727/1688	1633	1598
1:D-4_{MILL}	1728/1688	1633	1603
1:L-4_{MILL}	1731/1688	1631	1606
1:D4-4_{MILL}	1727/1693	1631	1603

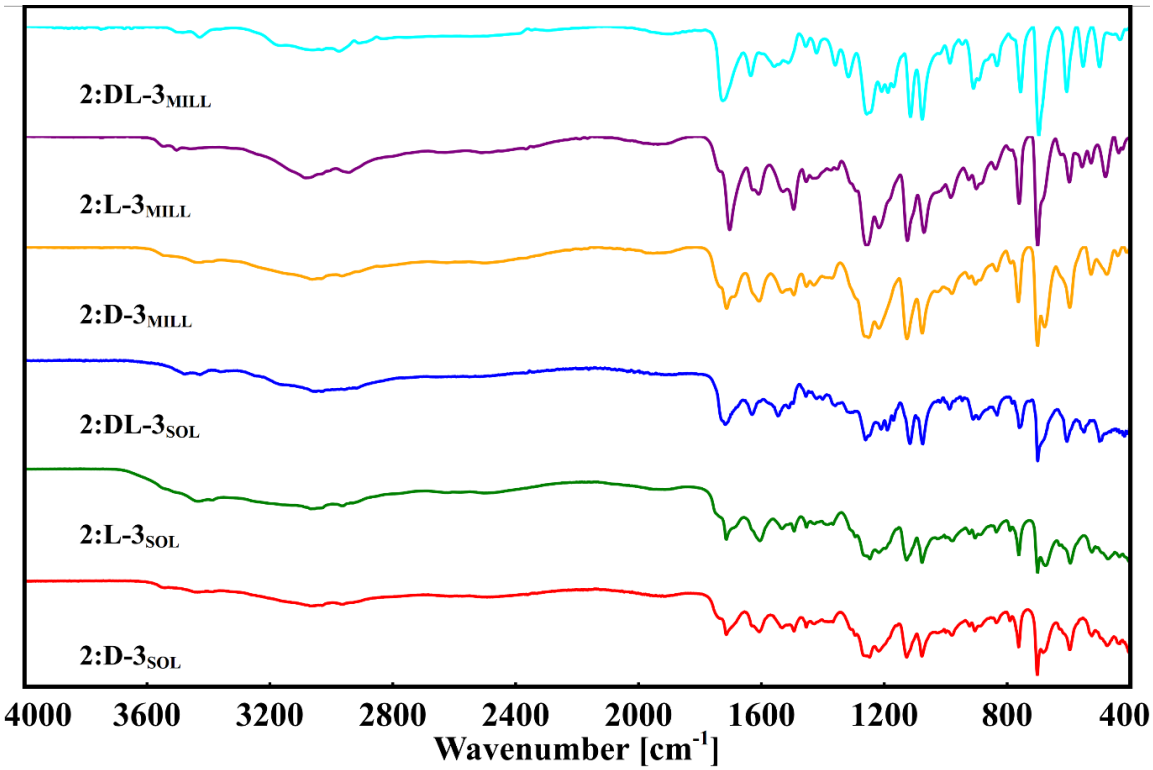

Figure S14. *Recorded IR-spectra of Phenibut:tartaric acid systems under different conditions in a range from 4000 cm^{-1} and 400 cm^{-1}. Samples from solution crystallization: (red)* ***2:D-3****, (green)* ***2:L-3*** *and (blue)* ***2:DL-3****. Samples from LAG with methanol: (orange) Phenibut and D-tartaric acid, (purple) Phenibut and L-tartaric acid and (cyan) Phenibut and DL-tartaric acid.*

Table S11. *Chosen bands corresponding to the carbonyl C=O stretching depicted in* ***Figure S14****.*

Compound	Carbonyl Bands [cm^{-1}]		
2:D-3$_{SOL}$	1743/1715	1631/1608	
2:L-3$_{SOL}$	1745/1715	1631/1605	
2:DL-3$_{SOL}$	1731/1718	1631	
2:D-3$_{MILL}$	1741/1714/1686	1631/1608	
2:L-3$_{MILL}$	1739/1703	1629/1609	
2:DL-4$_{MILL}$	1727	1635	

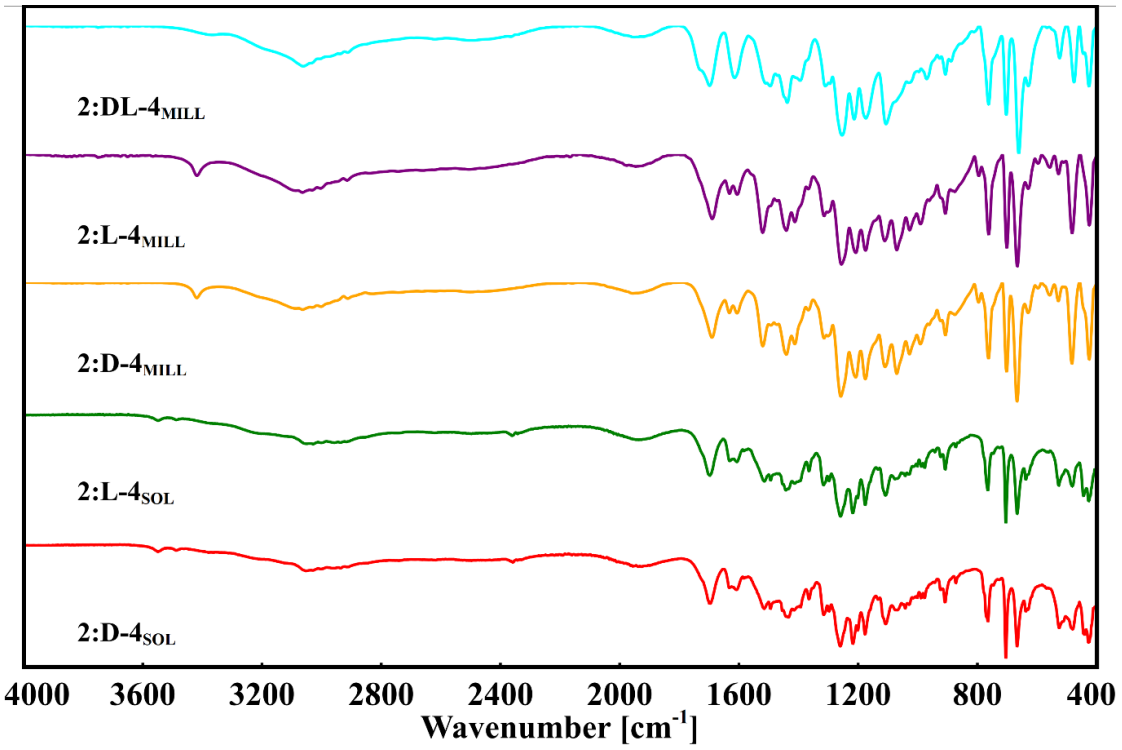

Figure S15. *Recorded IR-spectra of Phenibut:malic acid systems in a range from 4000 cm^{-1} and 400 cm^{-1}. Samples obtained from solution crystallization: (red)* ***2:D-4****, (green)* ***2:L-4*** *and from LAG experiments: (orange) Phenibut and D-malic acid, (purple) Phenibut and L-malic acid, (cyan) Phenibut and DL-malic acid.*

Table S12. *Chosen bands corresponding to the carbonyl C=O stretching depicted in* ***Figure S15****.*

Compound	Carbonyl Bands [cm^{-1}]	
2:D-4$_{SOL}$	1730/1699	1635/1608
2:L-4$_{SOL}$	1727/1698	1631/1607
2:D-4$_{MILL}$	1732/1691	1633/1607
2:L-4$_{MILL}$	1735/1690	1632/1606
2:DL-4$_{MILL}$	1733/1698	1614
2:D-4$_{SOL}$	1730/1699	1635/1608

IR-spectra show that carbonyl vibrational bands in multicomponent systems are multiplied and shifted regarding their positioning. In pure **1** and **2** a triple band at 1646/1625/1602 cm^{-1} and 1646/1627/1607 cm^{-1} is the only discernible carbonyl band. **3** shows a double band in 1735 cm^{-1} and 1712 cm^{-1}. **4** only exhibits a single band in 1696 cm^{-1}. In **1**:**3** systems, at least four signals are present in each system, ranging between 1727 cm^{-1} and 1599 cm^{-1}. As salt hydrates could be characterized by SCXRD in **1:D-3 • H_2O**, **1:L-3 • H_2O** and **1:DL-3 • H_2O**, and similar IR-bands are present in the milling products, it is probable that analogue compounds have formed as well. The same is true for **1**:**4** systems where **1:D-4 • H_2O** was characterized as a salt hydrate. Very similar IR-signals are present in **1:L-4 • H_2O**, and while the other systems show differing signals the splitting is similar. Multicomponent species with **2** exhibit less signals than their **1** counterparts, showing a maximum of two multi-signals each. Again, single crystal analysis of **2:L-3 • H_2O** and **2:DL-3** has revealed a proton transfer and herewith an ionized status of the molecules. The IR analysis indicates this for the other species as well. While no single crystals of **2:4** systems were measured, based on observations on all other species and a similar splitting of IR-bands present as in the previously mentioned compounds, it is highly probable that salts or hydrates of salts were obtained.

Thermogravimetric Analysis (TGA)

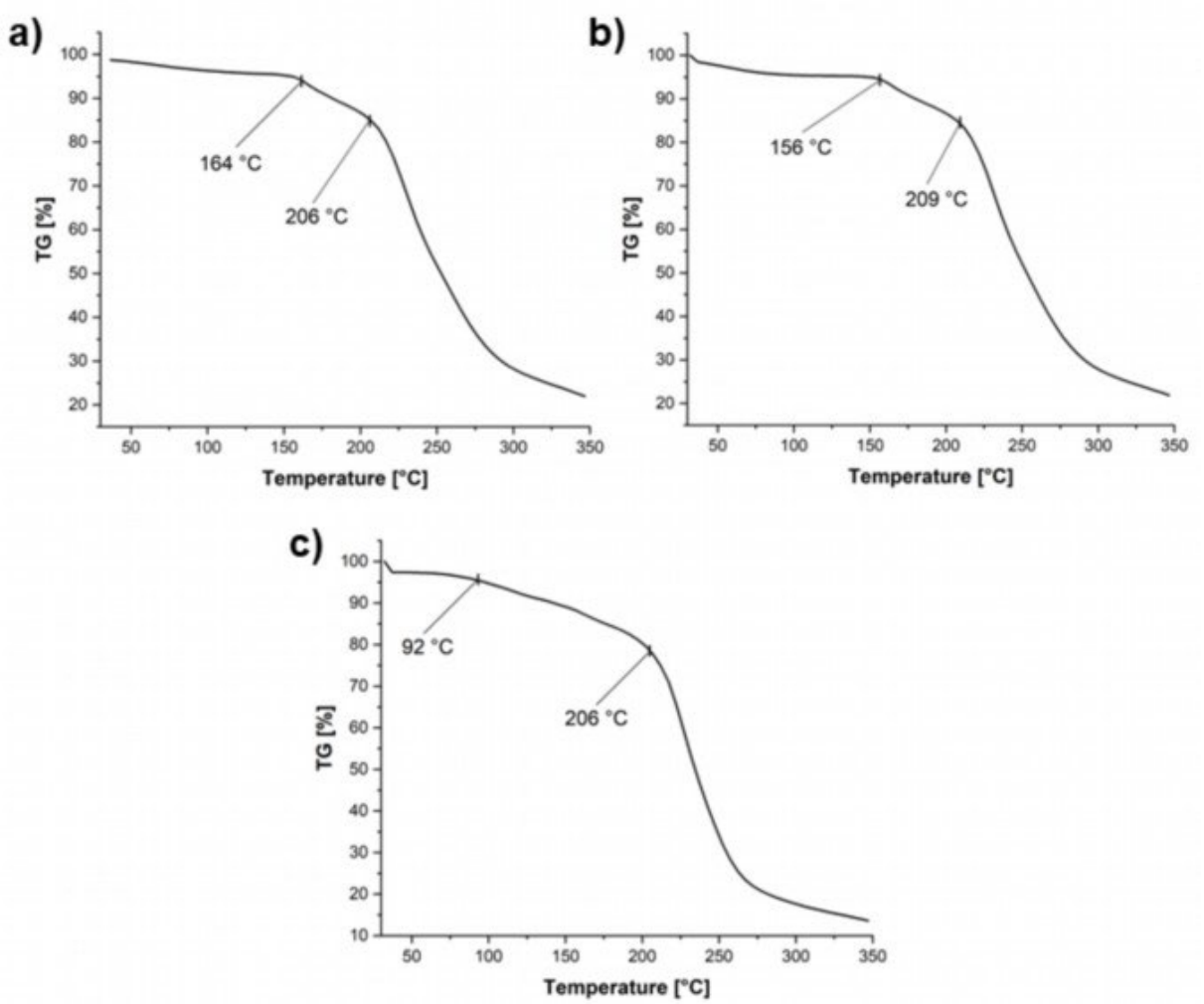

Figure S16. *TGA-data of **1:D-3 • H_2O** (a), **1:L-3 • H_2O** (b) and **1:DL-3 • H_2O** (c). TGA was heated at 10 °C min^{-1} in a range from 30 °C to 350 °C.*

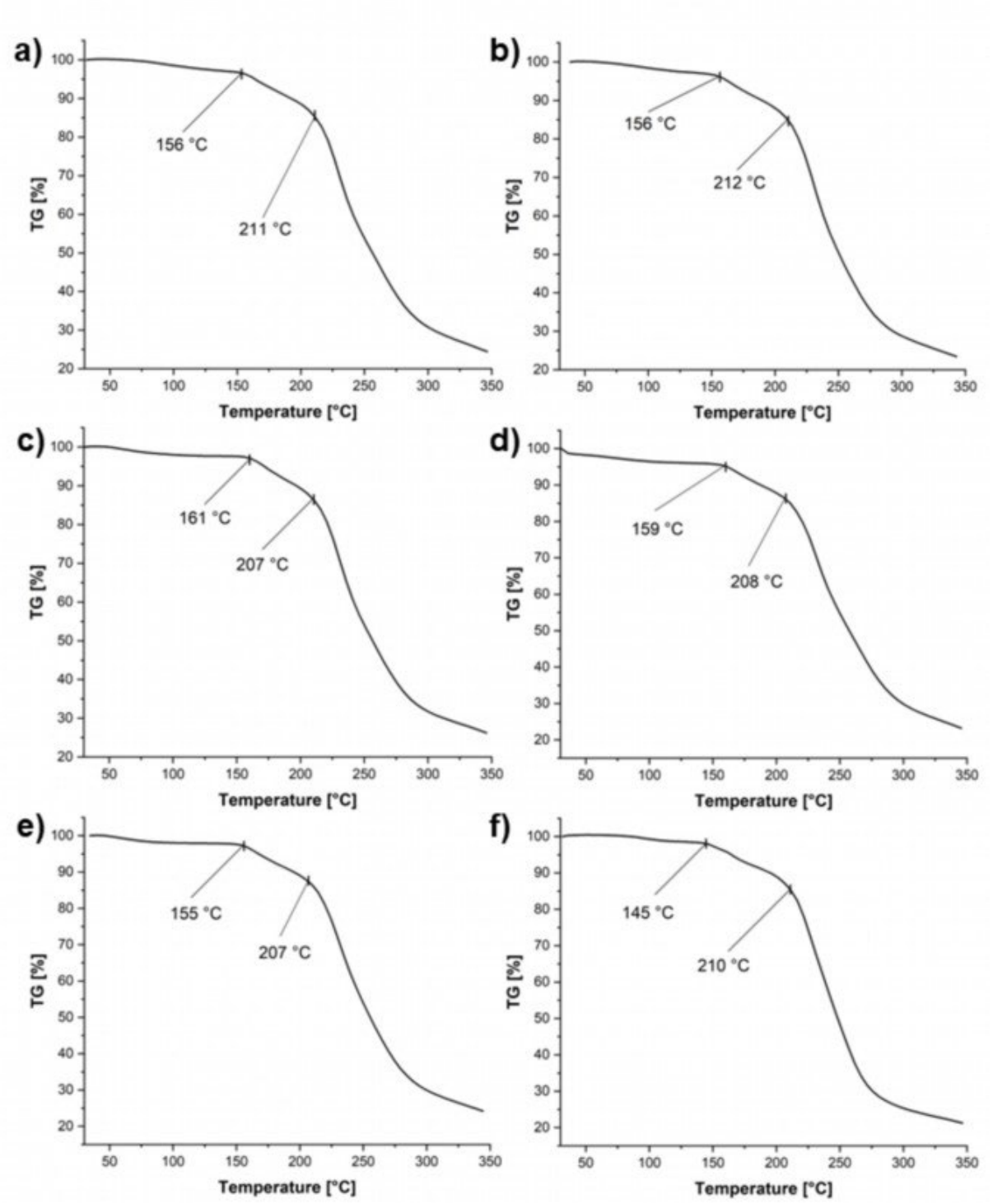

Figure S17. *TGA-data of a LAG sample of Baclofen and D-tartaric acid with methanol (a), a LAG sample of Baclofen and L-tartaric acid with methanol (b), a LAG sample of Baclofen and DL-tartaric acid with methanol (c), a vacuum dried sample of* ***1:D-3 • H_2O*** *(d), a vacuum dried sample of* ***1:L-3 • H_2O*** *(e) and a vacuum dried sample of* ***1:DL-3 • H_2O*** *(f). TGA was heated with 10 °C min^{-1} in a range from 30 °C - 350 °C.*

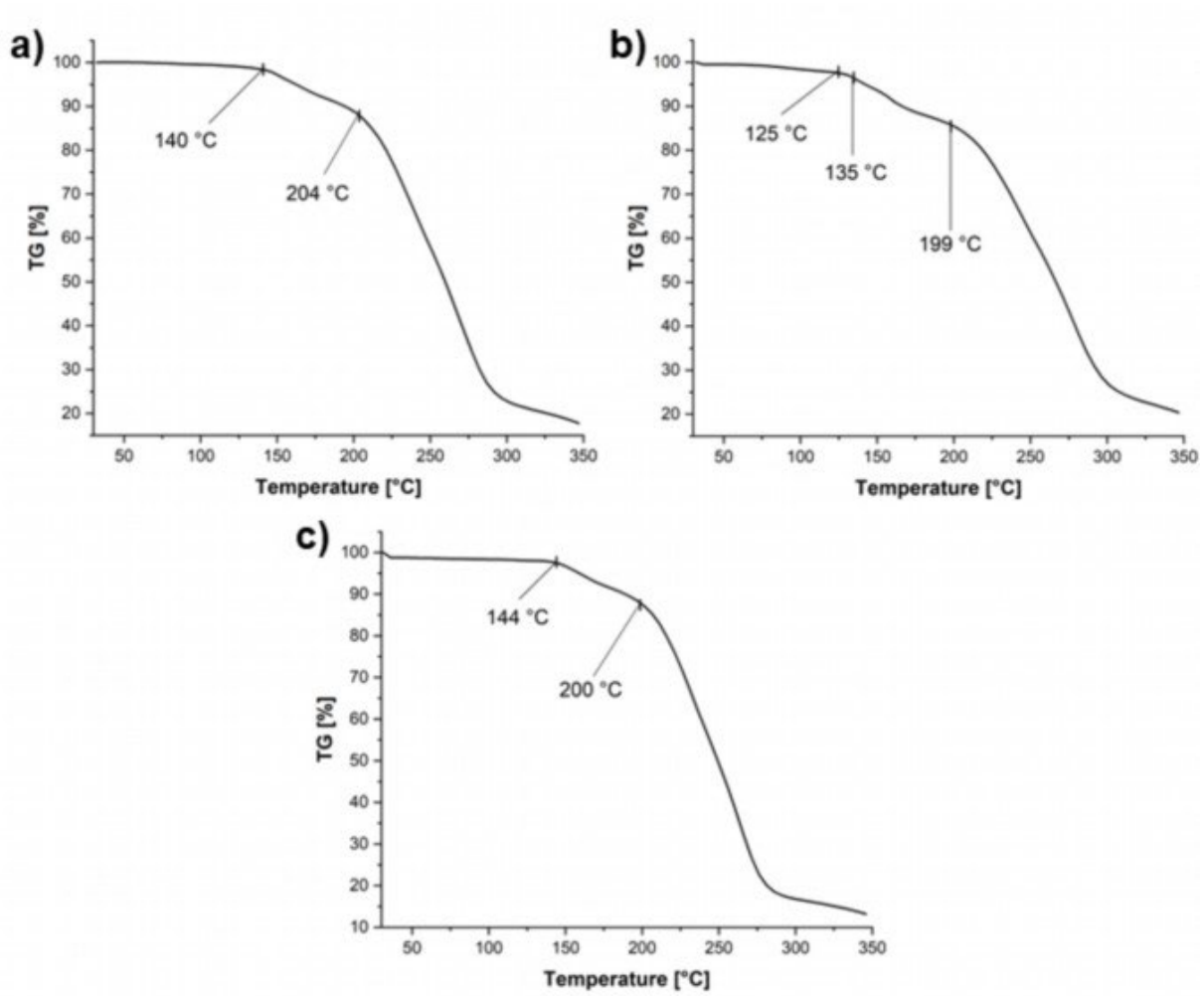

Figure S18. *TGA-data of a sample of **1:D-4** (a), a sample of **1:L-4** (b) and a sample of **1:DL-4** (c). TGA was heated at 10 °C min^{-1} in a range from 30 °C to 350 °C.*

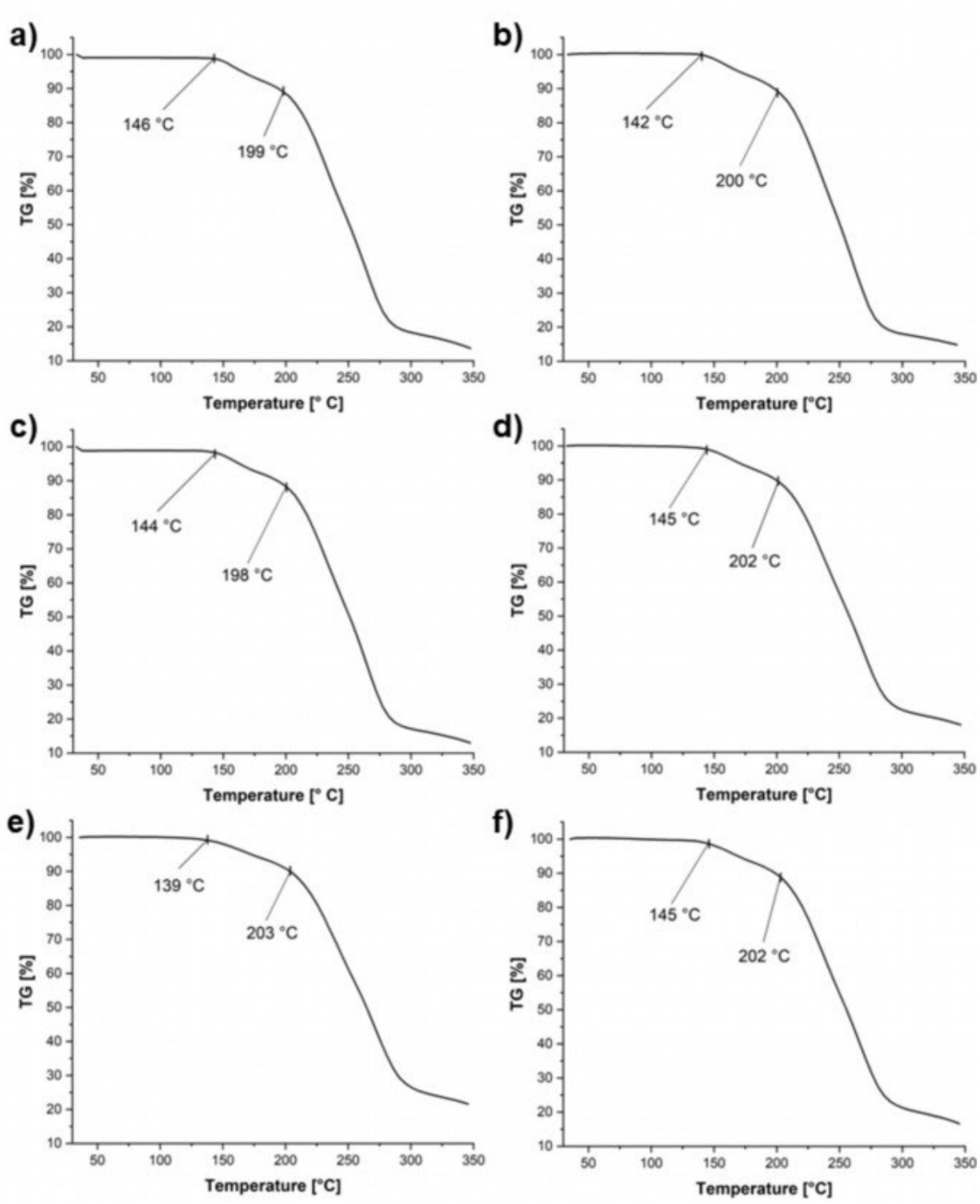

Figure S19. *TGA-data of a LAG sample of Baclofen and D-malic acid with methanol (a), a LAG sample of Baclofen and L-malic acid with methanol (b), a LAG sample of Baclofen and DL-malic acid with methanol (c), a vacuum dried sample of **1:D-4** (d), a vacuum dried sample of **1:L-4** (e) and a vacuum dried sample of **1:DL-4** (f). TGA was heated with 10 °C min^{-1} in a range from 30 °C - 350 °C.*

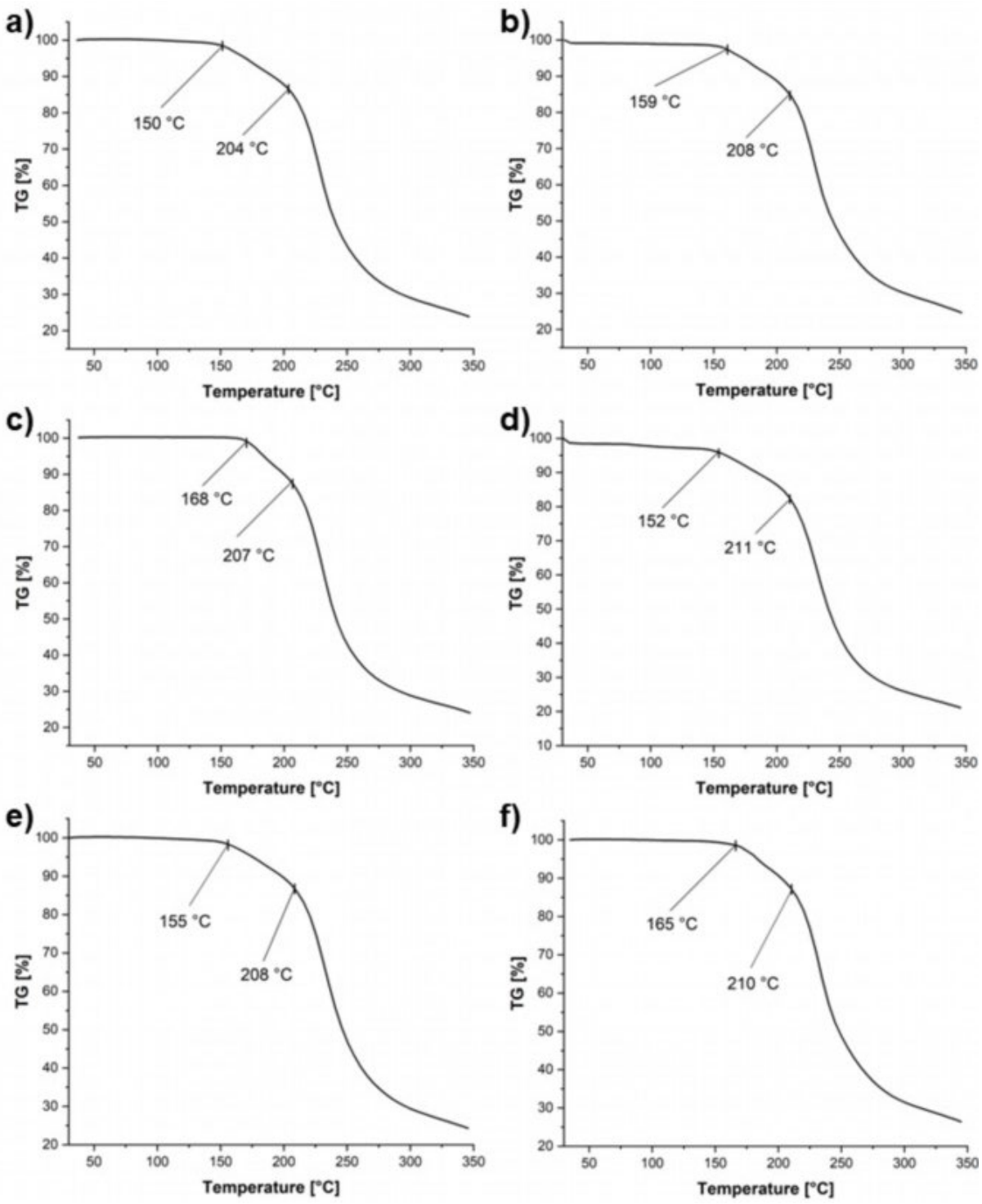

Figure S20. *TGA-data of a LAG sample of Phenibut and D-tartaric acid with methanol (a), a LAG sample of Phenibut and L-tartaric acid with methanol (b), a LAG sample of Phenibut and DL-tartaric acid with methanol (c), a vacuum dried sample of* ***2:D-3 • H2O*** *(d), a vacuum dried sample of* ***2:L-3 • H2O*** *(e) and a vacuum dried sample of* ***2:DL-3*** *(f). TGA was heated with 10 °C min^{-1} in a range from 30 °C - 350 °C.*

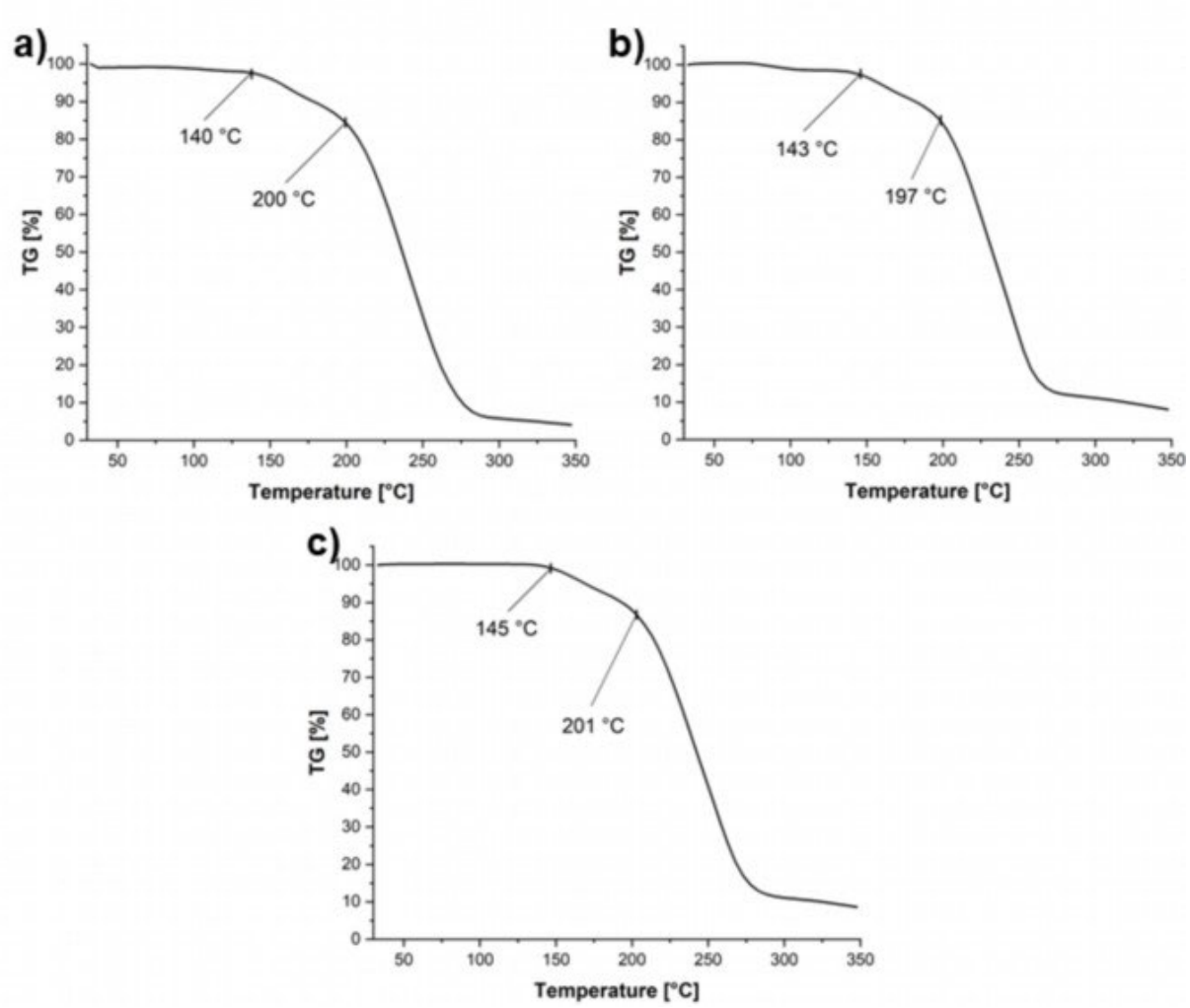

Figure S21. *TGA-data of a LAG sample of Phenibut and D-malic acid with methanol (a), a LAG sample of Phenibut and L-malic acid with methanol (b) and a LAG sample of Phenibut and DL-malic acid with methanol (c). TGA was heated with 10 °C min^{-1} in a range from 30 °C - 350 °C.*