

RIETVELD STRUCTURAL AND MICROSTRUCTURAL CHARACTERIZATION OF PHARMACEUTICAL PRODUCTS USING THE PROGRAM MAUD

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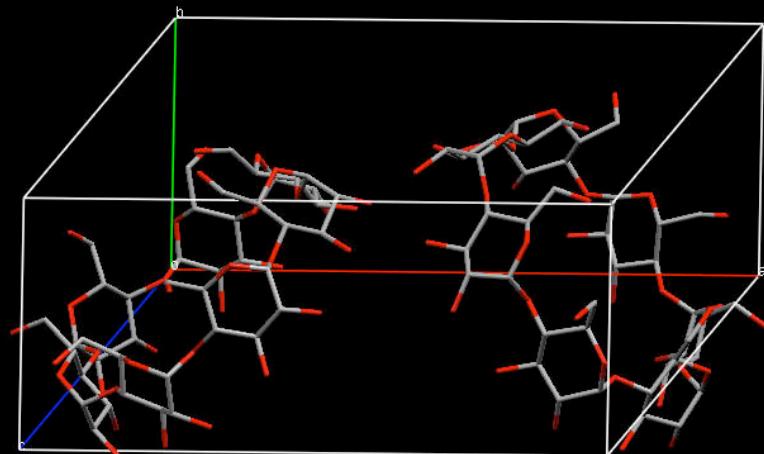
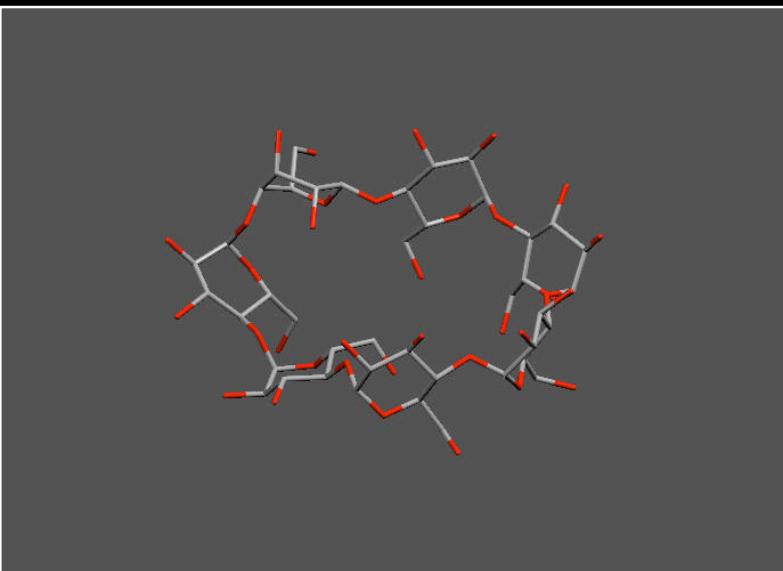
^cEurand International S.p.A., Trieste, Italy

Outline

- *Two examples studied:*
 - *β-CycloDextrin/drug (β-CD)*
 - *PolyVinylPirrolidone/drug (PVP)*
- *Experimental setting:*
 - *Normal Bragg-Brentano diffractometer*
 - *Curved Image Plate Diffractometer (IPD 3000x)*
- *Methodology:*
 - *Extended Rietveld analysis (other than structural and Quantitative Phase Analysis):*
 - *Microstructural analysis*
 - *Crystallinity*
 - *MEEM quantitative analysis*
- *Software: Maud*

β -CD/drug systems

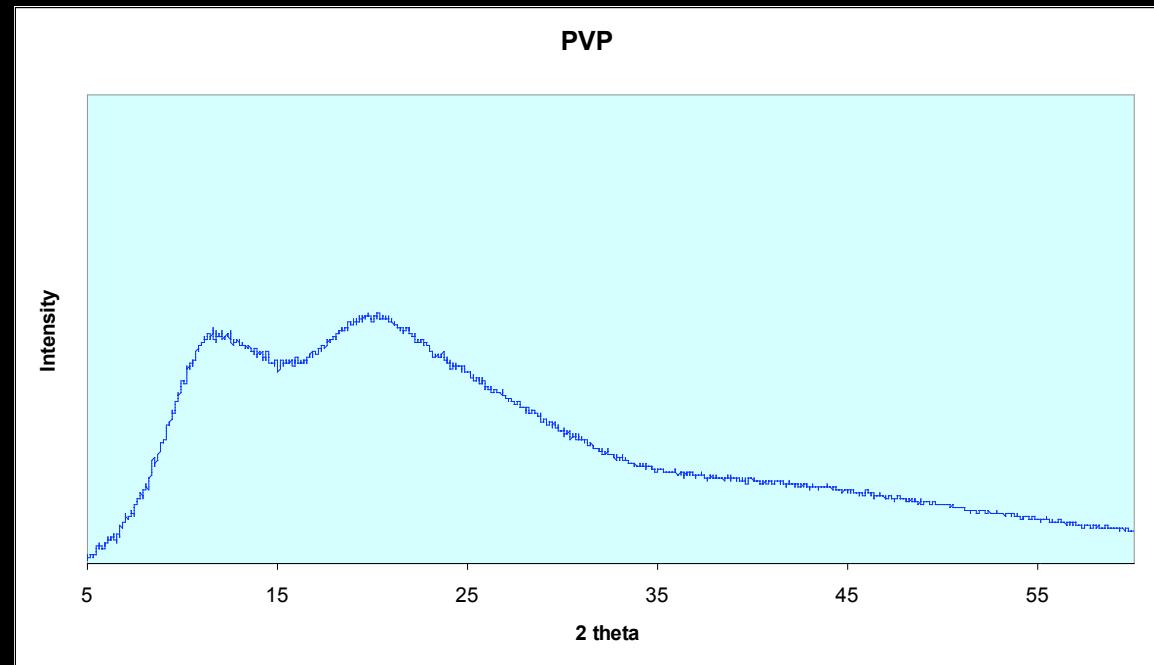
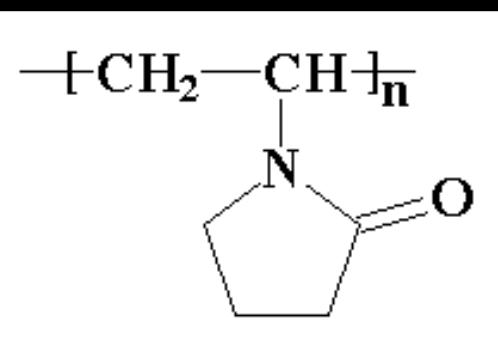
- Carrier: β -cyclodextrin, $C_{42}H_{70}O_{35}$
- Crystal structure: monoclinic, $P21:b$



- The drug molecule positions itself inside the β -CD ring

PVP/drug system

- *Polyvinylpirrolidone: polymer, 100% amorphous*



- *The drug is dispersed in the amorphous matrix*

Preparation of β -CD

- Different water content can be controlled by the relative humidity (R.H.)*



<i>R. H. (%)</i>	<i>Condition</i>
0	N_2 flux
11	$LiCl$
21	CH_3COOH
33	$MgCl_2 \times 6H_2O$
58	$NaBr$
76	$NaCl$
96	Na_2HPO_4

How to prepare the composites: the milling system

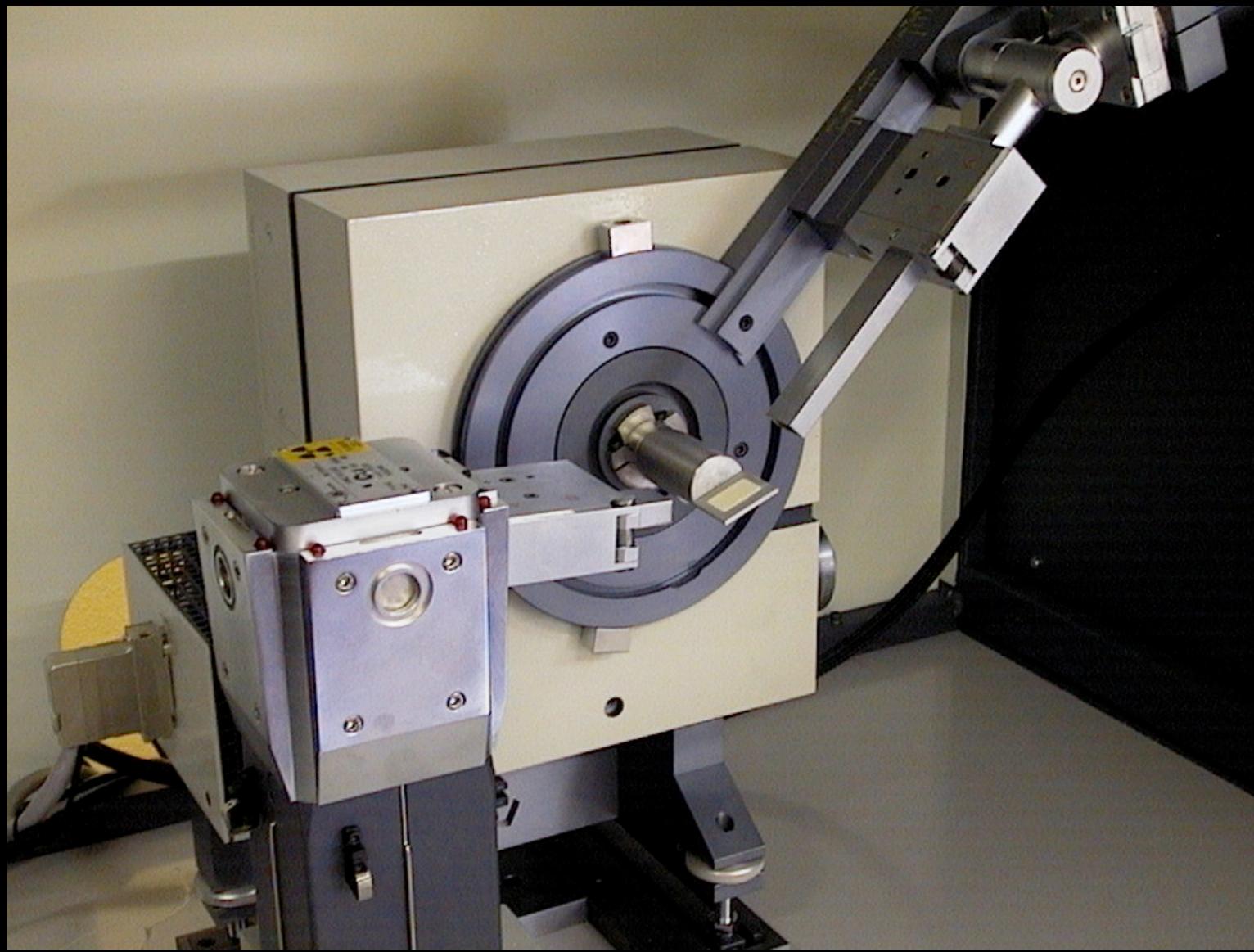
- *Planetary milling system: Fritsch Pulverisette 7*
- *Carrier/drug weight ratio: 3:1 for β -CD, 1:1 for PVP*



XRD data collection and analysis

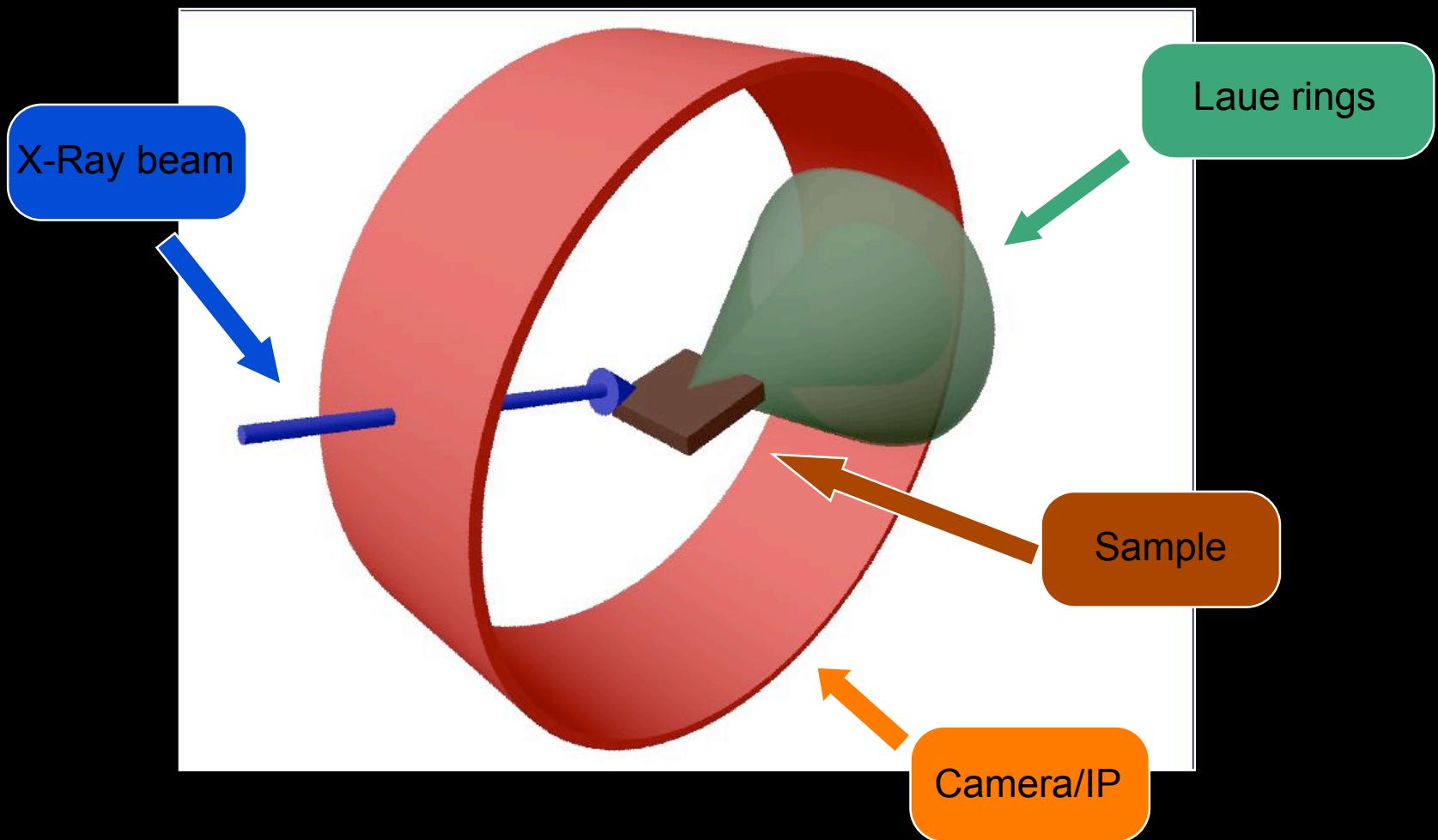
- *All the analyses were performed using an extended Rietveld method => full spectra needed*
- *Diffractometers:*
 - *APD 2000 (Bragg-Brentano instrument) for normal requirement, good compromise of resolution - intensity*
 - *IPD 3000 (Imaging Plate Diffractometer) for quick analyses of samples in critical condition or metastable systems*

APD 2000

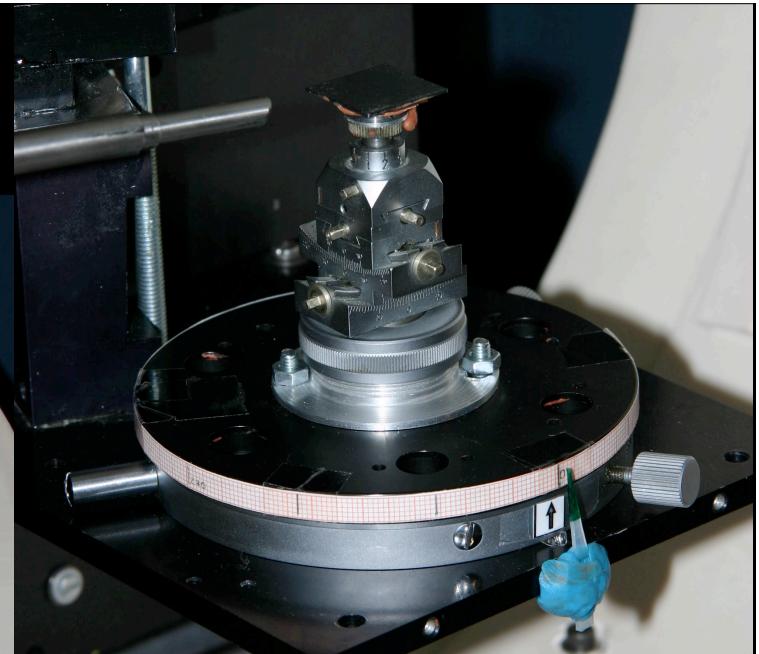
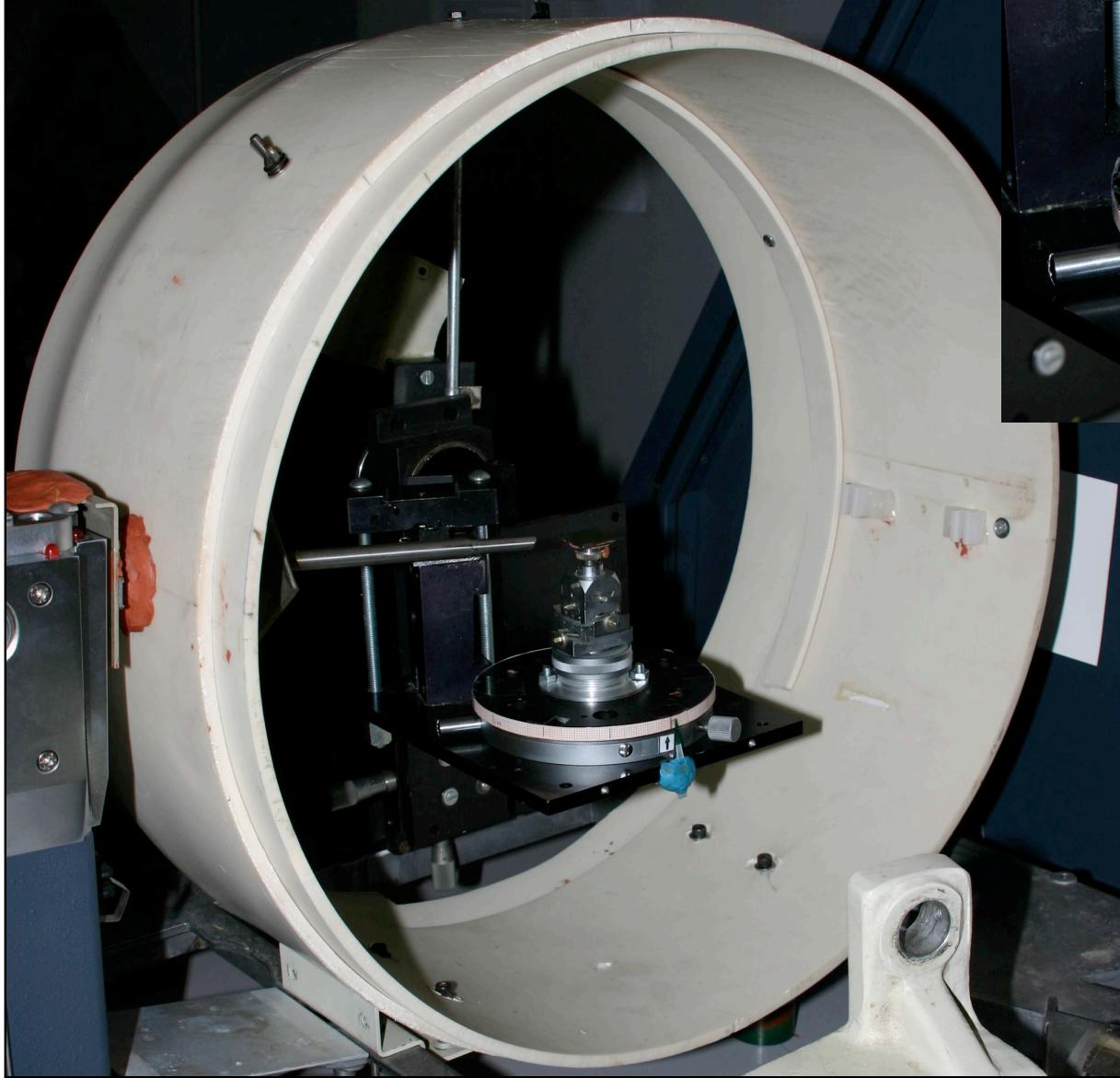


Imaging Plate Diffractometer

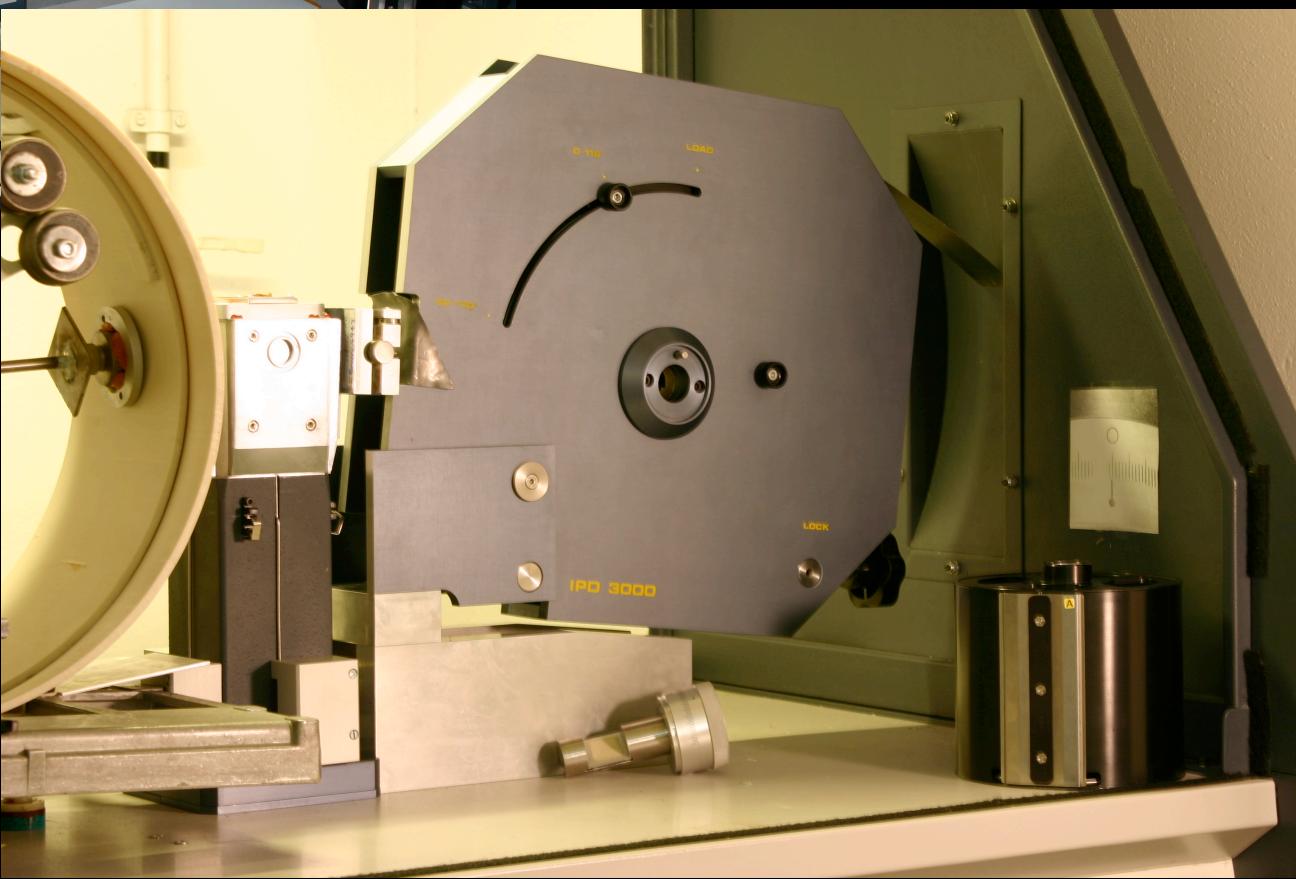
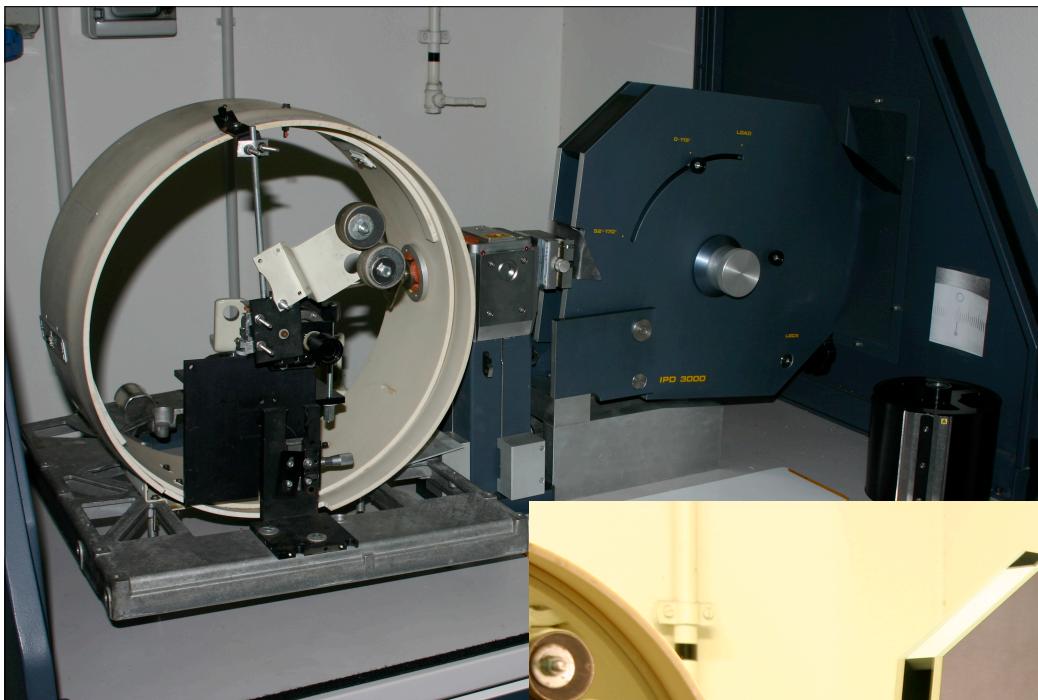
- *The general scheme*



The first prototype

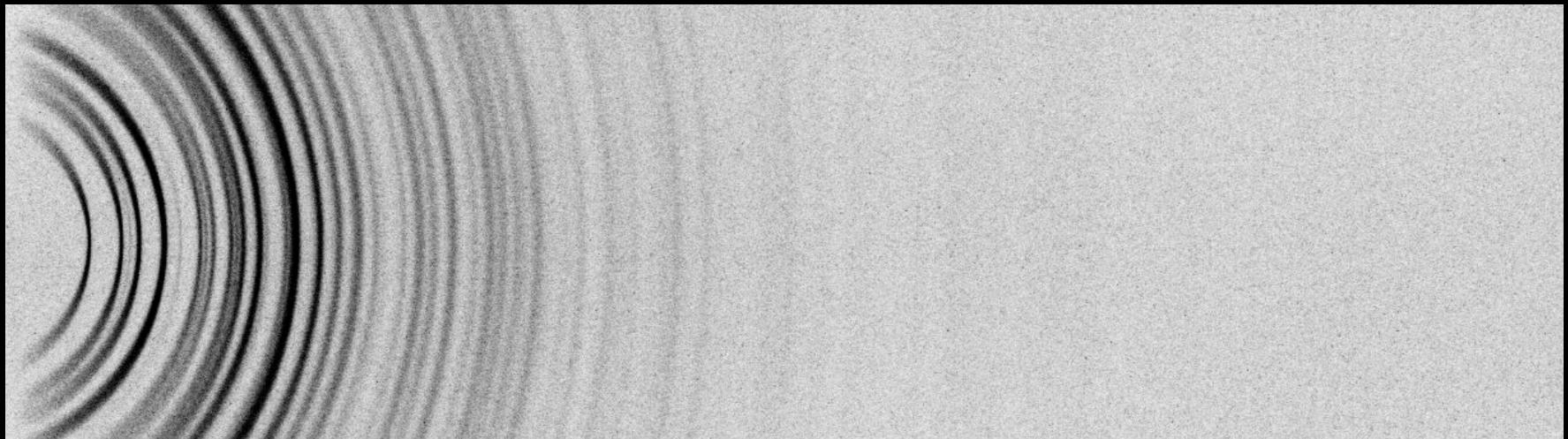


The IPD3000



Griseofulvine IP example

- *Imaging plate large, range 120 degrees*

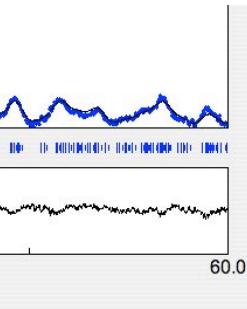
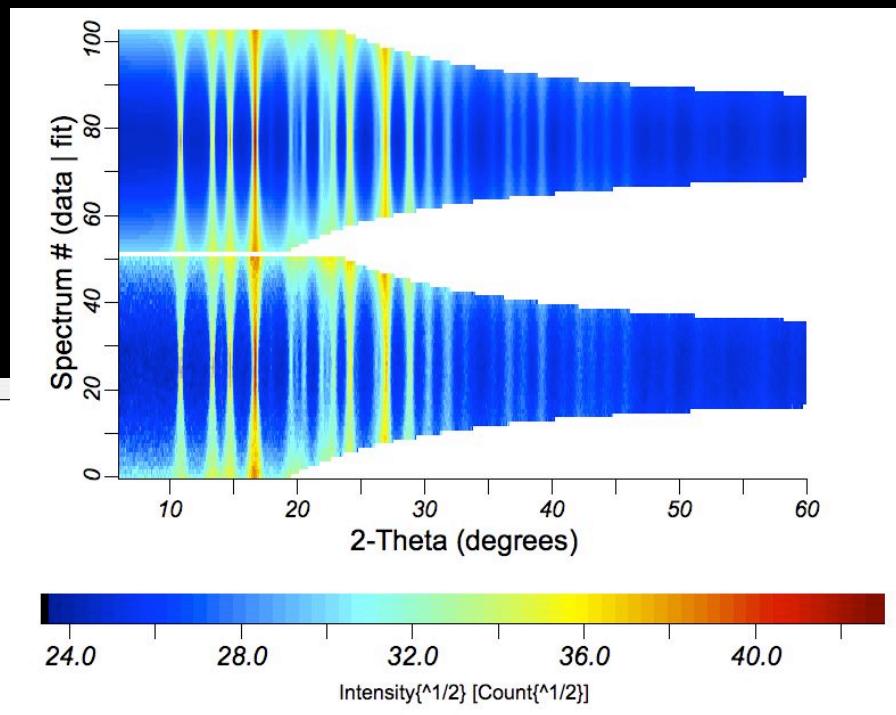
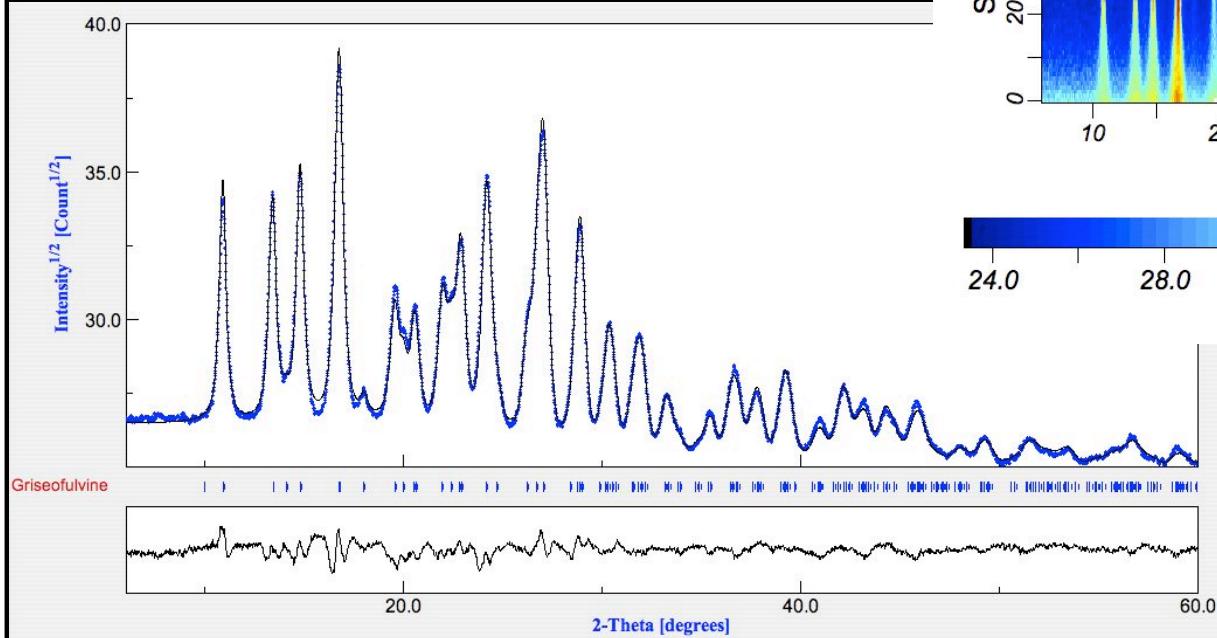


- *IPD3000*



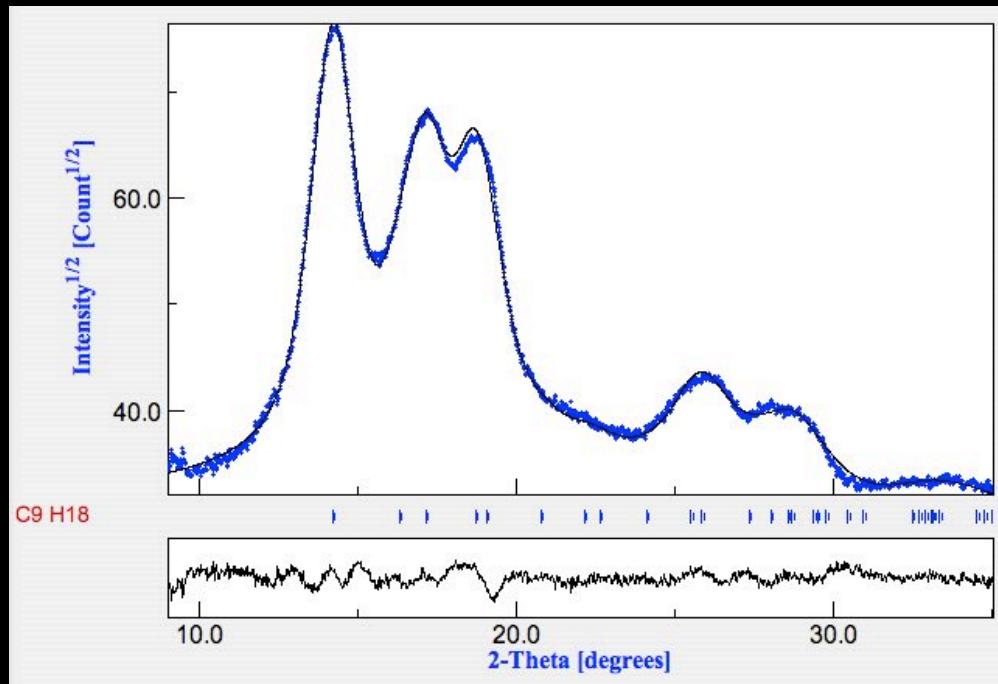
Griseofulvine Rietveld fit (Maud)

- $R_W = 3.42\%$, $R_W(\text{no bkg}) = 3.96\%$



Is it one spectrum/line sufficient?

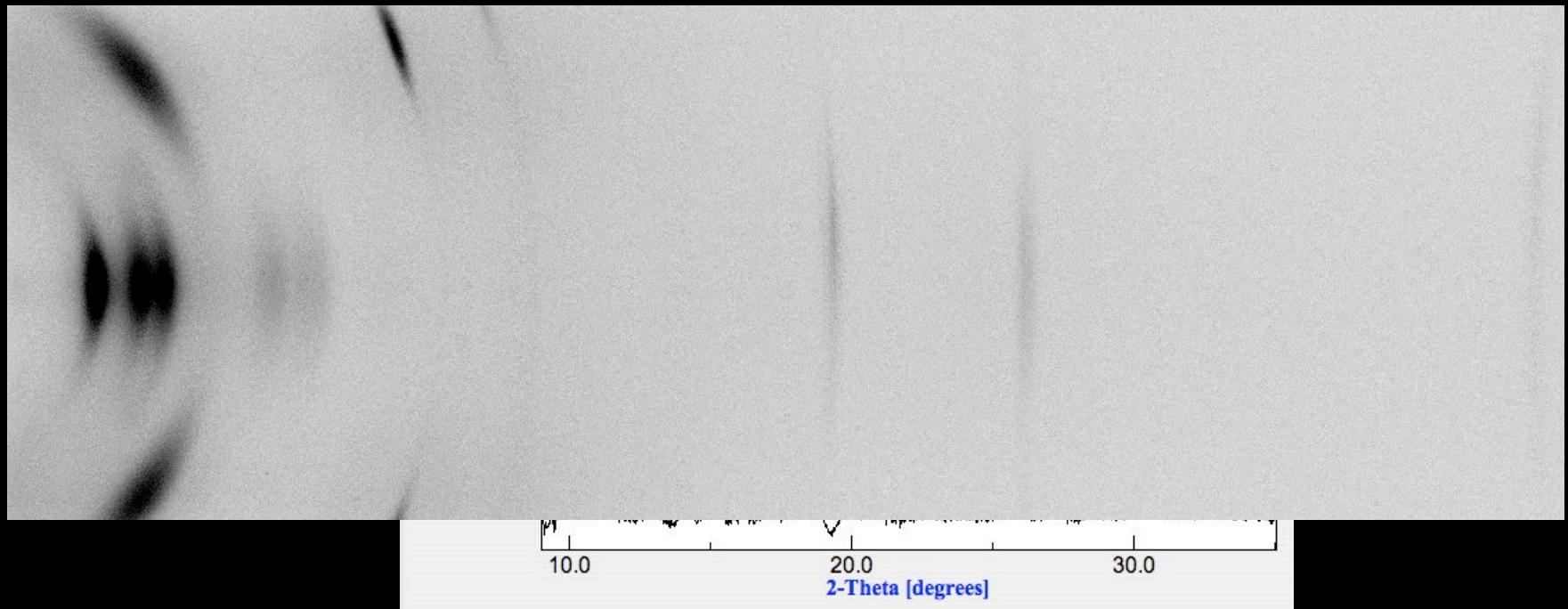
- *In the case of texture (polypropylene fibers):*



- *This is an extreme case but also the griseofulvine was a little textured by sample preparation*
- *Correction is important for quantitative analysis*

Is it one spectrum/line sufficient?

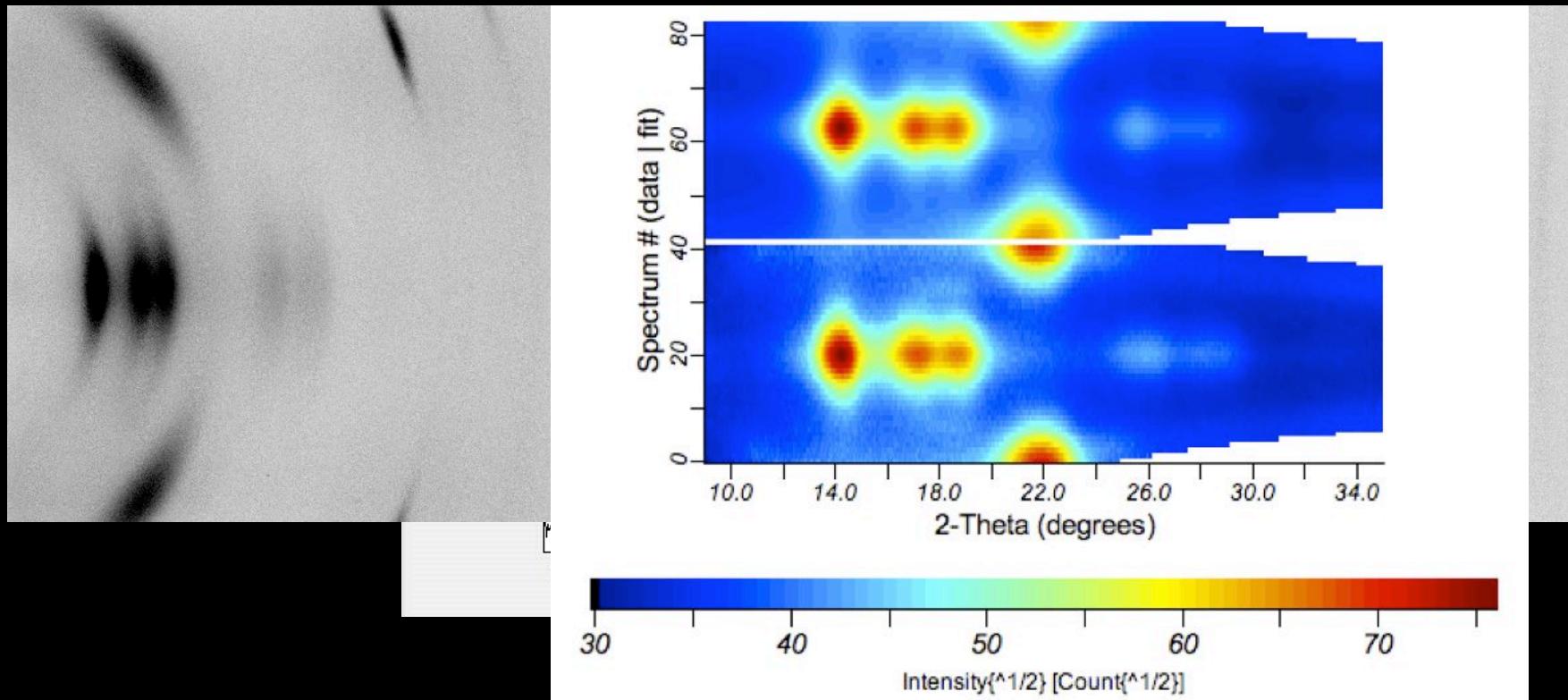
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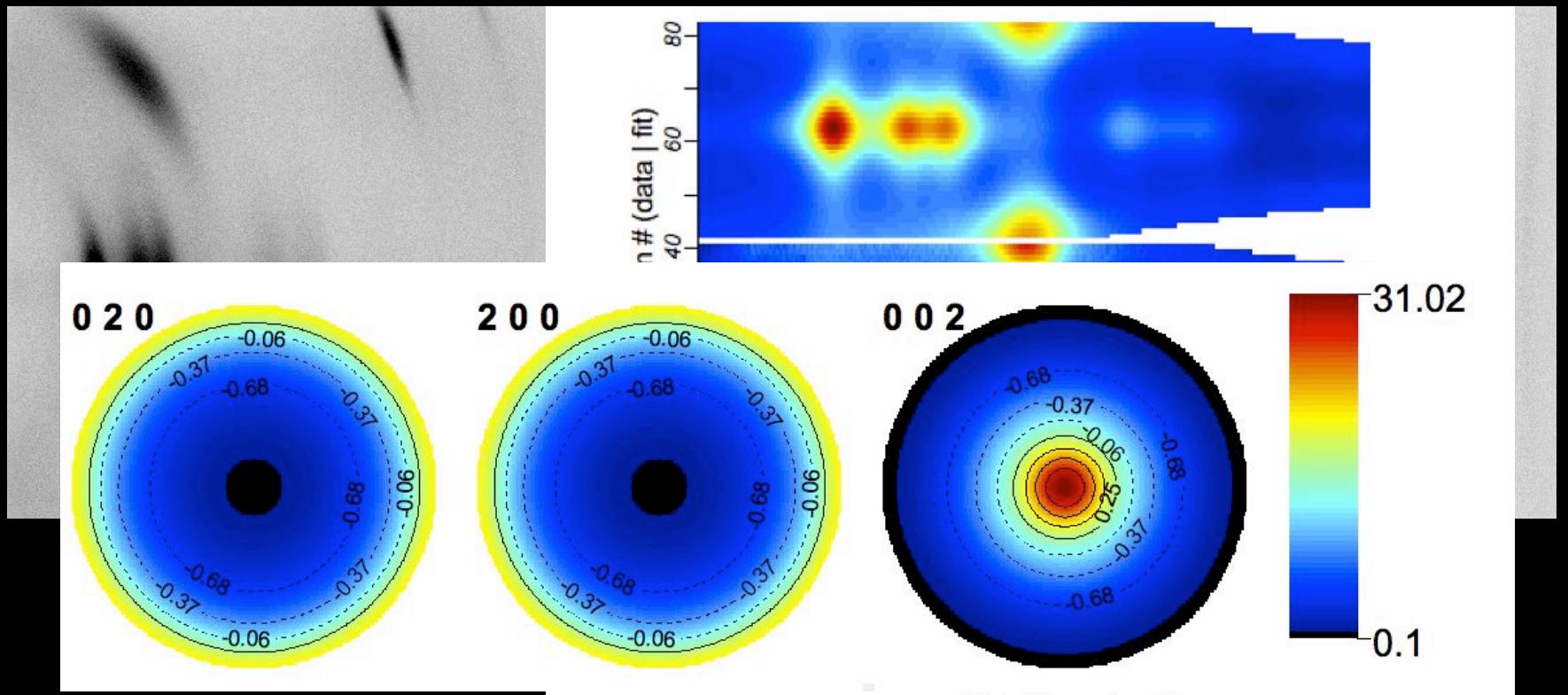
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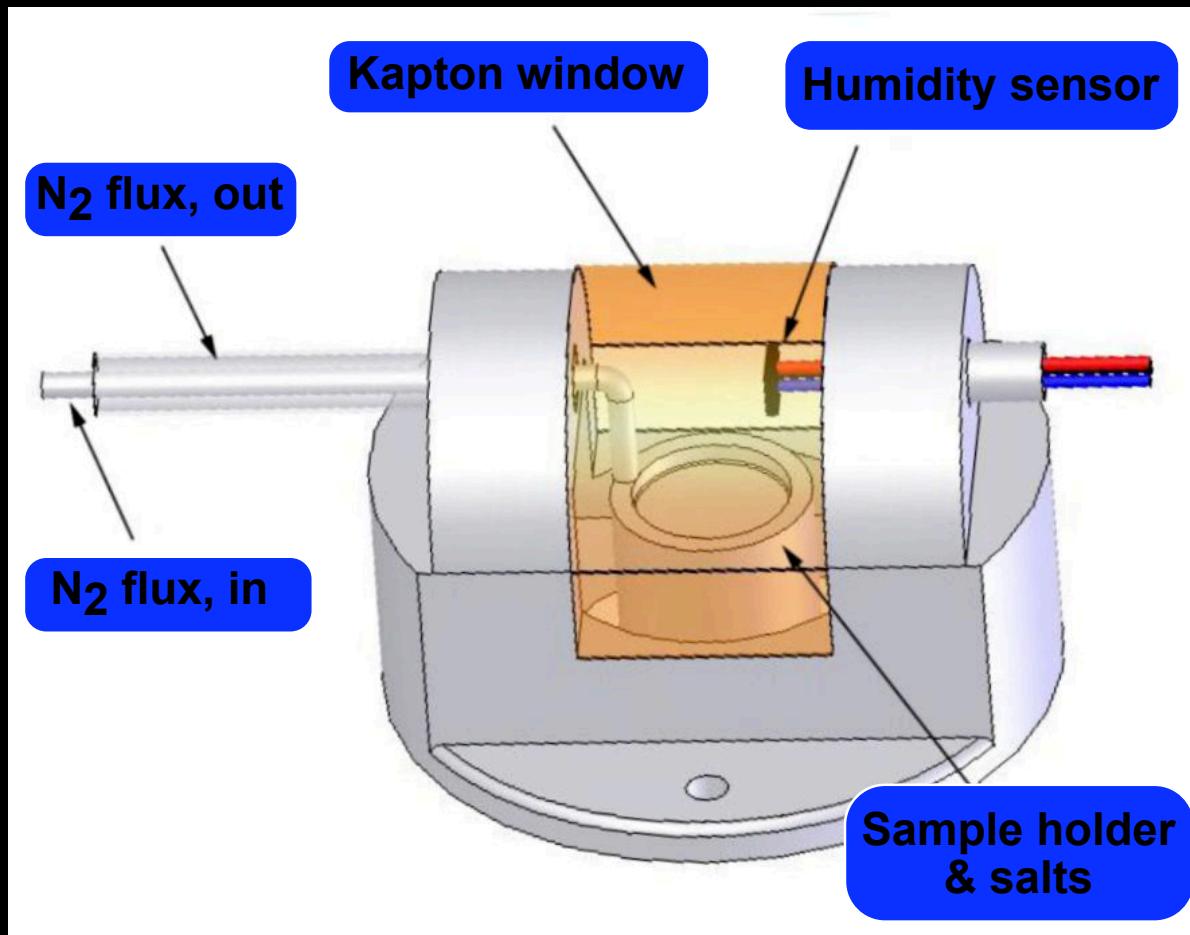
- *In the case of texture (polypropylene fibers):*



- *This is an extreme case but also the griseofulvine was a little textured by sample preparation*
- *Correction is important for quantitative analysis*

β -CD measurements: sample holder

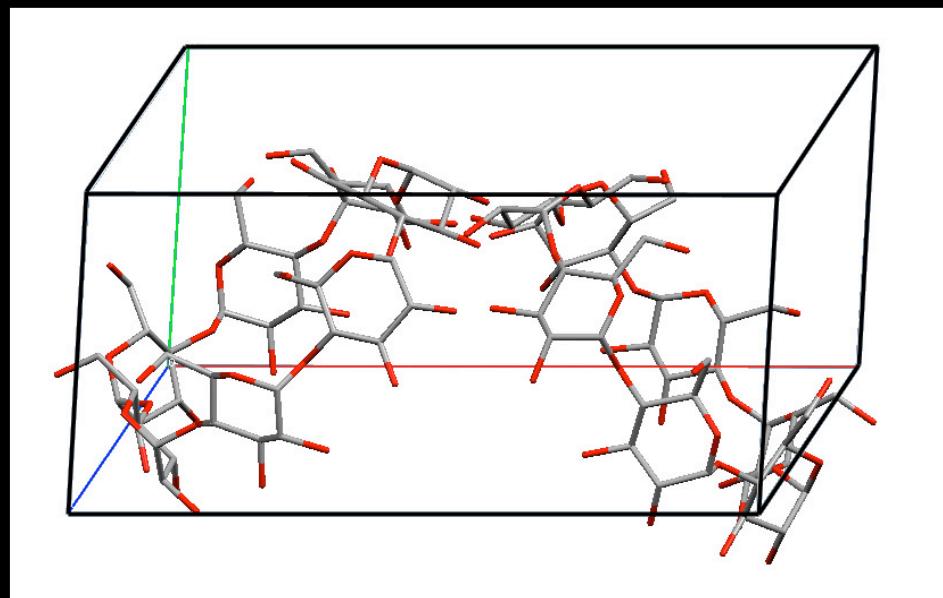
- Humidity control chamber



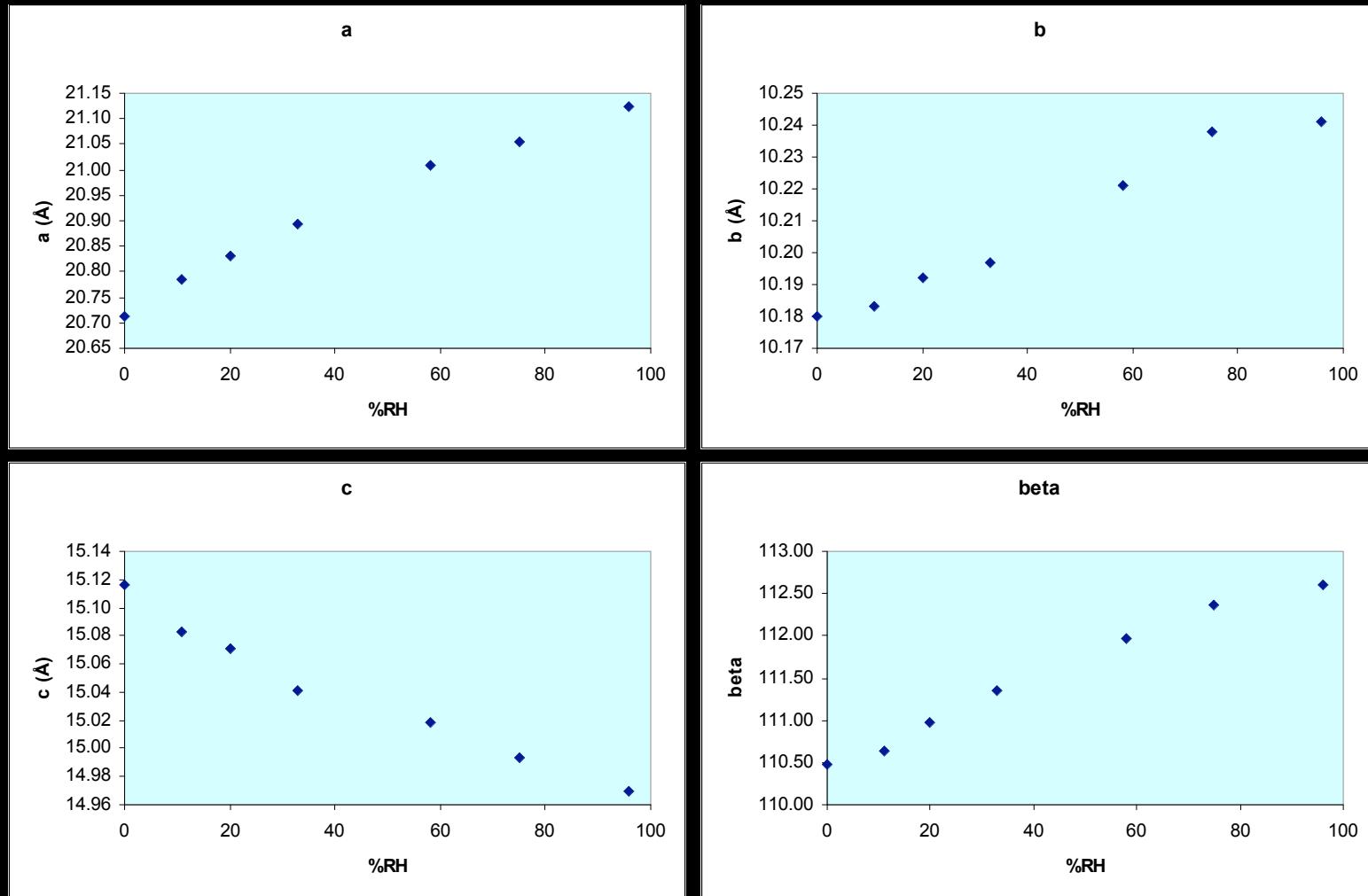
β -CD reference structure

- Monoclinic cell, space group: P21:b

<i>a</i>	21.0
<i>b</i>	10.2
<i>c</i>	15.1
<i>b</i>	111.0

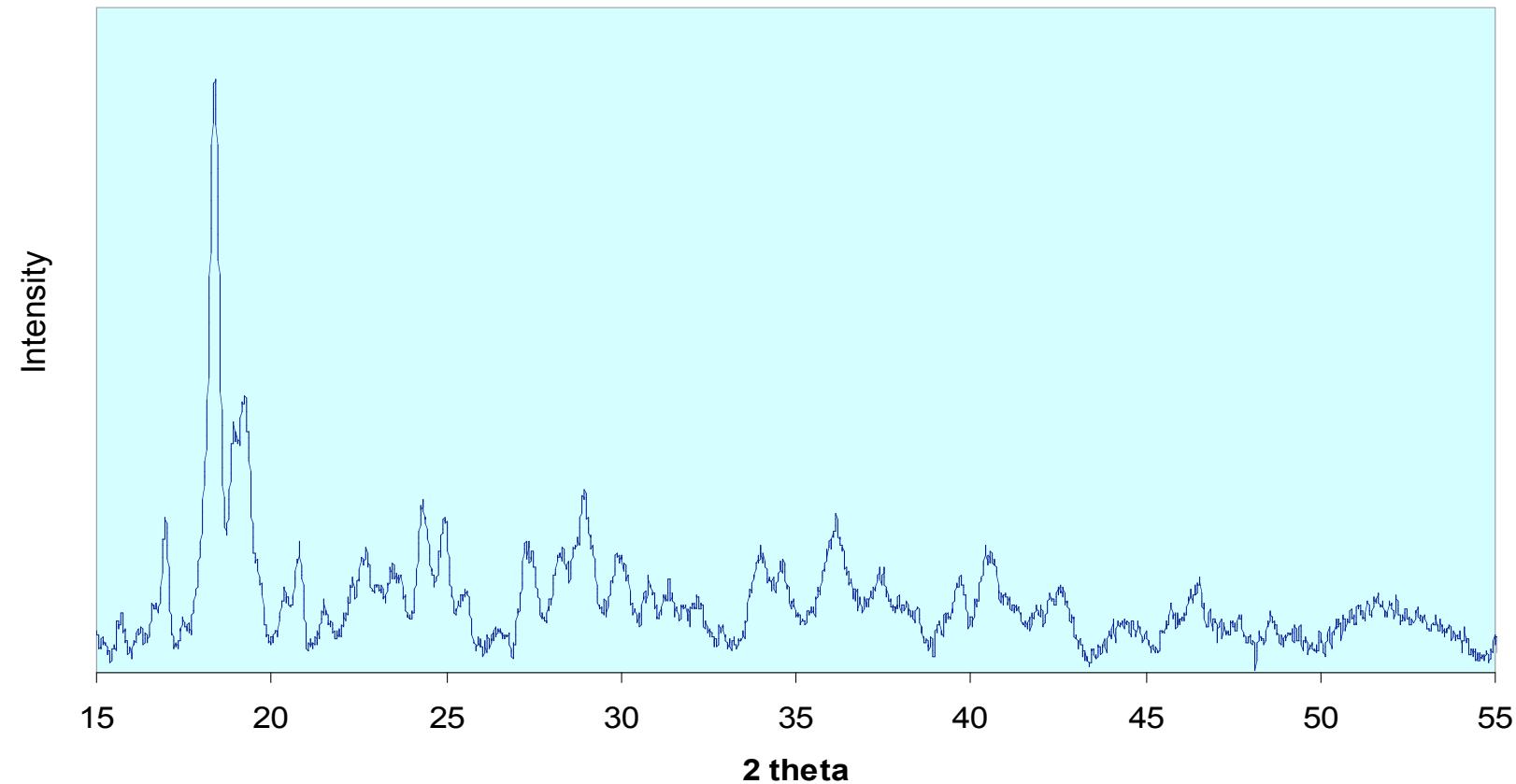


β -CD: Effect of humidity on cell parameters



β -CD at 0% Relative Humidity

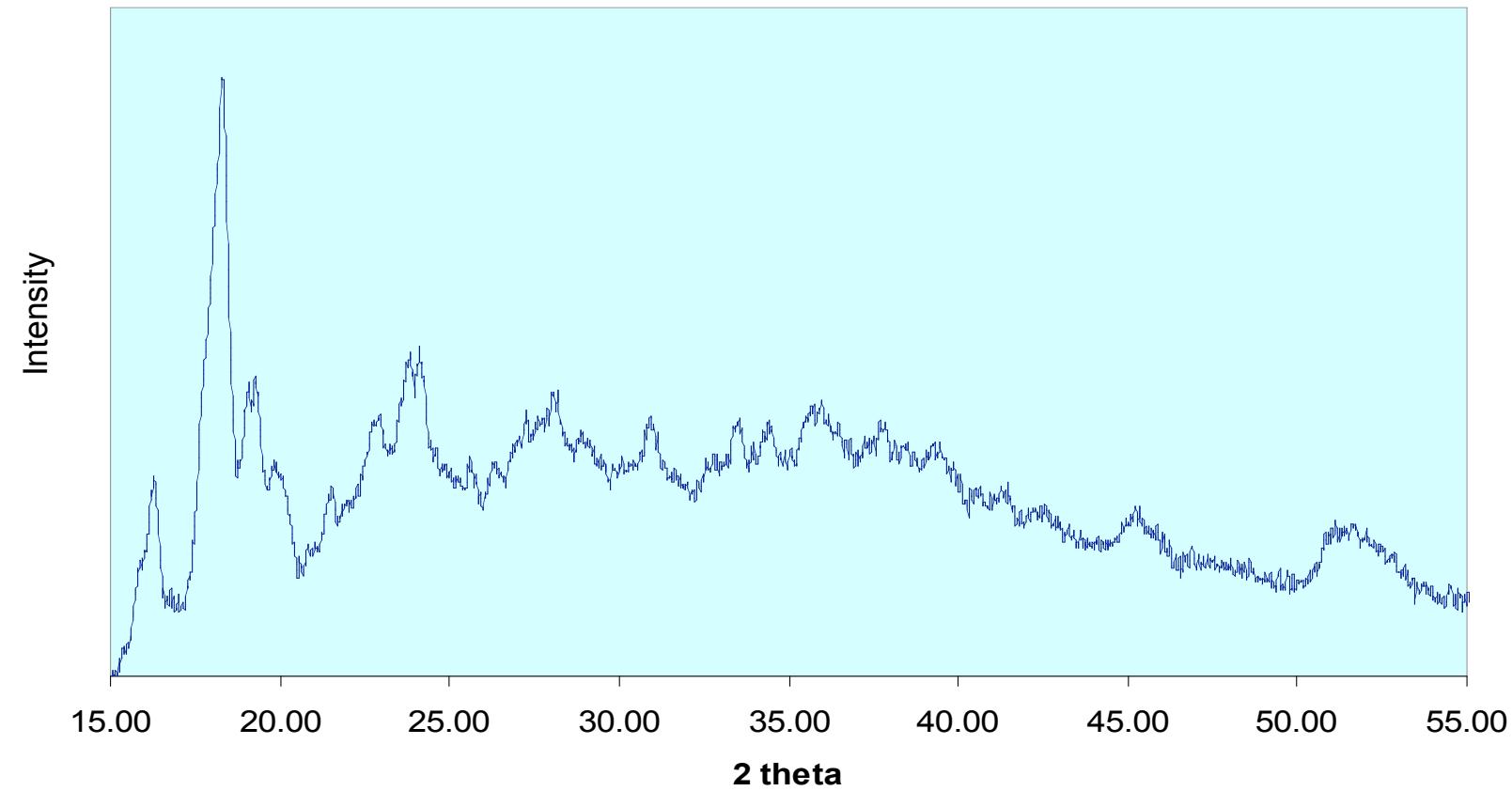
β -cyclodextrine 120°C pre-treatment 0% RH



- *Crystallinity: 98%, water molecules: 0*

β -CD at 33% Relative Humidity

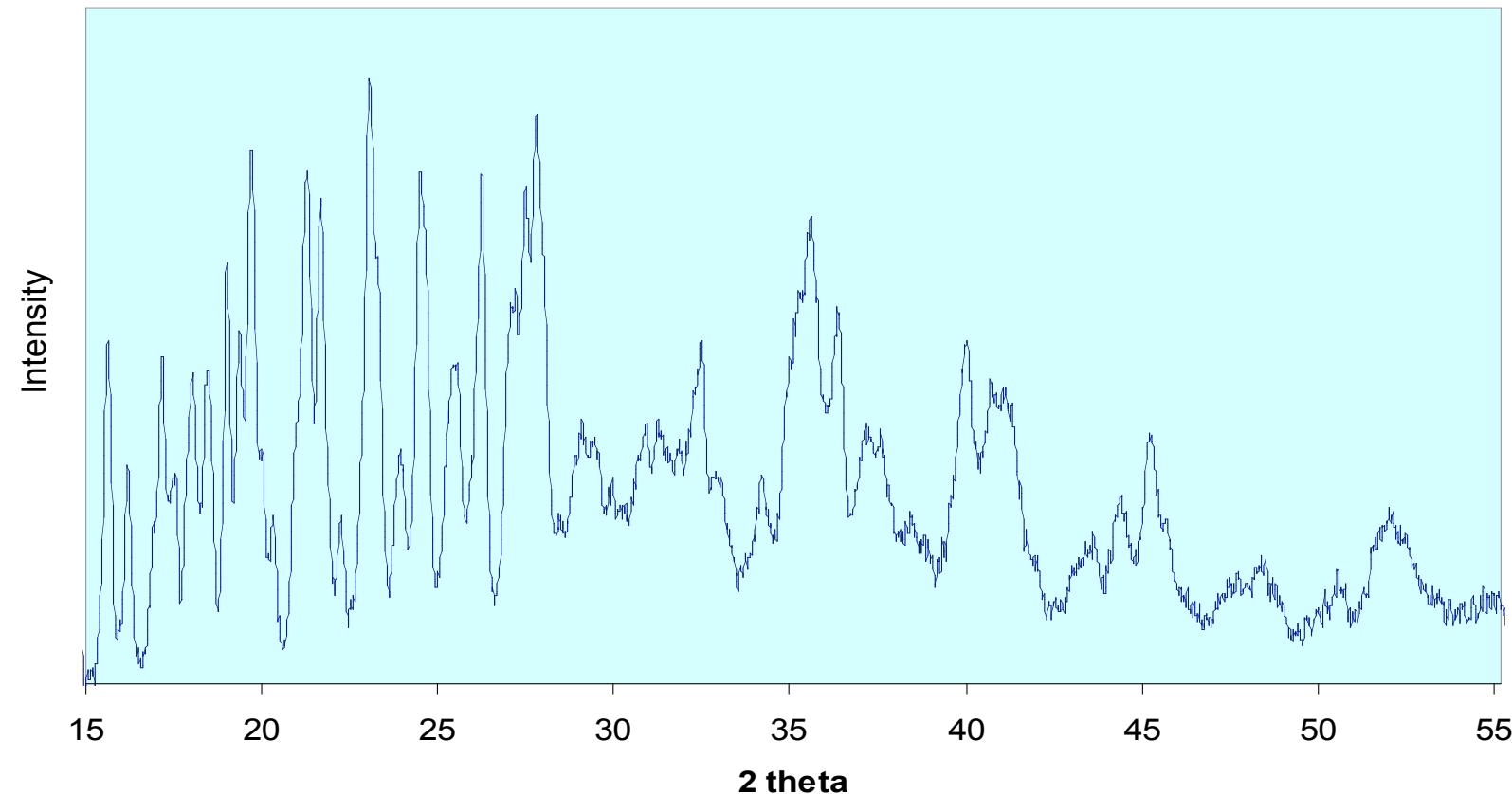
β -cyclodextrine 120°C pre-treatment 33% RH



- *Crystallinity: 30%, water molecules: 11*

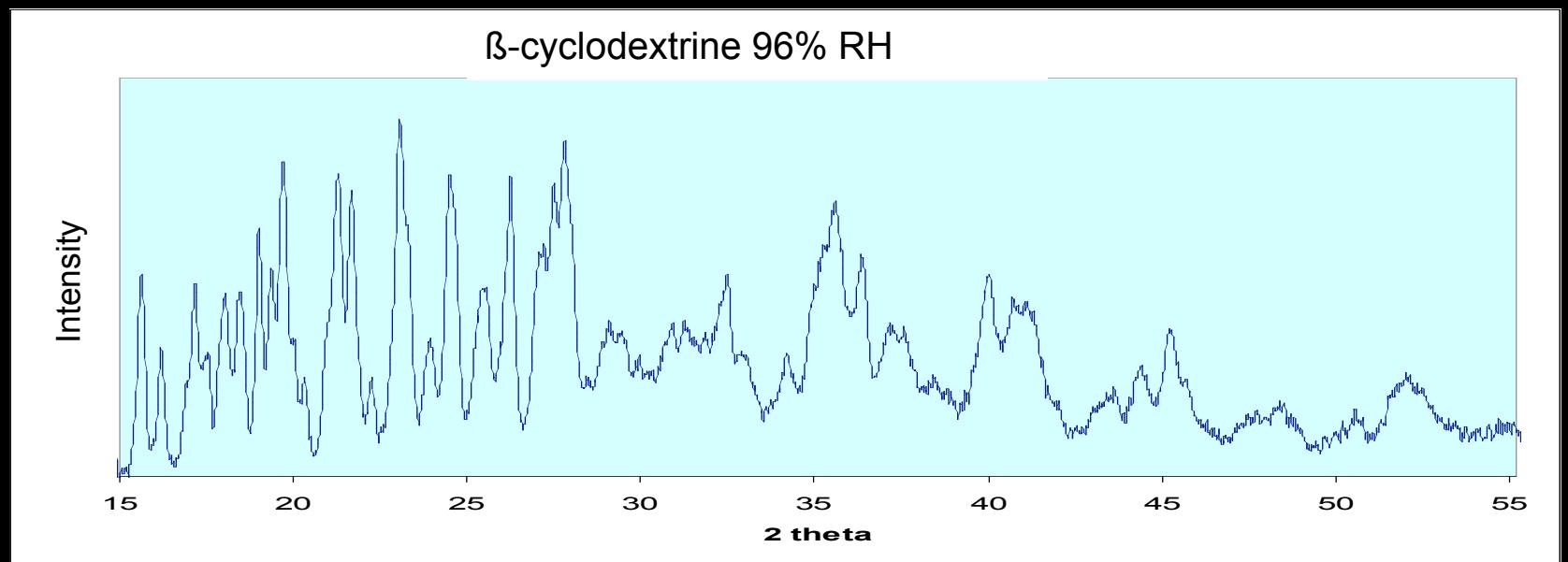
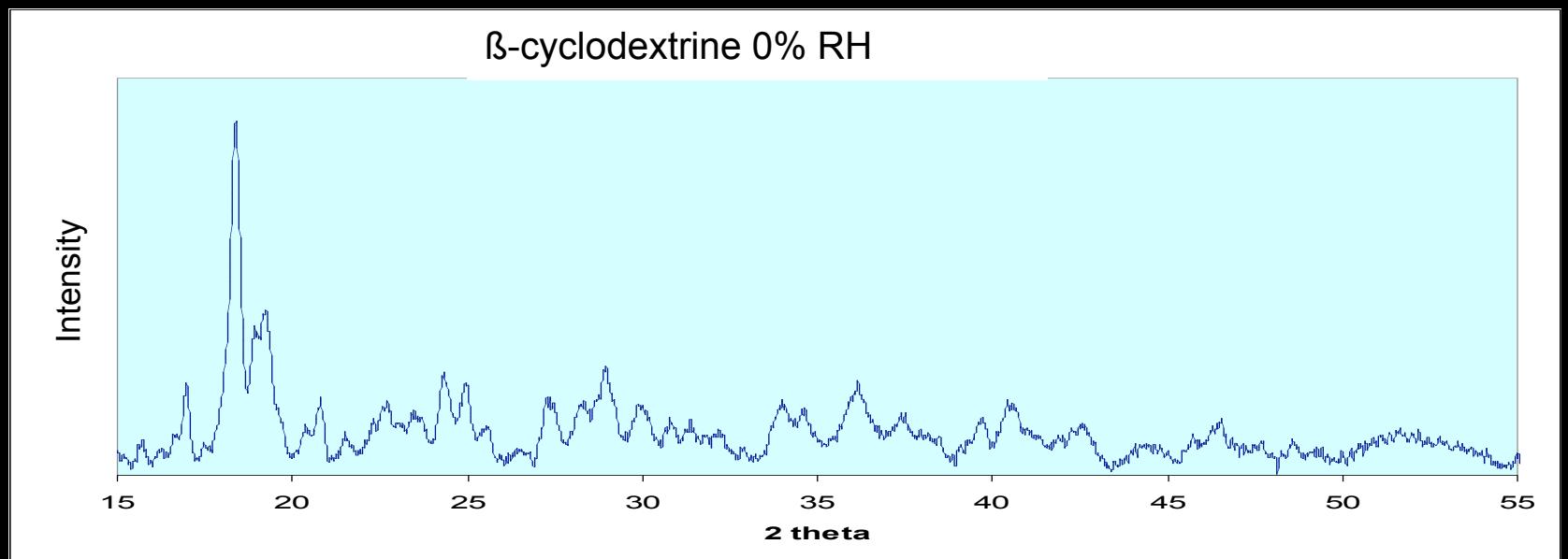
β -CD at 96% Relative Humidity

β -cyclodextrine 120°C pre-treatment 96% RH



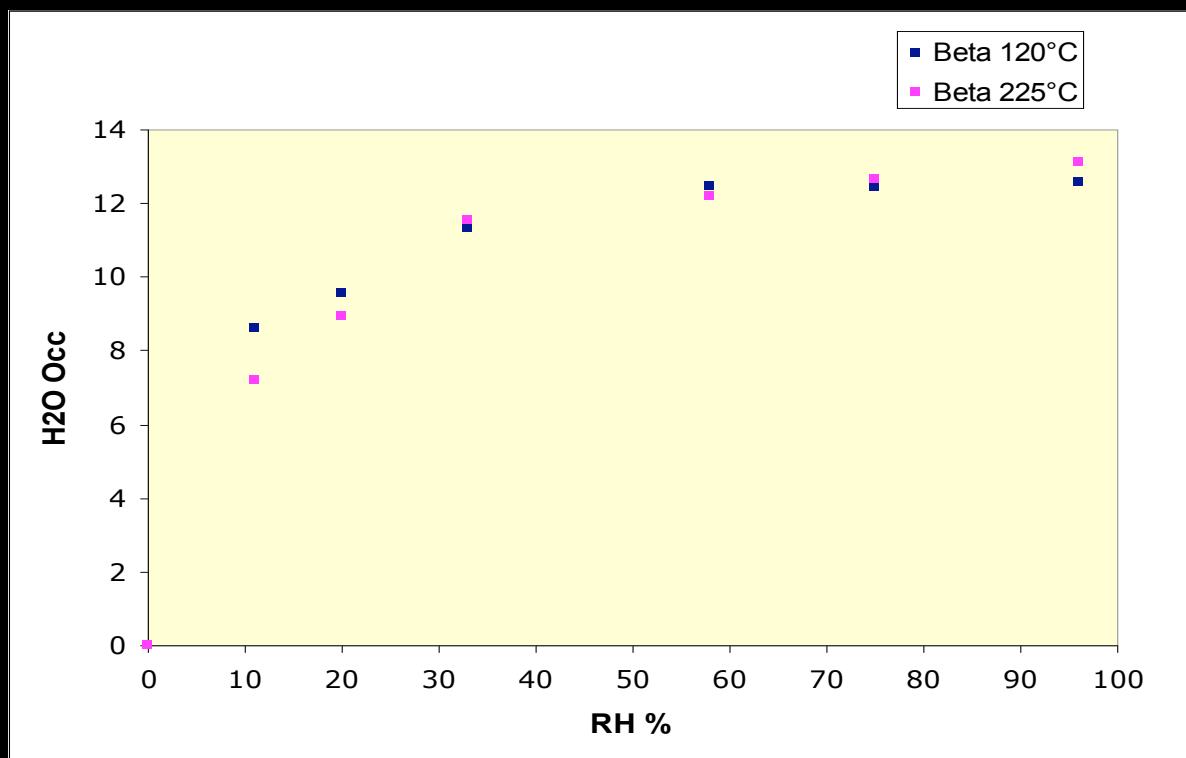
- *Crystallinity: 100%, water molecules: 12.6*

β -CD 0% and 96% RH

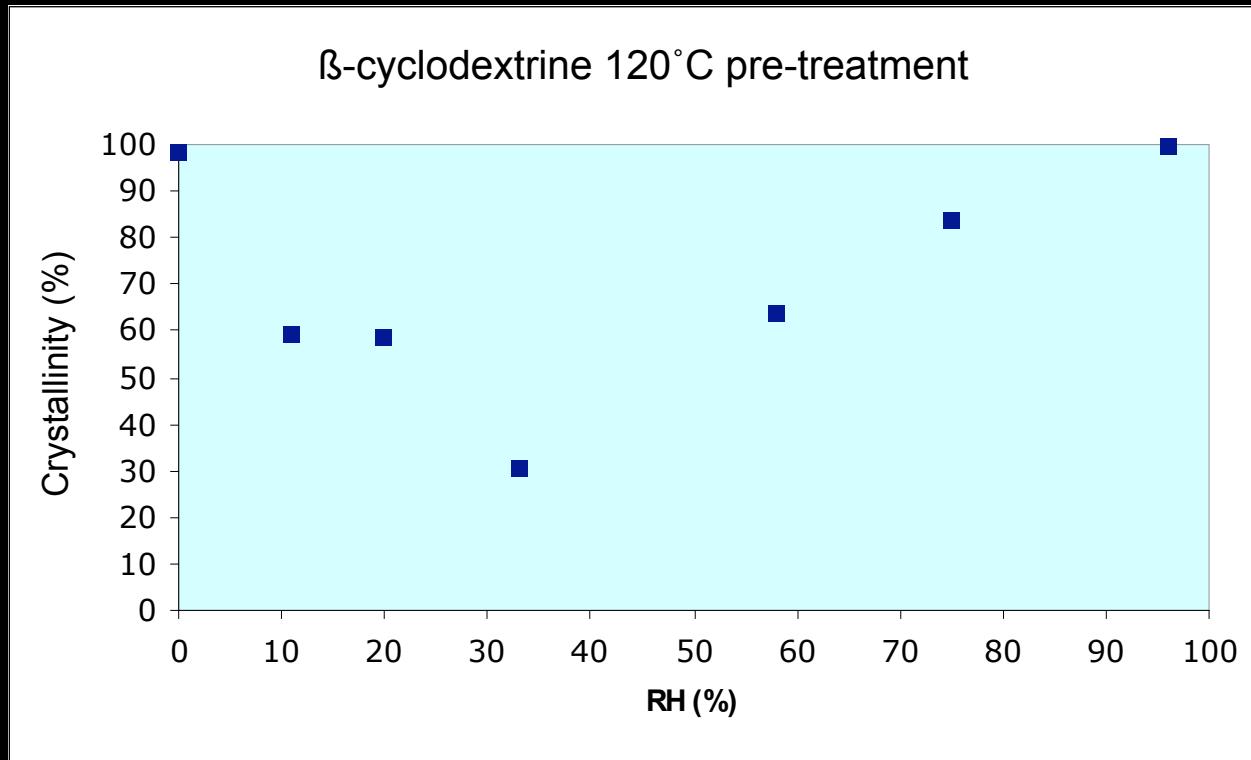


Water sites occupation in β -CD

Pre-treatment	0% RH	11% RH	20% RH	33% RH	58% RH	75% RH	96% RH
120°C	0.0	8.6	9.5	11.3	12.5	12.4	12.6
225°C	0.0	7.2	9	11.5	12.2	12.6	13.1



Effect of humidity on crystallinity

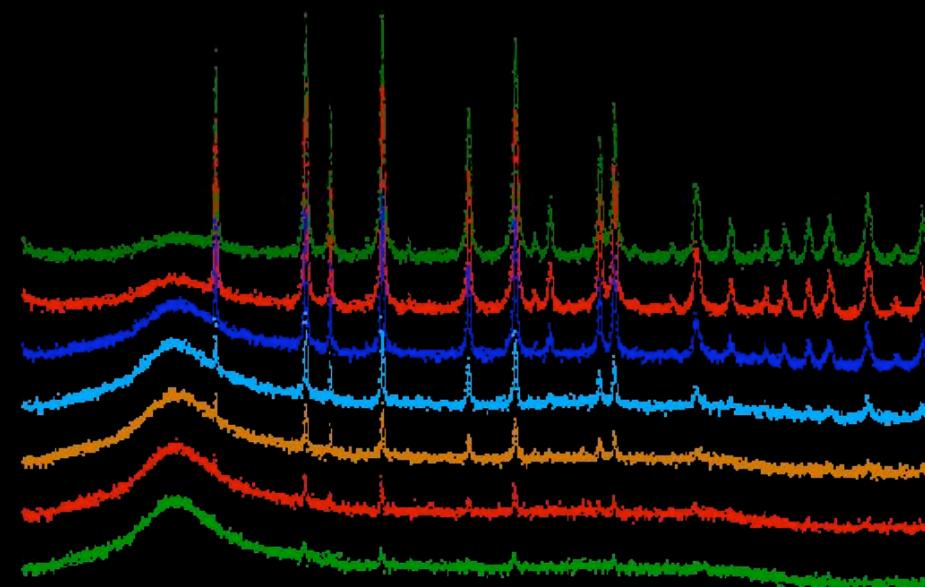
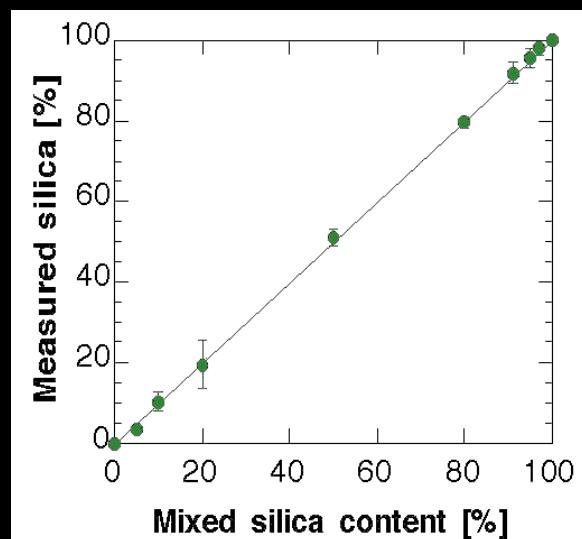


% RH	0	11	20	33	58	75	96
% Crystallinity	98.4	58.9	58.2	30.5	63.5	83.6	99.6

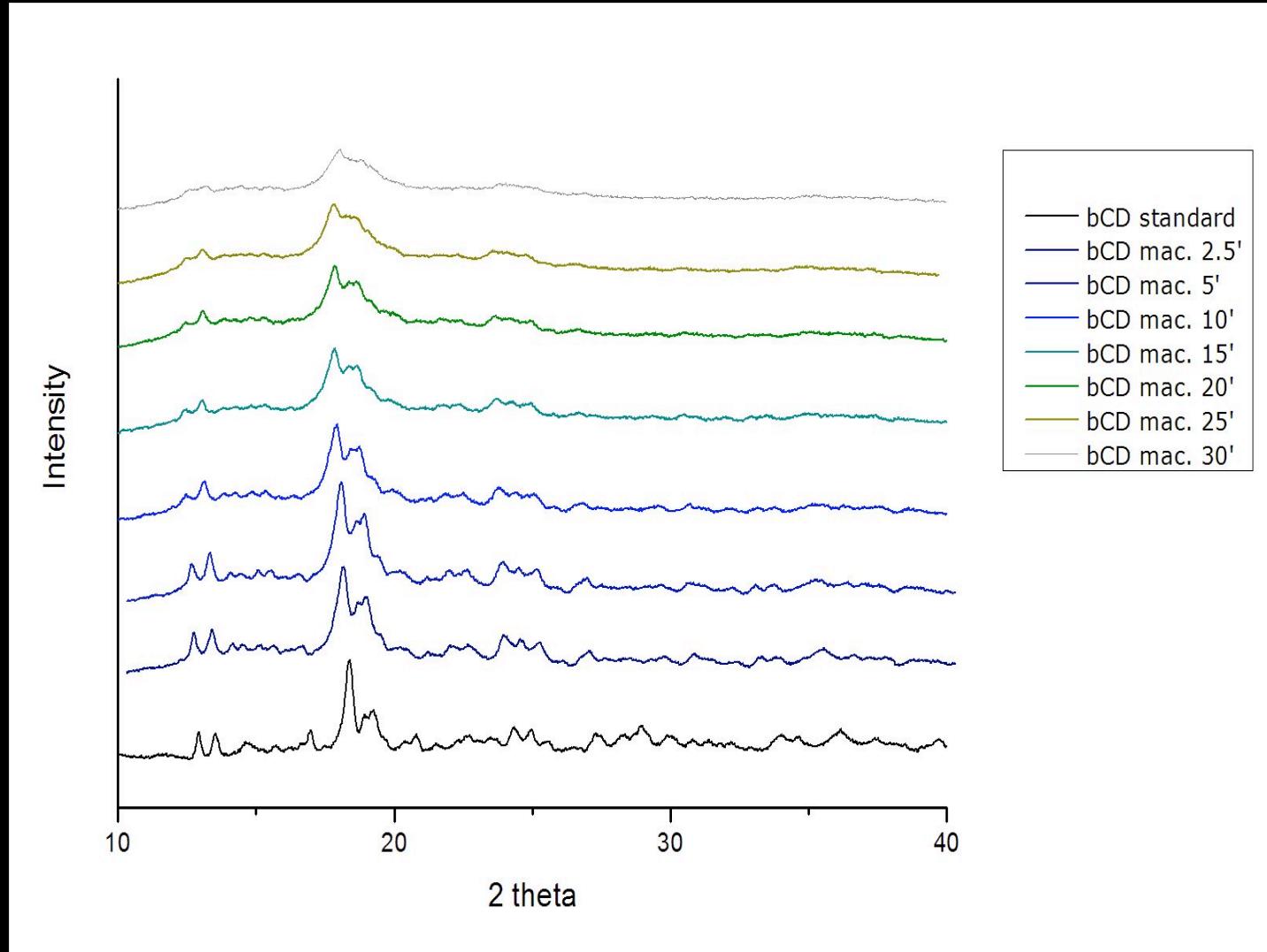
How was crystallinity determined?

- *By approximation of the amorphous structure with a pseudo-nanostructure having nearly the same structure as the corresponding β -CD at the same RH%*
- *Rietveld fitting for quantitative analysis, no internal or external standard needed*

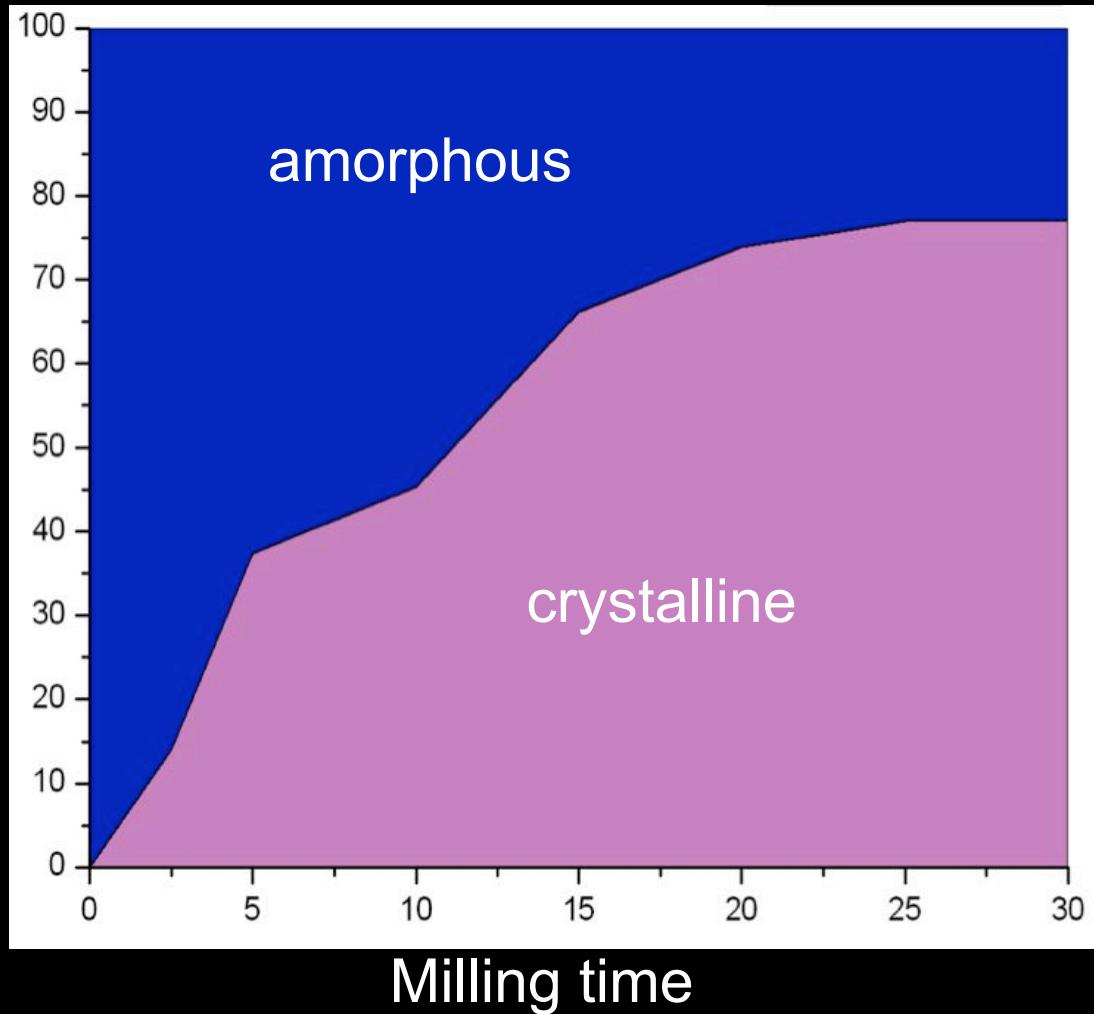
See work by Lutterotti et al.: Mater. Sci. Forum, 1998, 278, 87-92.



β -CD 0%RH, different milling time

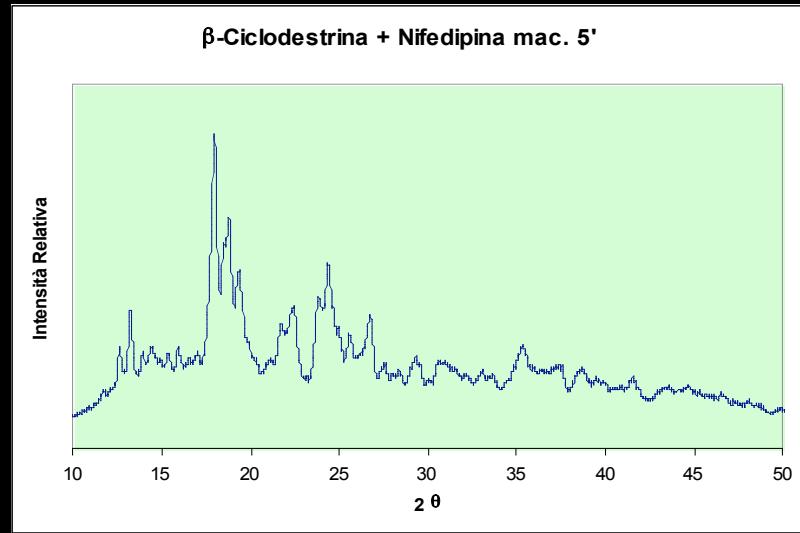
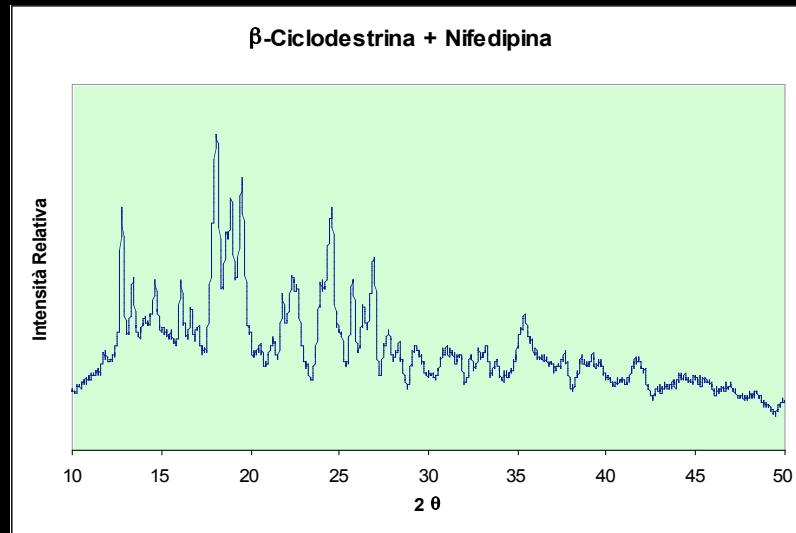
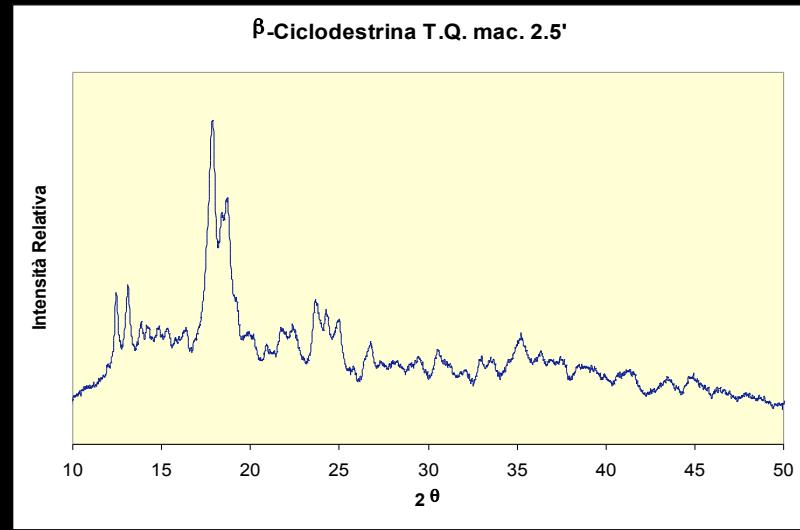
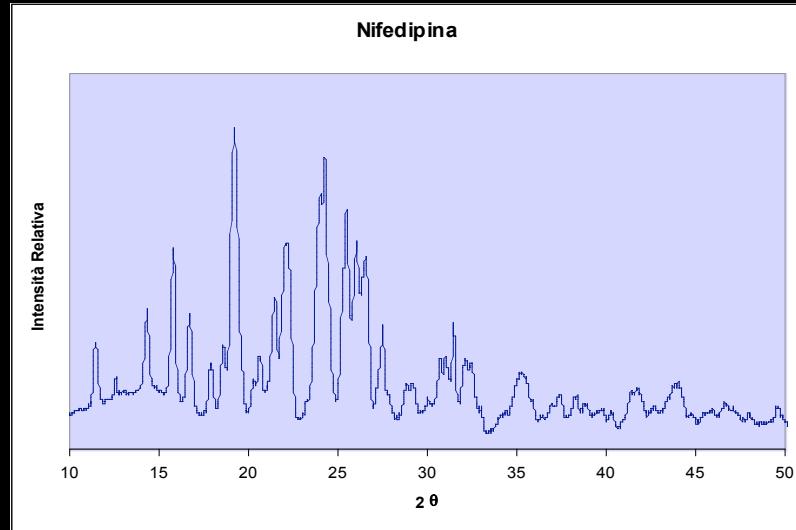


β -CD 0%RH, different milling time



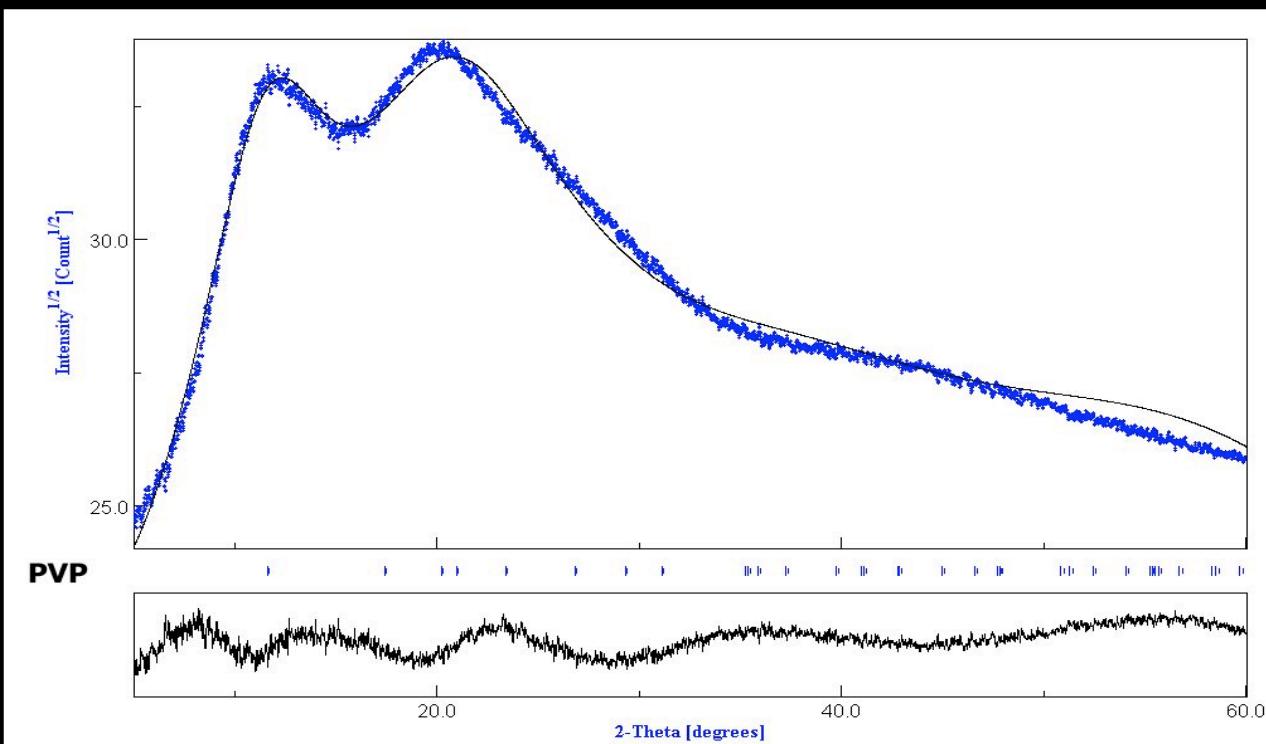
<i>Milling Time</i>	<i>Amorphous</i>
<i>0 min</i>	<i>0.0%</i>
<i>2.5 min</i>	<i>14%</i>
<i>5 min</i>	<i>37%</i>
<i>10 min</i>	<i>45%</i>
<i>15 min</i>	<i>66%</i>
<i>20 min</i>	<i>74%</i>
<i>25 min</i>	<i>77%</i>
<i>30 min</i>	<i>77%</i>

β -CD + nifedipine



PVP/drug system

- *PVP is amorphous*
- *The goal is to determine the crystallinity of the drug inside the amorphous PVP*
- *Difficult to fit the amorphous structure with the pseudo-nanocrystalline approach*



Determining the crystalline content

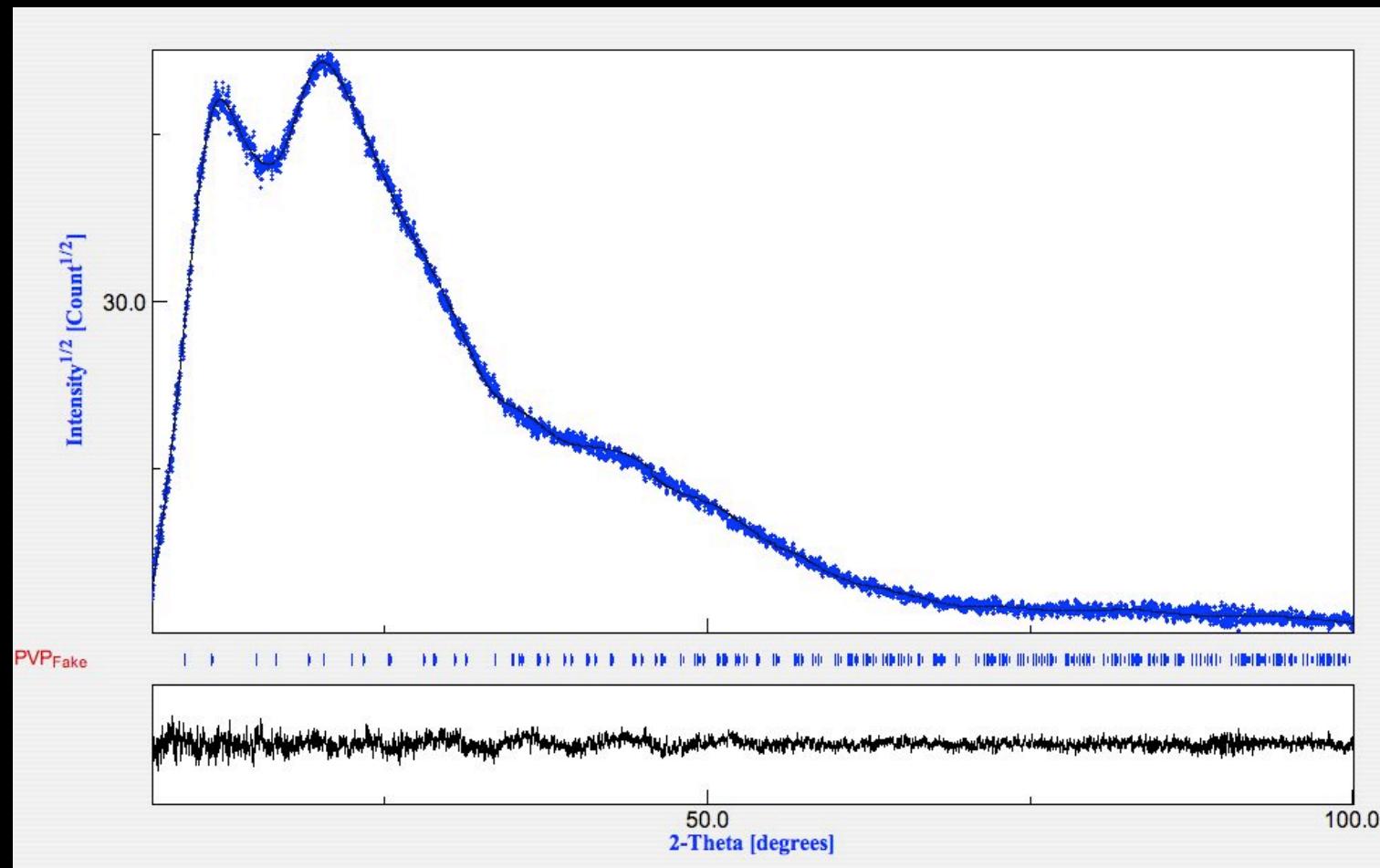
- *PVP amorphous pseudo-structure fitting:*
 - *Atomic model based on one PVP model*
 - *MEEM (maximum entropy electron map) for unknown structures (need calibration by one standard measurement)*
- *Application of the PVP amorphous pseudo-structure to the PVP/Griseofulvine system*
- *Griseofulvine amorphous well fitted by a pseudo-structure based on the crystalline structure (amorphous structure bound to the crystalline structure)*
- *The two amorphous have a different pattern*
- *Fitting the spectra by Rietveld (Maud)*

How MEEM works

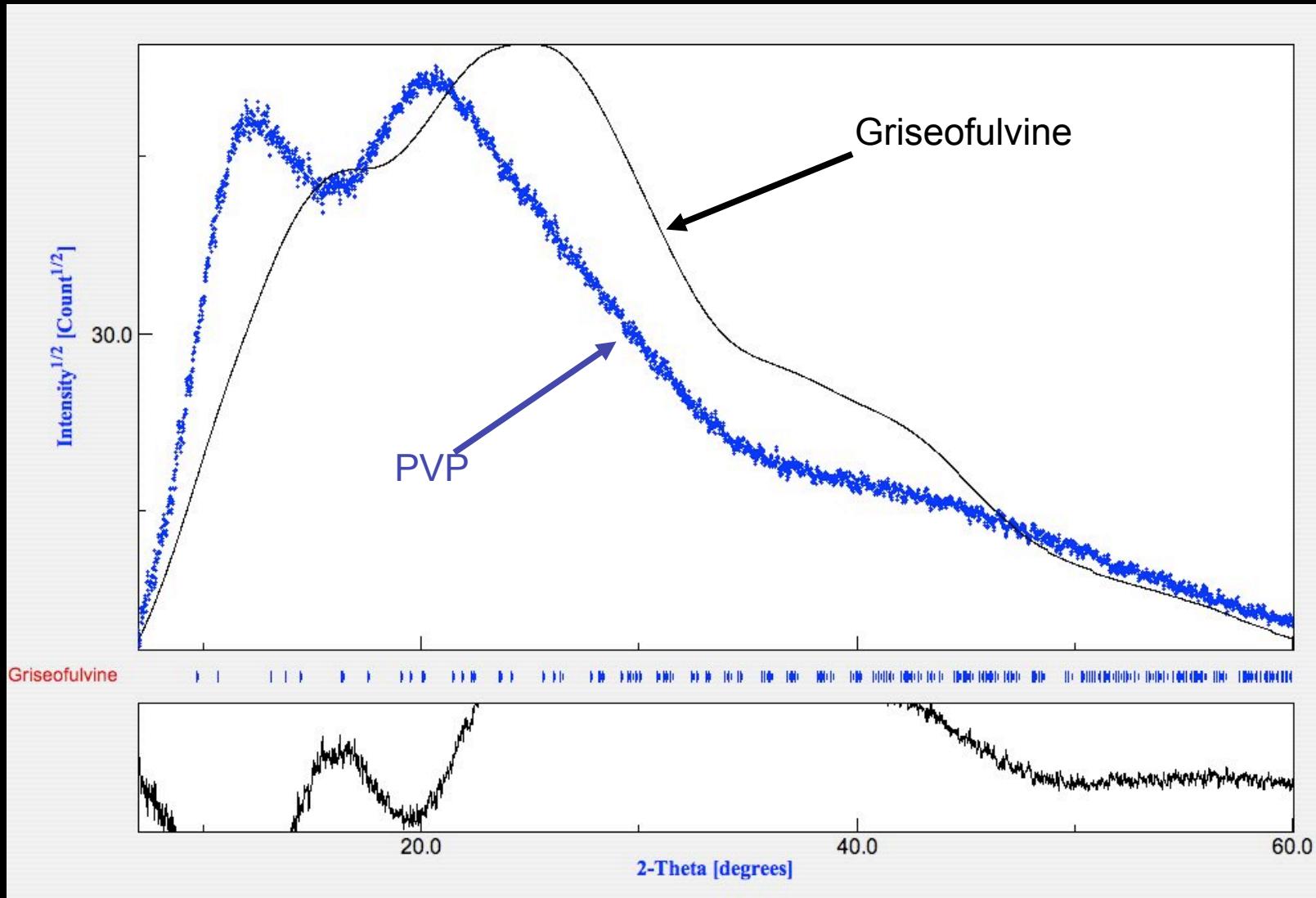
- *MEEM stands for Maximum Entropy Electron Map*
- *It is derived by MEED (S.Kumazawa et al., J.Appl.Cryst., 26, 453-457, 1993)*
- *A two cycle step is applied to fitting the spectrum in iterations:*
 - *First cycle:*
 - *Fobs extraction by Le Bail*
 - *MEED algorithm applied to obtain an electron density map*
 - *The electron density map is normalize to the nominal electron density*
 - *Second cycle:*
 - *One least square iteration in the Rietveld pattern fitting computing structure factors from the normalized electron density map*
- *For calibration a known amount of a second phase is added and a phase scale factor is optimized for the MEEM simulated phase*

The PVP amorphous pseudo-structure by MEEM

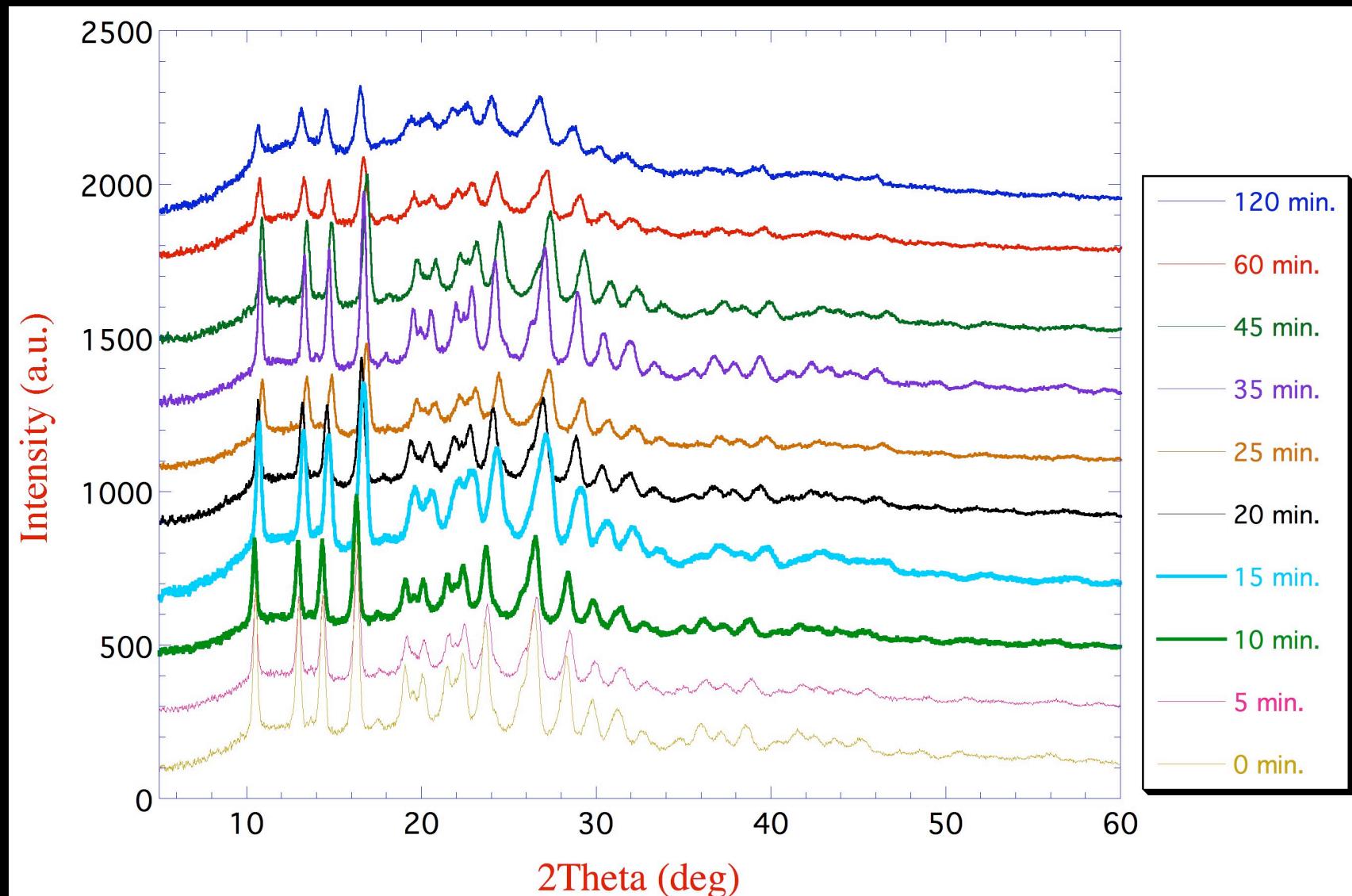
- $R_W = 0.58\%$, $R_W(\text{no bkg}) = 0.64\%$, linear bkg
- Crystallites = 15 Angstrom, microstrain = 0.02



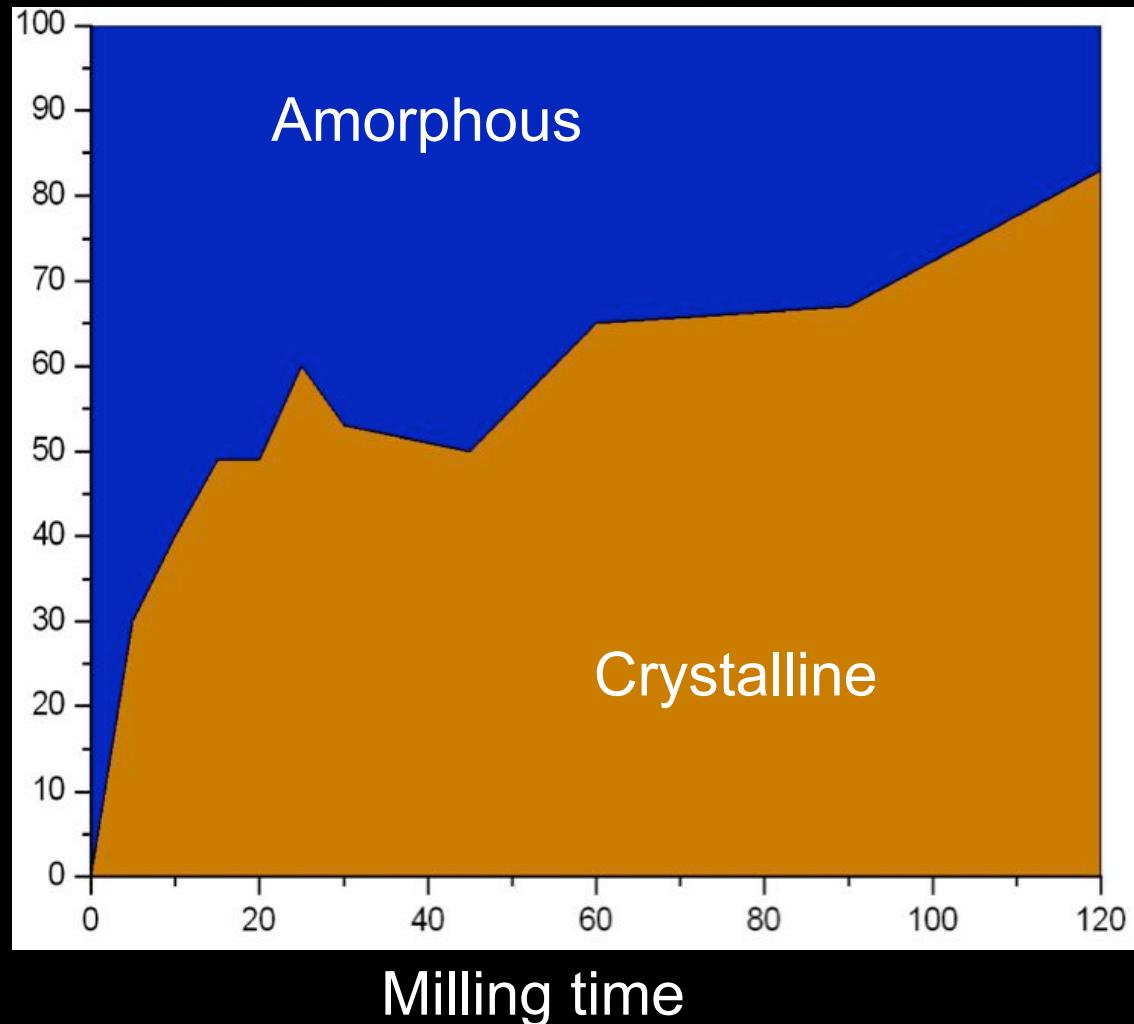
Griseofulvine-PVP amorphous comparison



PVP+Griseofulvine (ball milled)



Results: Griseofulvine crystallinity (inside the PVP)



<i>Milling time</i>	<i>amorphous</i>
<i>0 min</i>	<i>0.0%</i>
<i>5 min</i>	<i>30%</i>
<i>10 min</i>	<i>40%</i>
<i>15 min</i>	<i>49%</i>
<i>20 min</i>	<i>50%</i>
<i>25 min</i>	<i>60%</i>
<i>30 min</i>	<i>54%</i>
<i>45 min</i>	<i>50%</i>
<i>1 h</i>	<i>65%</i>
<i>1.5 h</i>	<i>68%</i>
<i>2 h</i>	<i>83%</i>

Results

- *Maud (extended Rietveld method) is a powerful tool to analyze pharmaceutical systems*
- *The image plate diffractometer is a quick, versatile and not expensive instrument*
- *We were able to determine the crystallinity of:*
 - *β -CD at different RH*
 - *β -CD at different milling time*
 - *Drug inside the β -CD or PVP amorphous matrix*
- *To characterize the structural changes in the carrier/drug system*
- *To analyze the microstructure of the crystalline structures*

Maud is available

- At: <http://www.ing.unitn.it/~luttero/maud> (*free version, not a demo*)
- Through *Italstructures* <http://www.italstructures.com> (*customized full version*)
- *For demo or questions see Italstructures desk here at the meeting*

