MechSustInd

Influence of mechanochemical processing to phase transition of carbamazepine polymorphs and formation of Inclusion Complex with cyclodextrin

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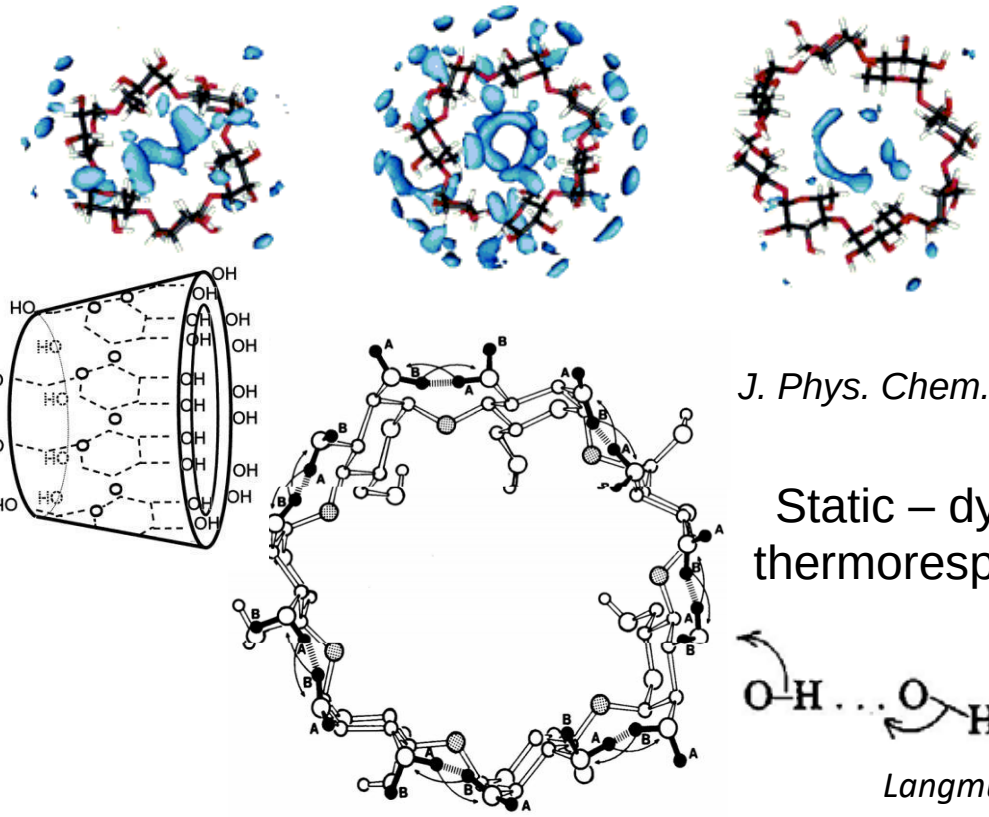
Outline

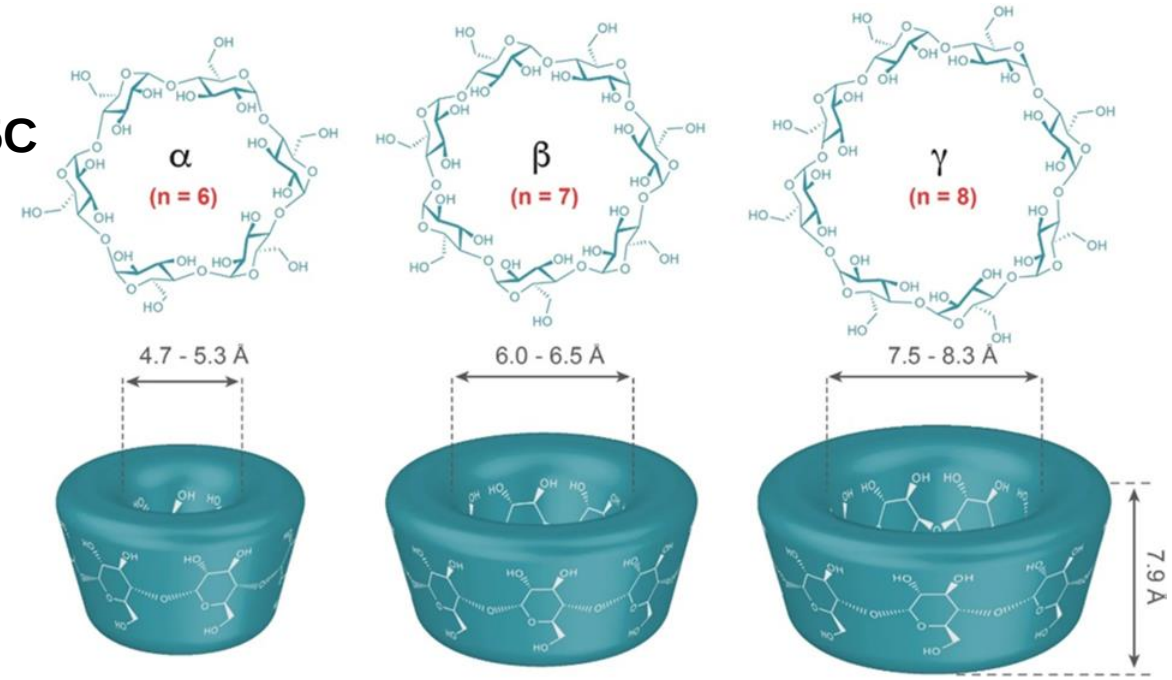
- *Molecular & Crystal Structures of Cyclodextrins (CDs)*
- *The Crystal Structure of drug model Carbamazepin (CBZ) polymorphs III & I*
- *CD Inclusion Complexes (ICs)*
- *Role of Mechanochemistry in IC formation*
- *Experimental Design for IC CBZ polymorphs / BCD*
- *Results*

Molecular & Crystal Structures of Cyclodextrins (CDs)

Why anomalous solubility of β-CD in water?

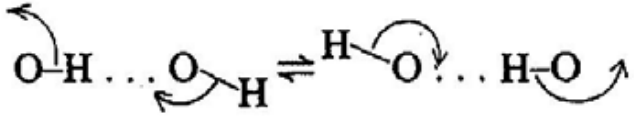
α-	β-	γ-CDs
145	18.5	232 g/L @ 25C



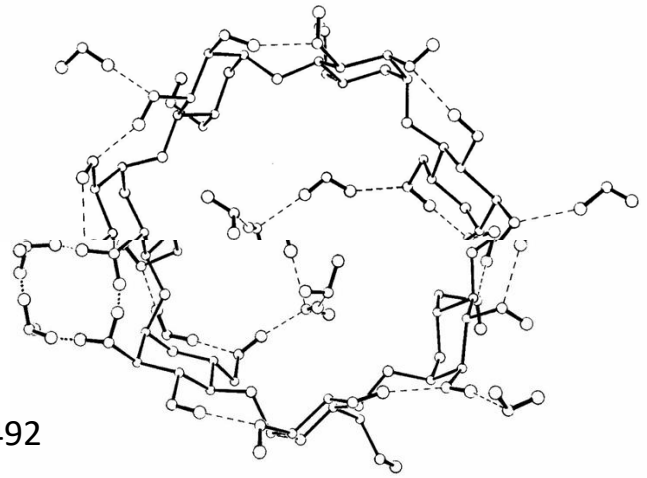


J. Phys. Chem. B 2004, 108

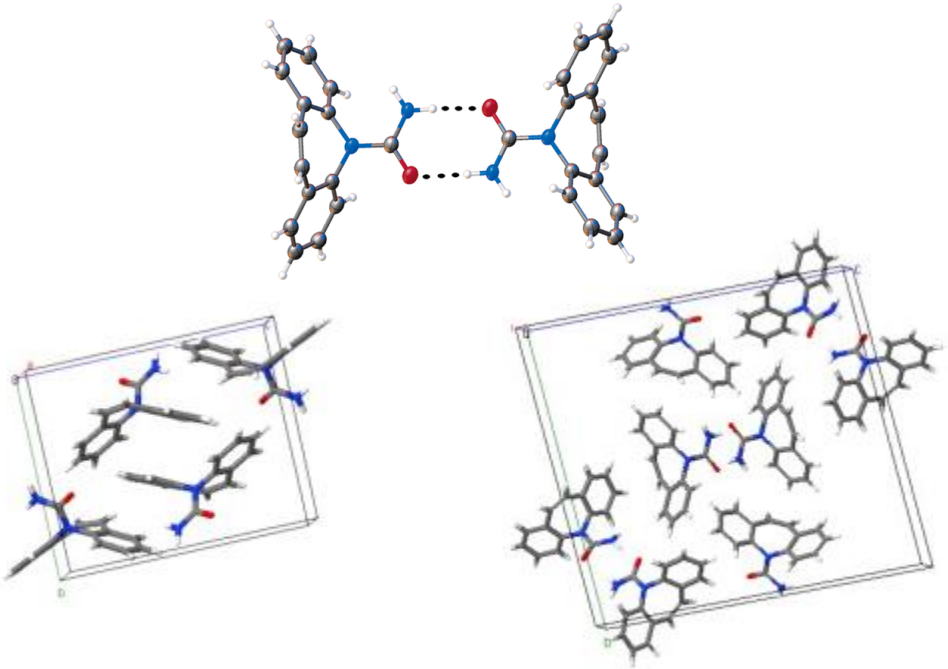
Static – dynamic, flip-flop thermoresponsive H-bonds



Langmuir 2017, 33, 34, 8483–8492



The Crystal Structure of drug model Carbamazepin (CBZ) polymorphs III & I

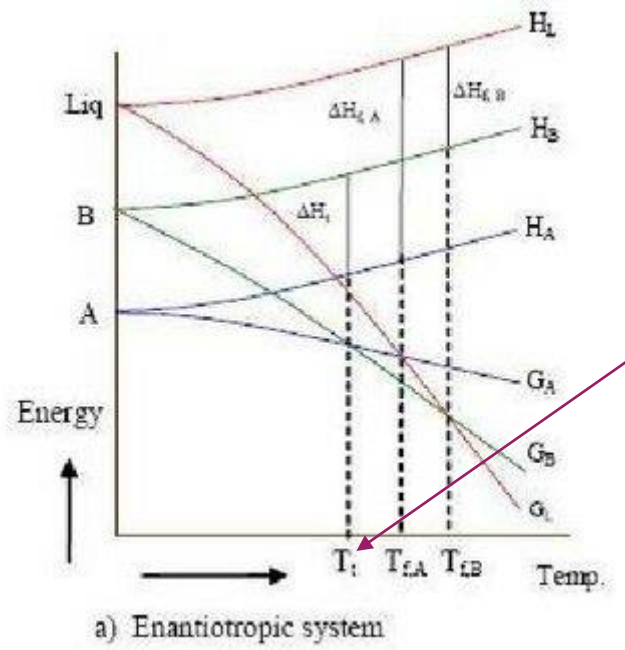


CBZ III

Tm 177 ℃

CBZ I

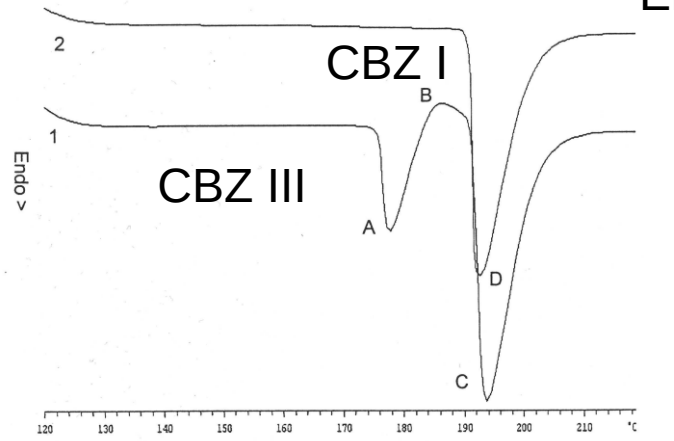
Tm 19 ℃



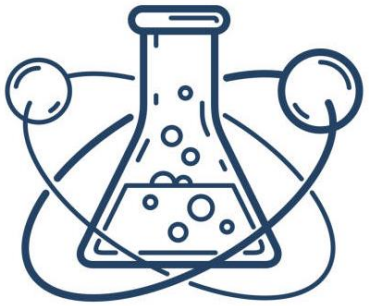
a) Enantiotropic system

Tt ≈ 78 ℃

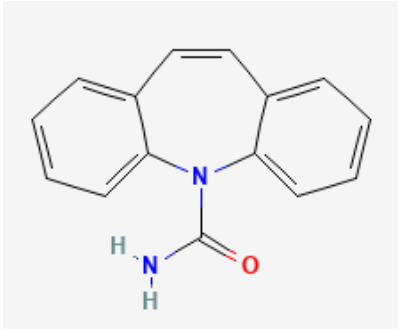
Enantiotropic polymorphs

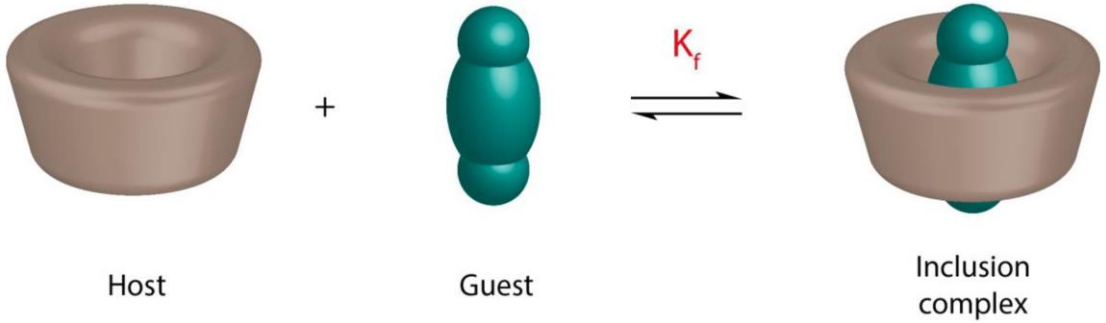


CD Inclusion Complexes (ICs)

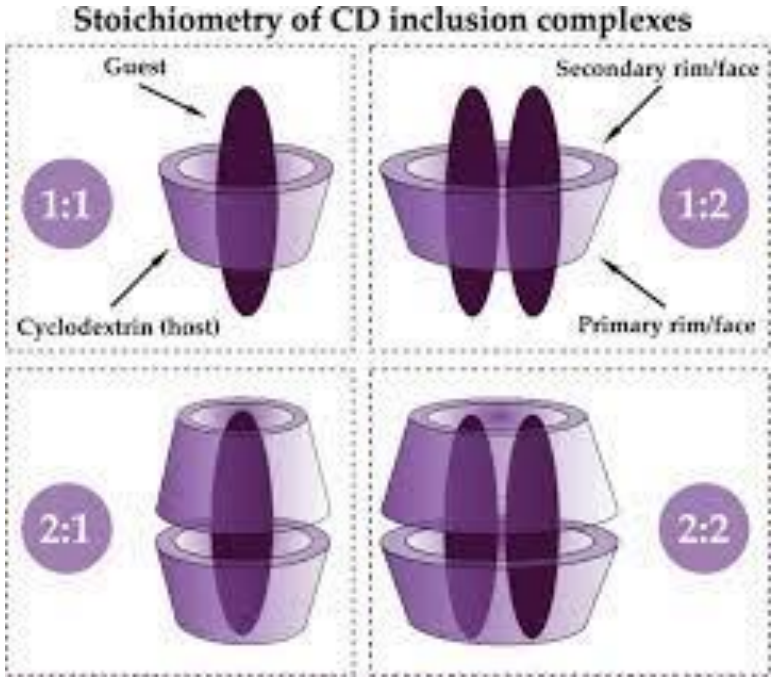


Solution chemistry

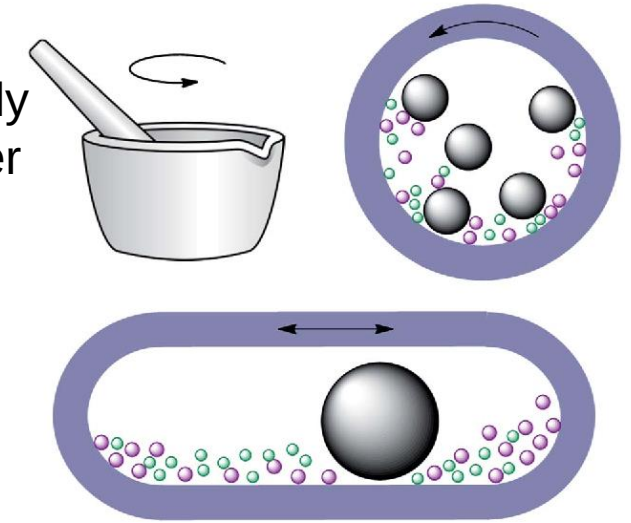




Host Guest Inclusion complex



Role of Mechanochemistry in IC formation



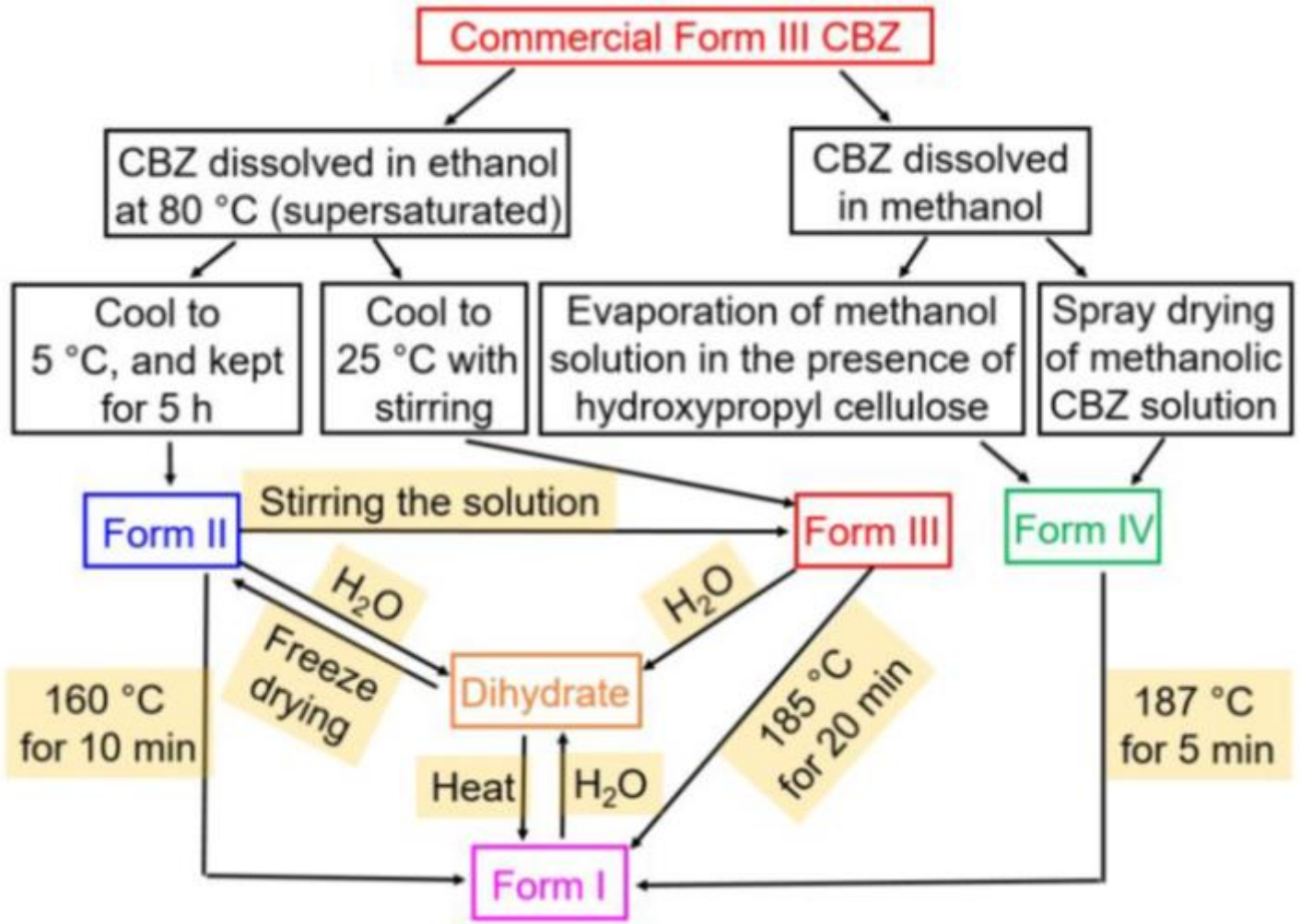
- ✓ Upon grinding both the reactivity and the reaction selectivity are usually improved resulting in a reduced reaction time and a decreased number of purification steps.

- ✓ The solid-state reactivity is much more linked to diffusion phenomena in the crystalline parts of the material than to the increase in the surface area of the CD particles resulting from grinding.
- ✓ supramolecular effects (diffusion through channels)
- ✓ the reaction rate is not directly proportional to the aggregate total active area of contact between the reactants
- ✓ mechanically assisted reaction proceeds with higher selectivity with change of pH value
- ✓ The quantification of the grinding contribution in the reactivity was lacking at this stage (it was not clear whether the increase in reactivity was only a consequence of the formation of inclusion complexes, or whether the grinding process was also involved).
- ✓ Water molecule in cavity loses out 2 H-bonds, higher degree of freedom; enthalpically driven hydrophobic inclusion

Beilstein J. Org. Chem. **2020,** *16,* 2598–2606.

ACS Omega 2020, 5, 40, 25655–25667

Experimental Design for IC CBZ polymorphs / CD



CrystEngComm, 2019, **00**, 1-3

Experimental Design for IC CBZ polymorphs / CD

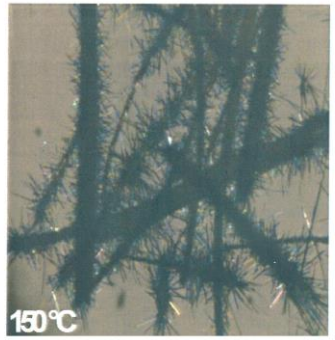
Molar ratio (*M/M*)	Binary systems grinded						Binary systems Kneaded					
	CBZ III/BCD			CBZ IBCD			CBZ I/BCD			CBZ I/BCD		
1/1			x			x			x			x
1/1.25												
1/1.5												
1/1.75												
1/2												
	5	15	30	5	15	30	5	15	30	5	15	30
	Processing time (min)											

Results

Table 1 Peak temperatures and fusion enthalpy of CBZ samples. Mean values (S.D.) (n=3)

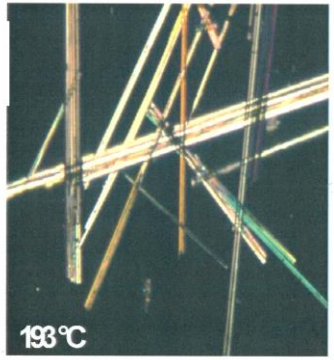
Sample		Onset/°C	Peak/°C	Enthalpy/J g^{-1}	Onset/°C	Peak/°C	Enthalpy/J g^{-1}
CBZ form	Treatment						
III		175.1	177.6	40.7 (0.4)	190.7	193.8	134.1 (1.4)
III	ground 5 min	175.0	177.4	40.6 (0.6)	190.4	193.5	133.6 (1.3)
III	ground 15 min	176.0	178.8	39.5 (0.5)	191.4	193.8	129.8 (0.5)
III	ground 30 min	175.5	178.2	41.2 (4.3)	190.6	193.1	128.6 (2.2)
III	kneaded 5 min	145.6	162.4	8.9 (2.2)	190.2	192.6	120.7 (0.9)
III	kneaded 30 min	146.8	159.7	6.0 (2.1)	191.6	194.3	127.7 (9.5)
I					190.8	192.9	138.9 (6.6)
I	ground 5 min				190.6	192.5	138.0 (6.1)
I	ground 15 min				190.9	193.1	133.5 (5.7)
I	ground 30 min				191.2	193.9	131.3 (1.2)
I	kneaded 5 min				189.6	192.0	120.3 (1.6)
I	kneaded 30 min				190.3	192.6	125.0 (6.3)
III	slurry method	144.2	157.9	4.4 (0.05)	191.1	193.7	122.9 (3.9)

HTM: CBZ III



CBZ III → I

Melting CBZ III

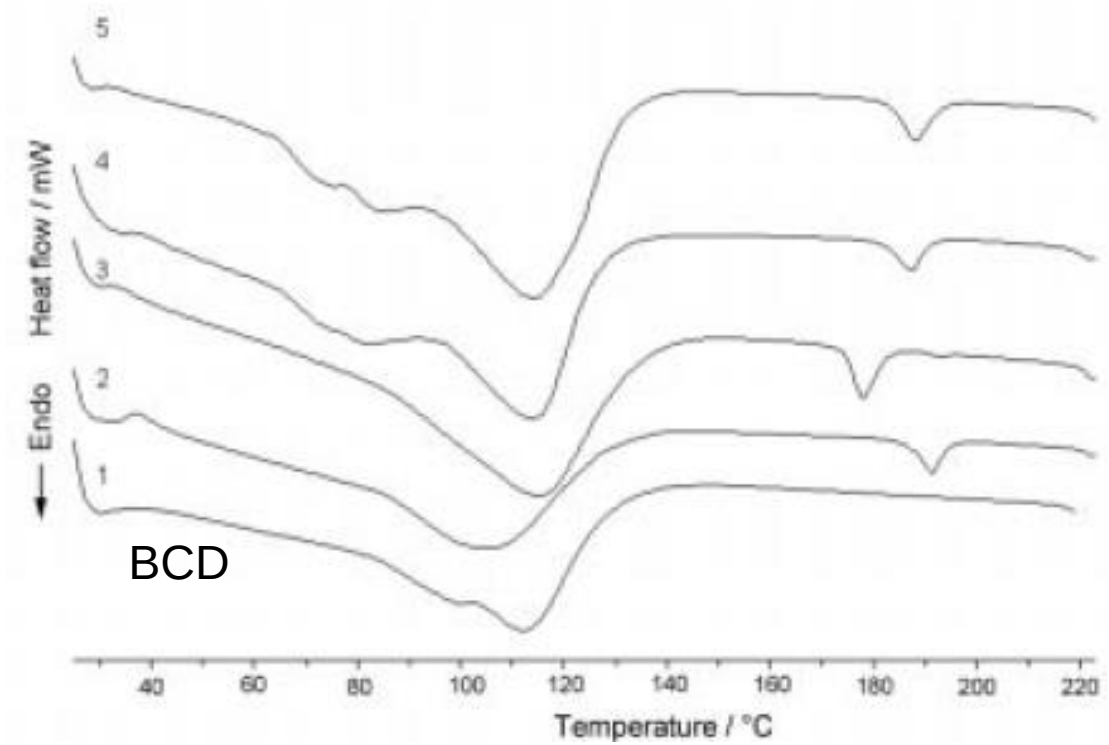


CBZ I

Results

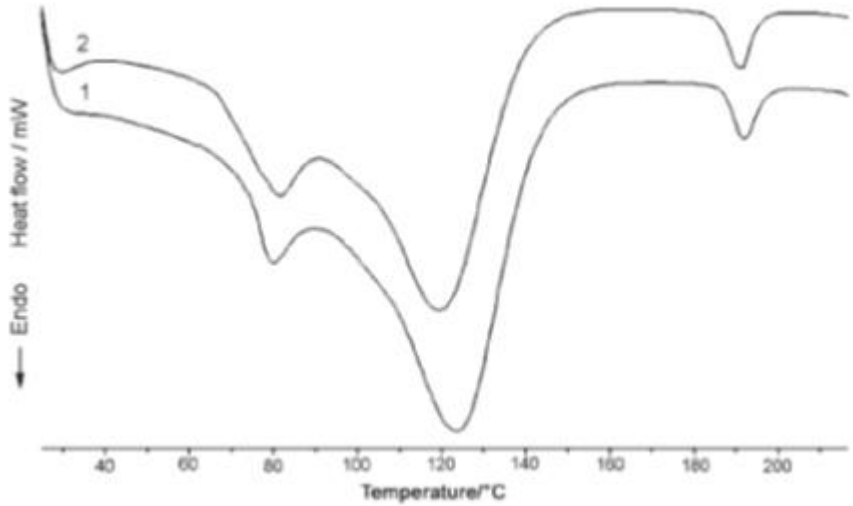
Table 2 Peak temperatures and fusion enthalpy of CBZ/β-CD 1:1 molar ratio binary mixtures. Mean values (S.D.) (n=3)

Sample			Onset/°C	Peak/°C	Enthalpy/J g^{-1}	Onset/°C	Peak/°C	Enthalpy/J g^{-1}
	CBZ form	Treatment						
3	III	grinded 30 min	173.6	177.7	101.7 (2.4)	188.6	192.5	7.3 (4.8)
5	III	kneaded 30 min				181.5	187.2	100.7 (4.7)
2	I	grinded 30 min				186.3	192.0	91.3 (5.0)
4	I	kneaded 30 min				181.9	187.6	104.2 (14)



BCD

ΔHf ≈40.1 Jg^{-1} CBZ III polymorph

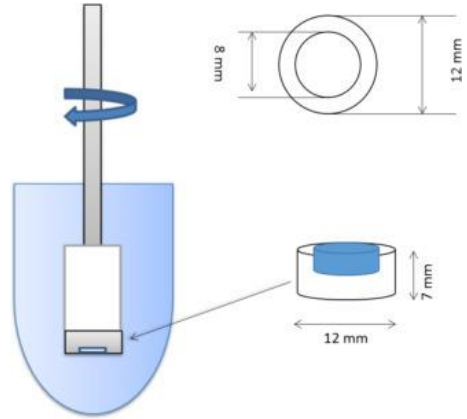


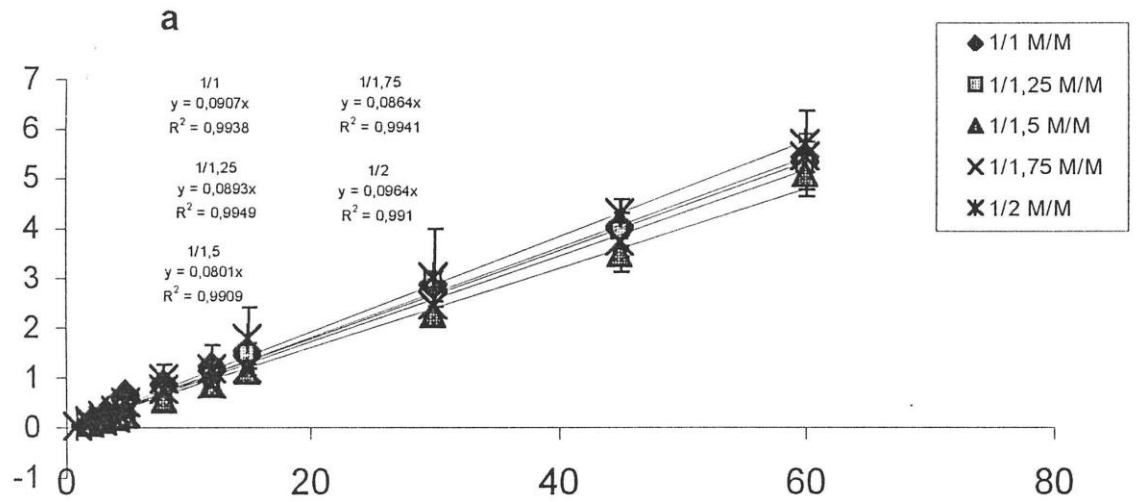
1 Grinded CBZ dihydrate (III) /BCD
2 Grinded CBZ dihydrate (II) /BCD

Measuring Intrinsic Dissolution Rate (IDR)

In pure water media

1/1 *M/M*	Method of processing	IDR $\mu g \cdot cm^{-2} \cdot min^{-1}$
CBZ form I/BCD	grinded	94.84
CBZ form III/BCD	grinded	287.36
CBZ form I/BCD	Kneaded	72.02
CBZ form III/BCD	kneaded	77.11





Conclusions

- CBZ Forms I and III interact in a different way with b-CD upon heating. This probably occurs because CBZ, molten as Form III, can interact with b-CD. Melting of Form III, the interaction of liquid CBZ with b-CD hinders the recrystallisation of CBZ as Form I.

- CBZ dihydrate is considered, heating in the presence of b-CD always leads to the formation of CBZ Form I because of CBZ dehydration, regardless of the CBZ crystal form from which the hydrate has been prepared

Thank you for your attention

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