Using XRD to monitor the influence of milling on physical properties of a hydrate

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Quality, Affordable Healthcare Products

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Outline

Introduction: Micronized particles in the pharmaceutical industry

The goal – micronized hydrate

Product description

Monitoring milling with XRD

Micronized particles in the pharmaceutical industry

1. Crystallization with/without additives
2. Spray drying (to make a hydrate?)
3. Size reduction (mills, homogenizers)
4. Various methods with super-critical CO_2

The goal

Reproducible production of micron-size particles of a hydrate, while maintaining both its crystal form and stoichiometric water content

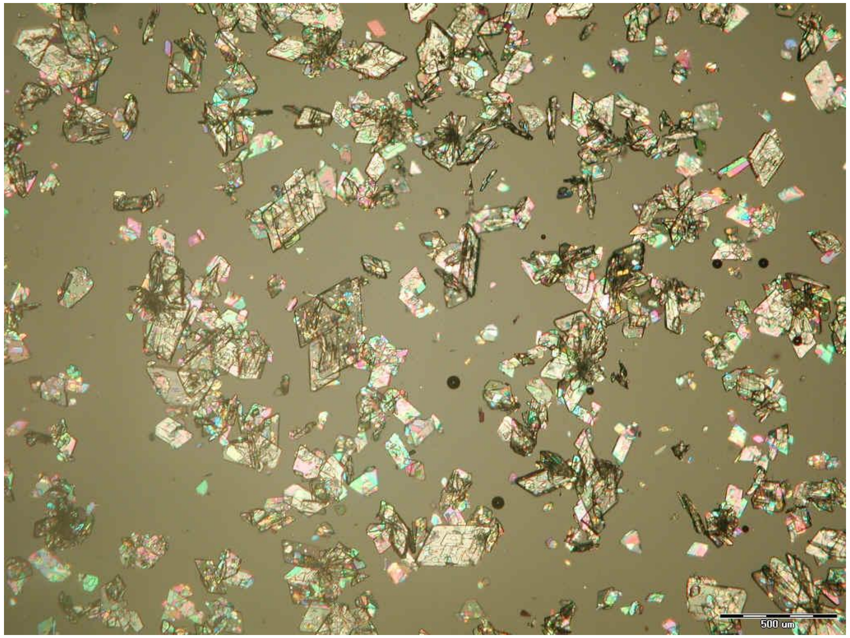
Product description

Channel Monohydrate, 3.3% water

Soft, flat parallelogram particles

Target size: <10 microns

Target water content: >3.1% (KF)



500 µm

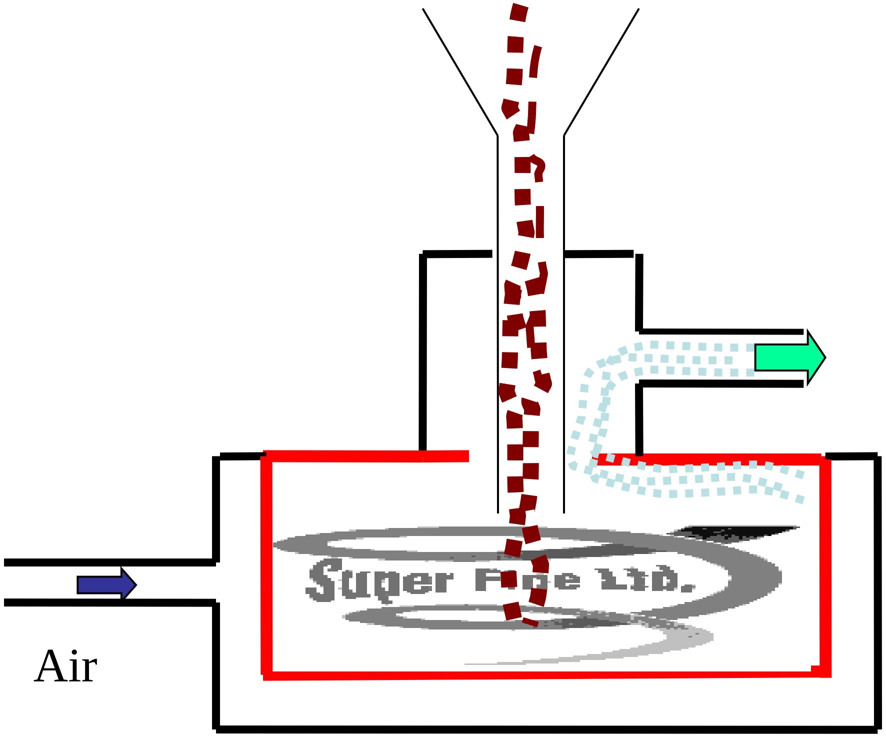
Vortex mill

✓ Vortex mill described in US patent **6,789,756** owned by **<u>Super Fine Ltd</u>** (Yokneam, Israel).

✓The vortex mill uses pressure gradient in a vortex chamber, to break the particles along their structural weak points.

✓ Theoretically, no damage to the crystals

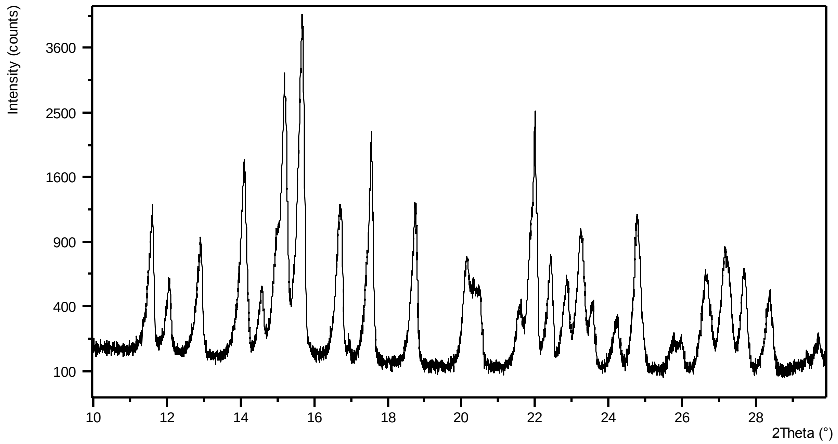
✓ **Practically, severe damage detected during early milling campaigns.**



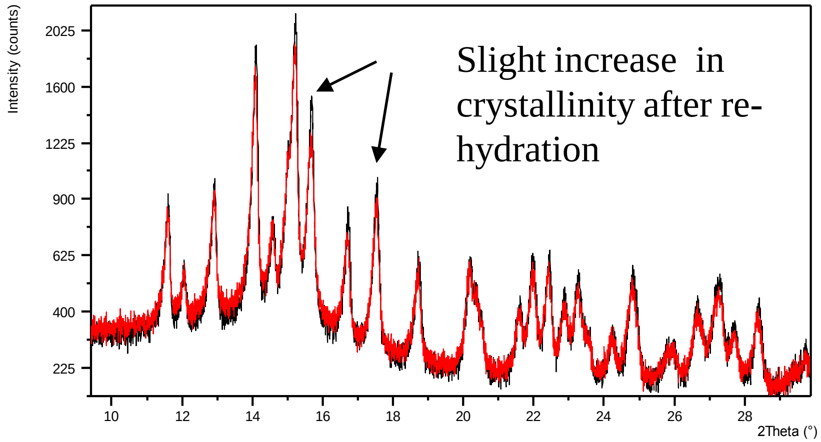
Proprietary Super Fine Ltd. mill

Original process

- ❑ Size reduction by milling
- ❑ Focus on size
- ❑ No significant improvement in crystallinity and water content after re-hydration



Before milling

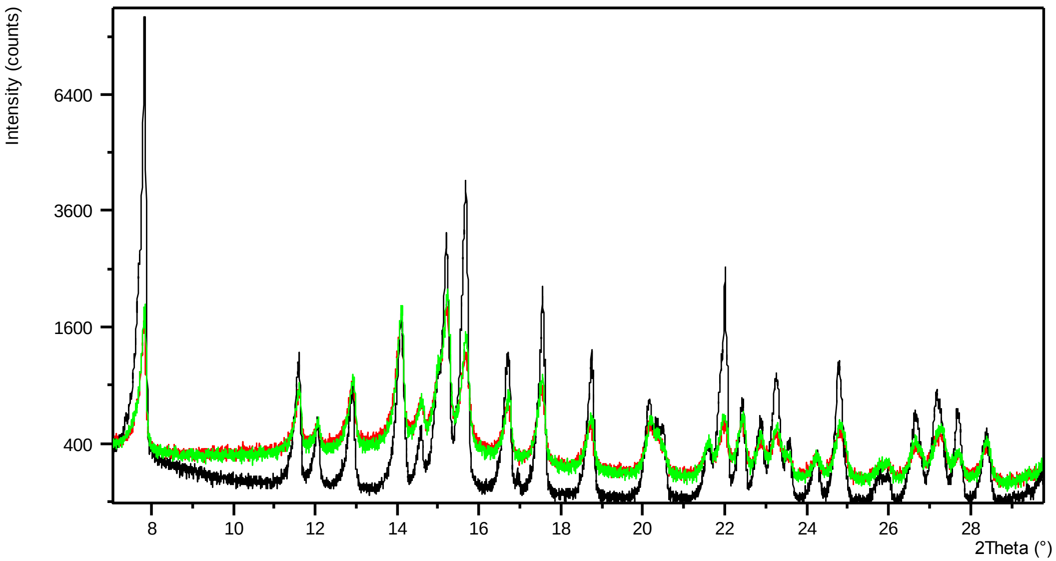


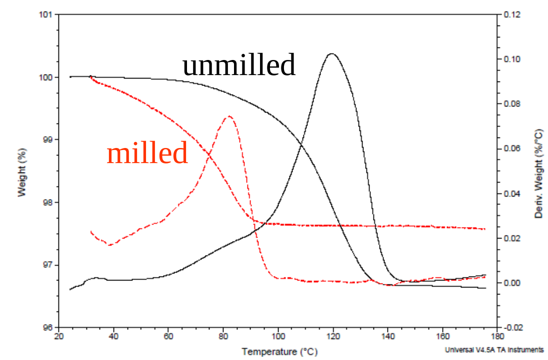
Milled – red

Re-hydrated - black

<u>Re-hydration needed after milling</u>

Is it all about size?





Black - before milling

Red – After milling

Green – After re-hydration

Methodology

Optimization of milling process

Correlating milling parameters and **both** size distribution and degree of crystallinity by XRD

Correlating water content after re-hydration step to milling parameters and degree of crystallinity

Milling parameters

* Size distribution before milling

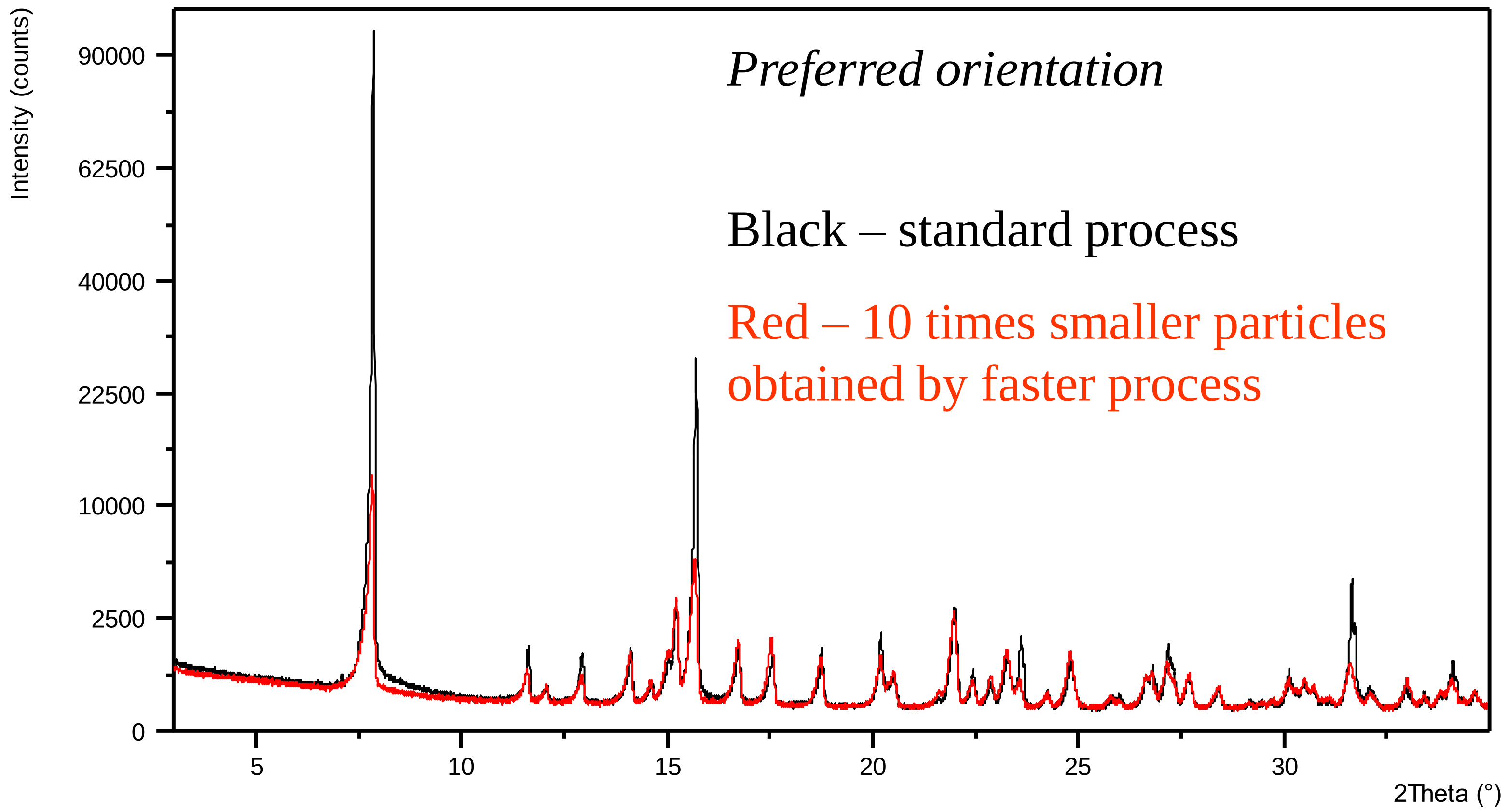
Milling pressure

(Milling feed rate, size of entry and exit…)

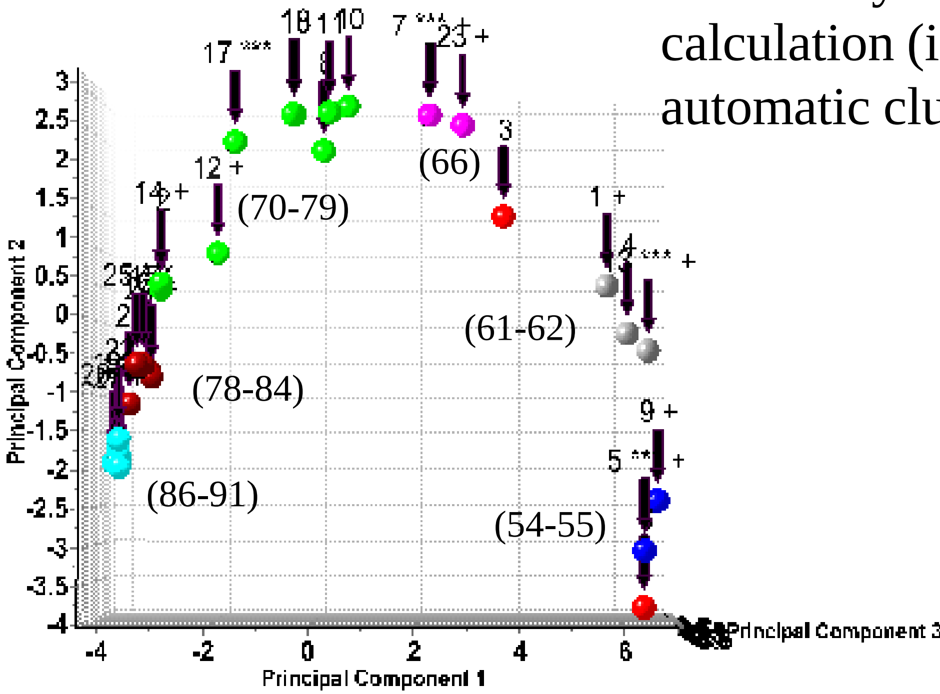
Number of milling cycles

Results and Discussion

Influence of preparation procedure on initial XRD pattern and crystallinity



XRD Cluster analysis

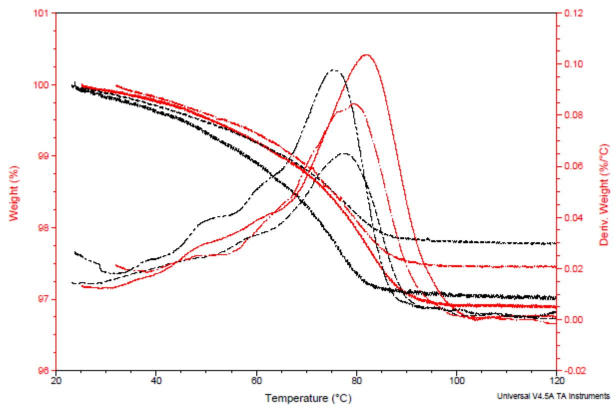


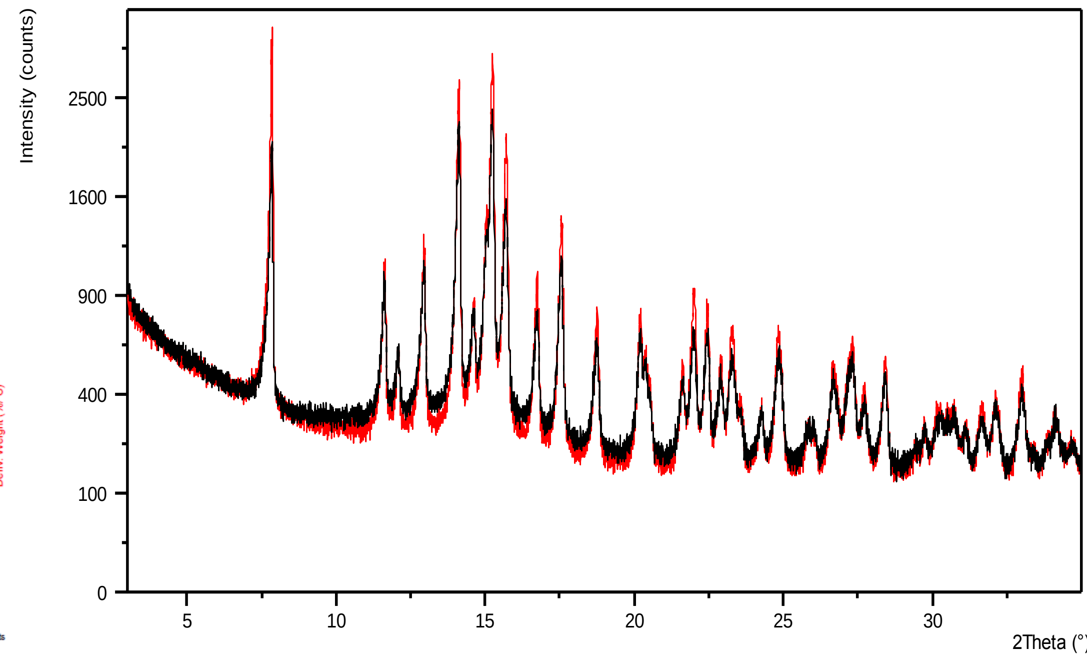
- Correlation between manual crystallinity calculation (in brackets) and automatic clustering

1. initial particles size

Milling pressure:
6 Bar

Milling cycles: 1



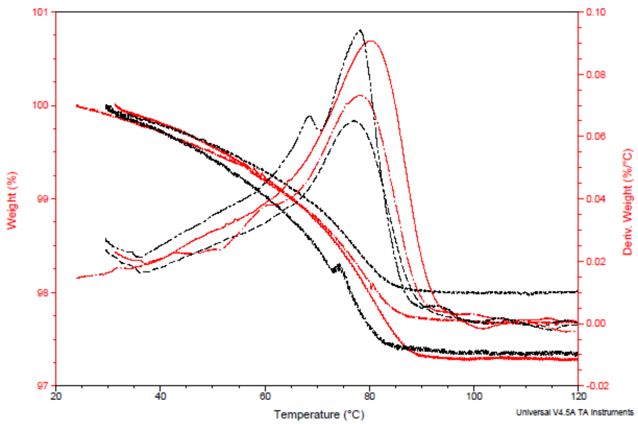


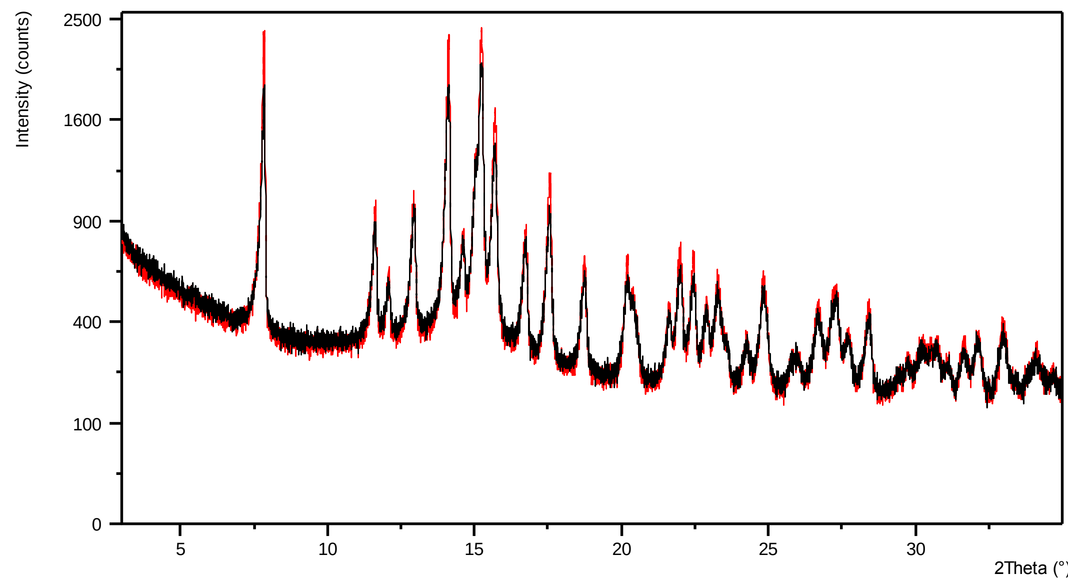
Initial size D(V,0.9), µm	Size after milling, D(V,0.9), µm	% Crystallinity after milling	% Crystallinity After re-hydration	Weight loss by TGA in final material, % weight
650 µm	6.1	61	78	3.0 (91)
60 µm	5.4	73	89	3.1 (94)

1. initial particles size

Milling pressure:
3 Bar

Milling cycles: 3

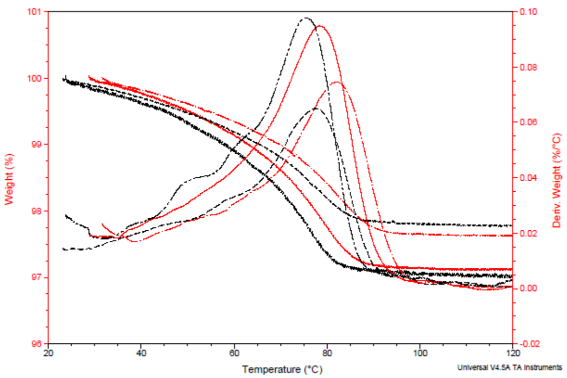


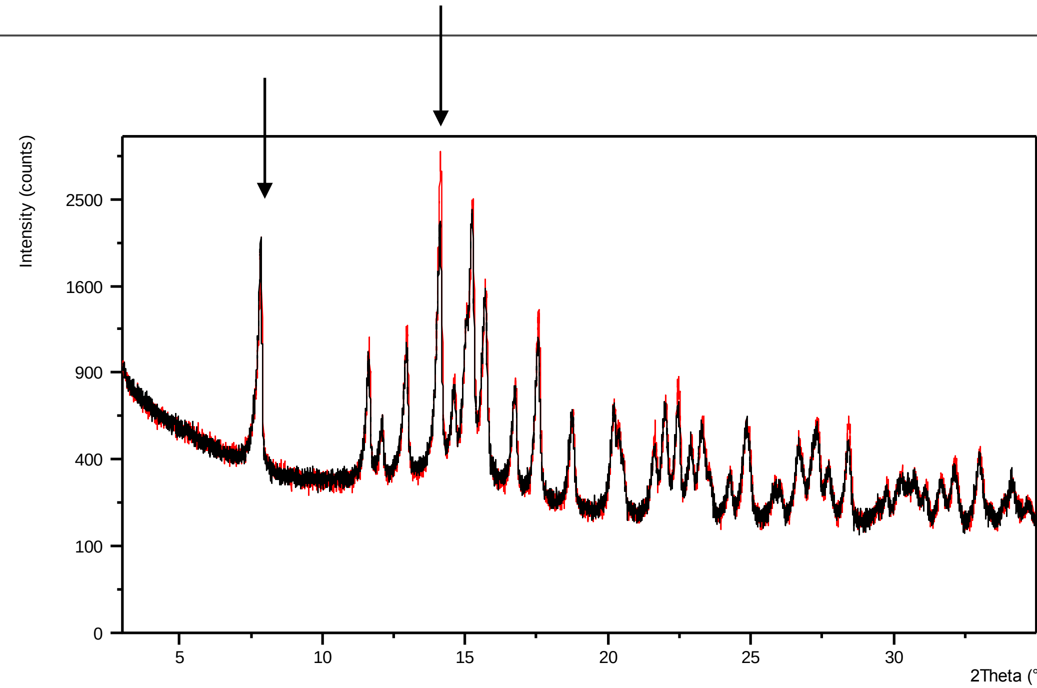


Initial size D(V,0.9), µm	Size after milling, D(V,0.9), µm	% Crystallinity after milling	% Crystallinity After re-hydration	Weight loss by TGA in final material, % weight
650 µm	3.4	55	74	2.8 (85)
60 µm	4.1	60	79	2.7 (82)

2. Milling pressure

Initial size: 650 µm





Milling pressure, Bar	Size after milling, D(V,0.9), µm	% Crystallinity after milling	% Crystallinity After re-hydration	Weight loss by TGA in final material, % weight
6	5.4	61	78	3.0 (90.9)
3	7.8	64	84	2.9 (87.9)

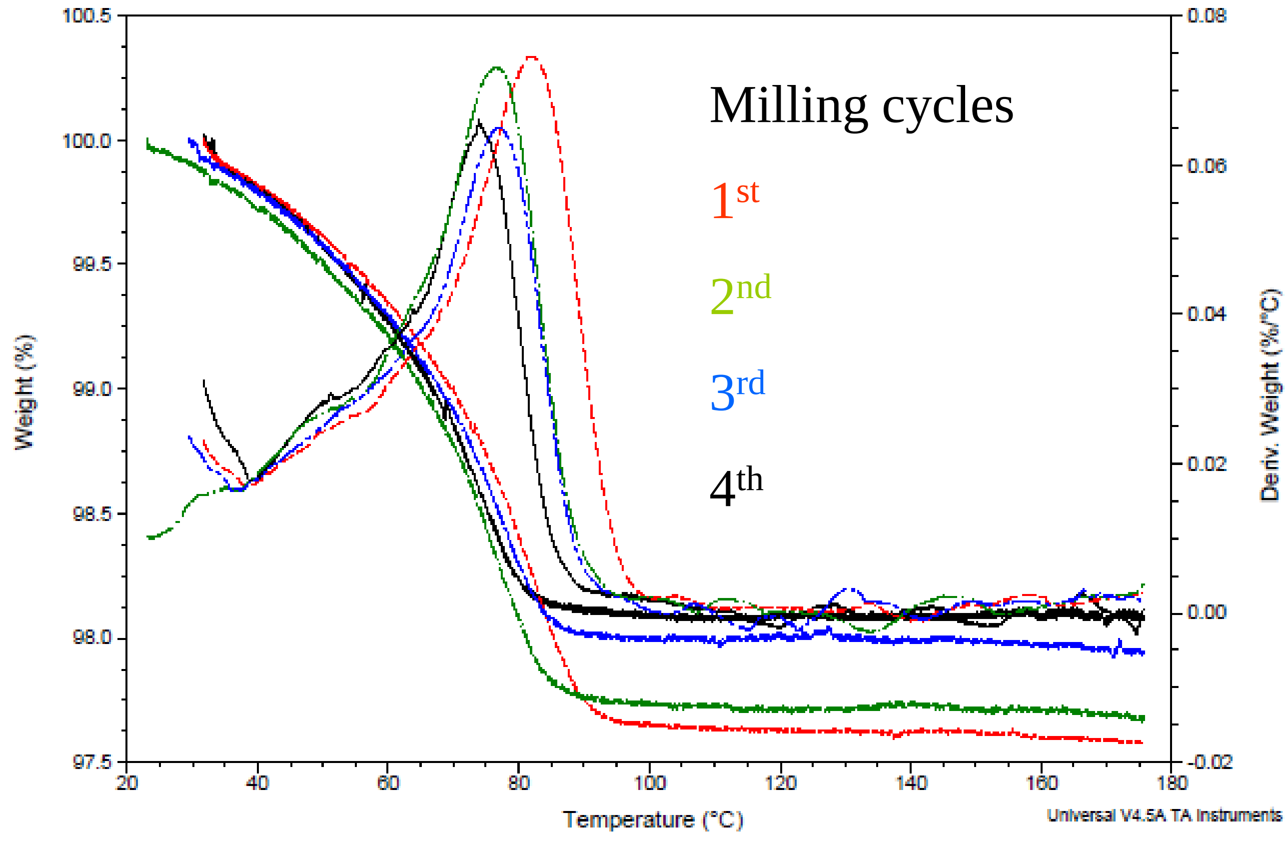
3. Number of milling cycles

Initial size: 650 µm

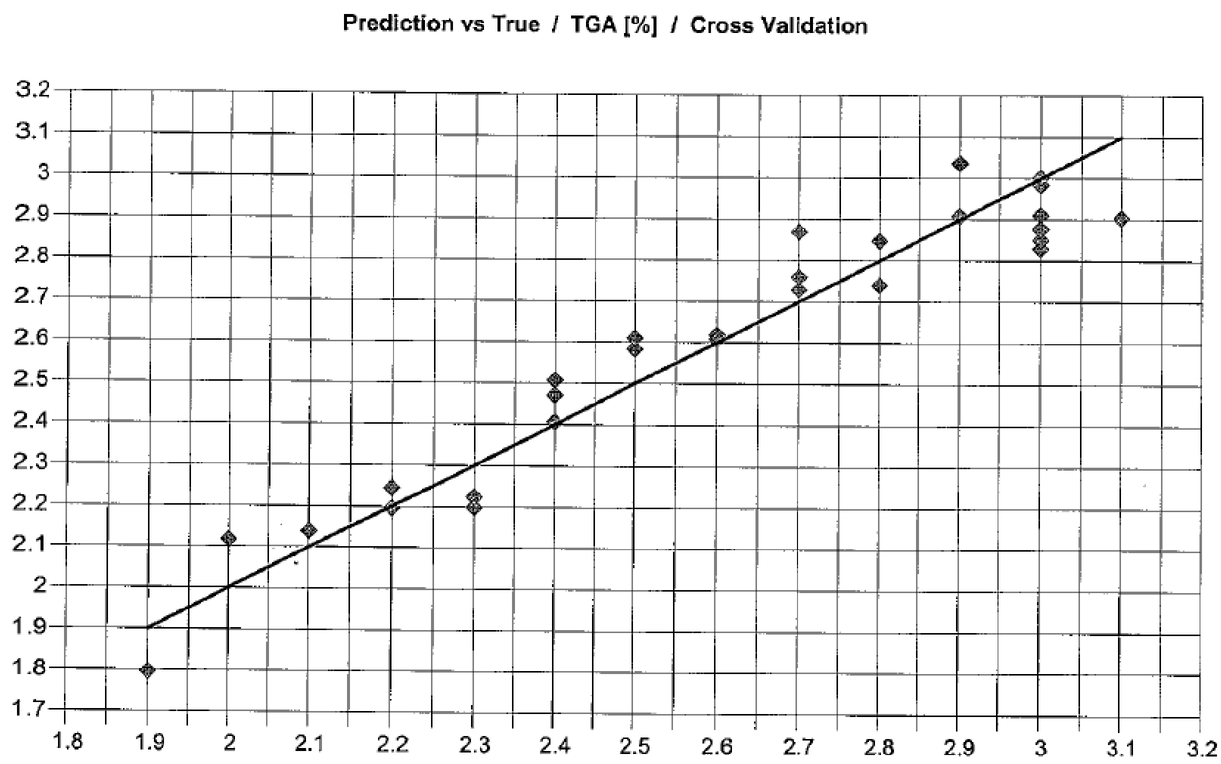
Milling pressure: 3 Bar

Milling cycles	Size after milling, D(V,0.9) µm	% Crystallinity after milling	TGA after milling, % weight	Final crystallinity after re-hydration	Final TGA, % weight
1	7.8	64	2.4 (73)	84	2.9 (88)
2	5.1	61	2.3 (70)	79	2.8 (85)
3	3.4	55	2.0 (61)	74	2.7 (82)
4	3.0	50	1.9 (58)	73	2.6 (79)

Structural effects - 4 milling cycles

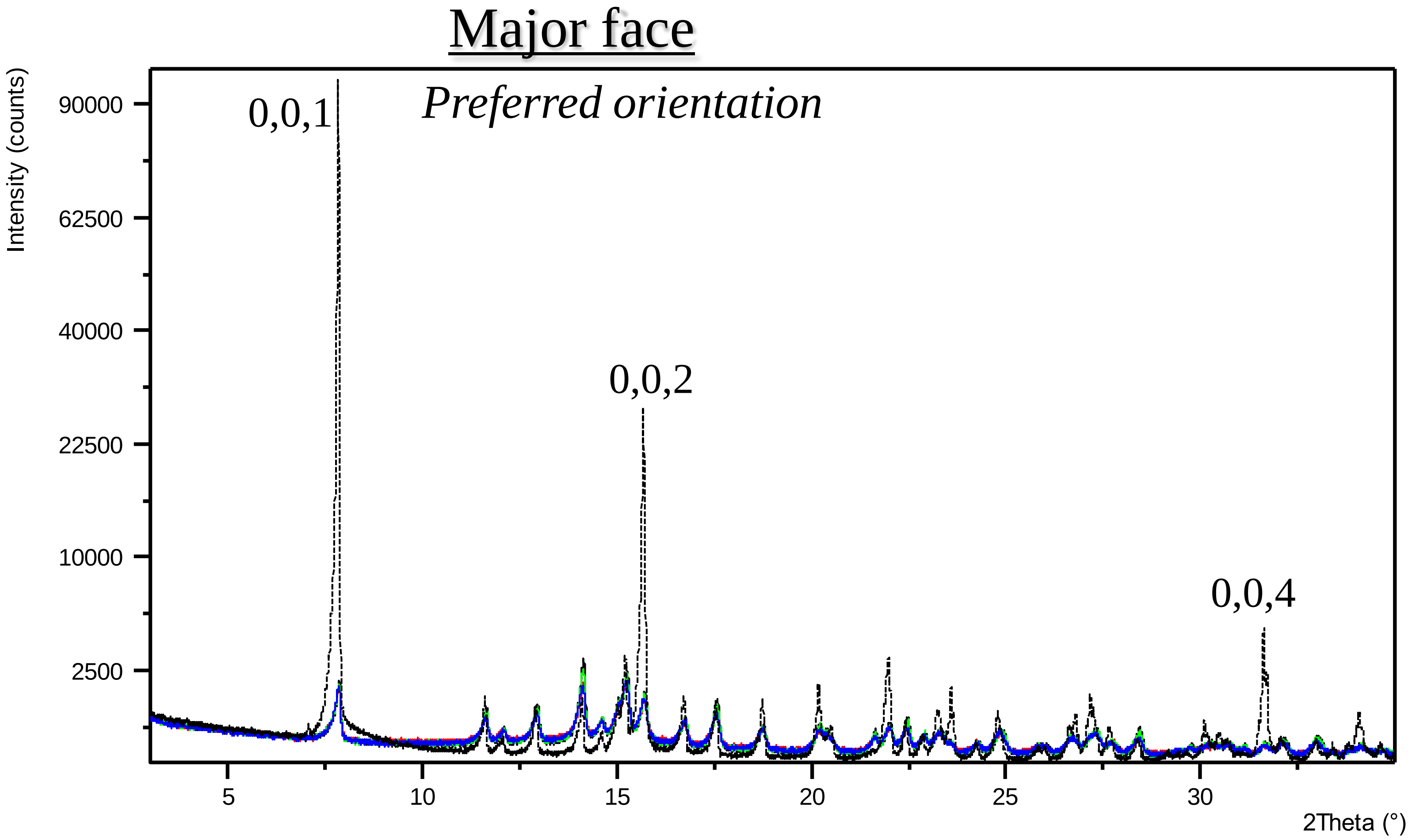


Chemometric correlation of percent water content (TGA) and predicted percent crystallinity form XRD



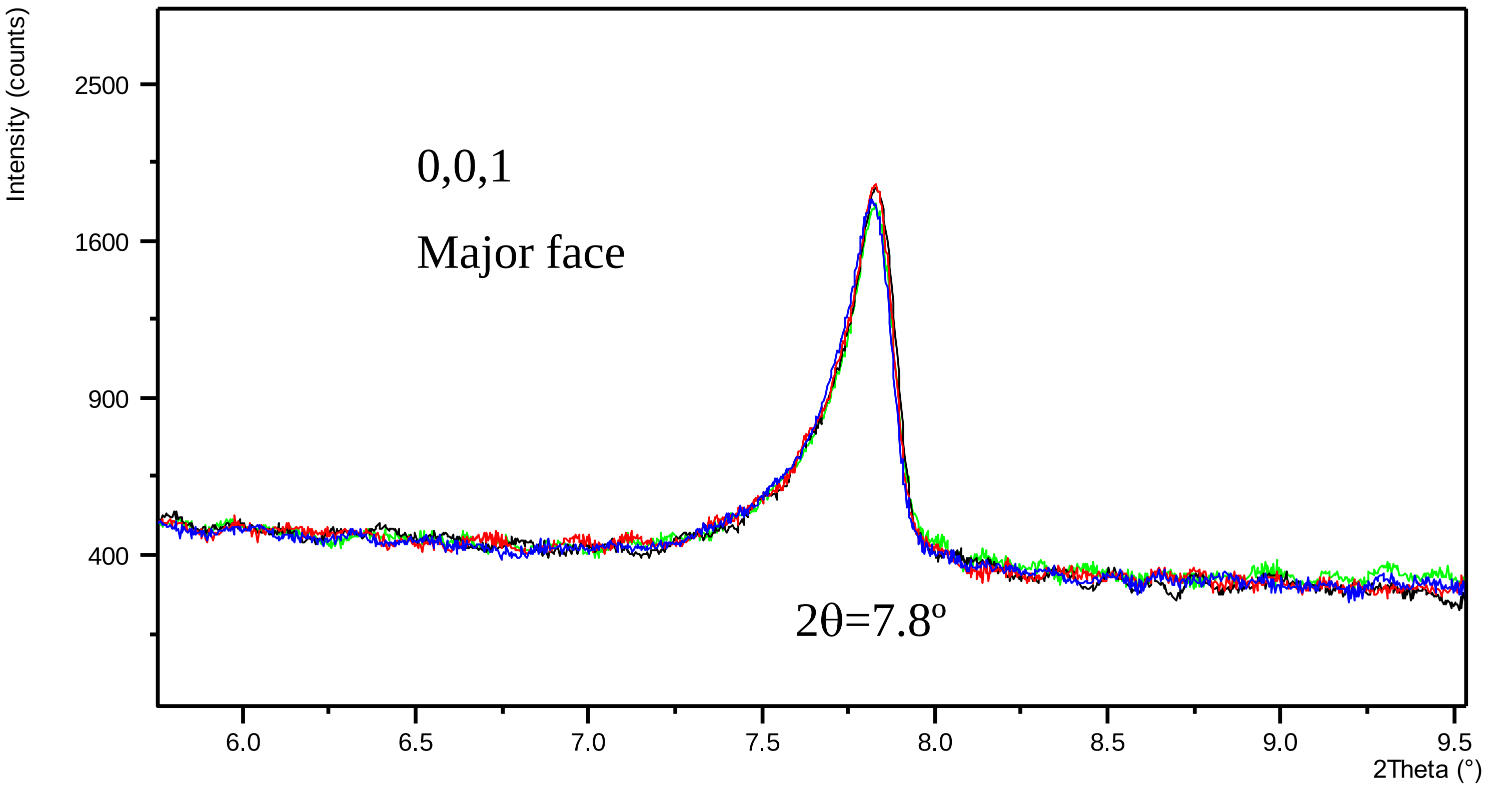
Rank: 4 R^2 = 92.25 RMSECV = 0.0947 Bias: 0.00115 RPD: 3.59

Milling effects



Milling effects

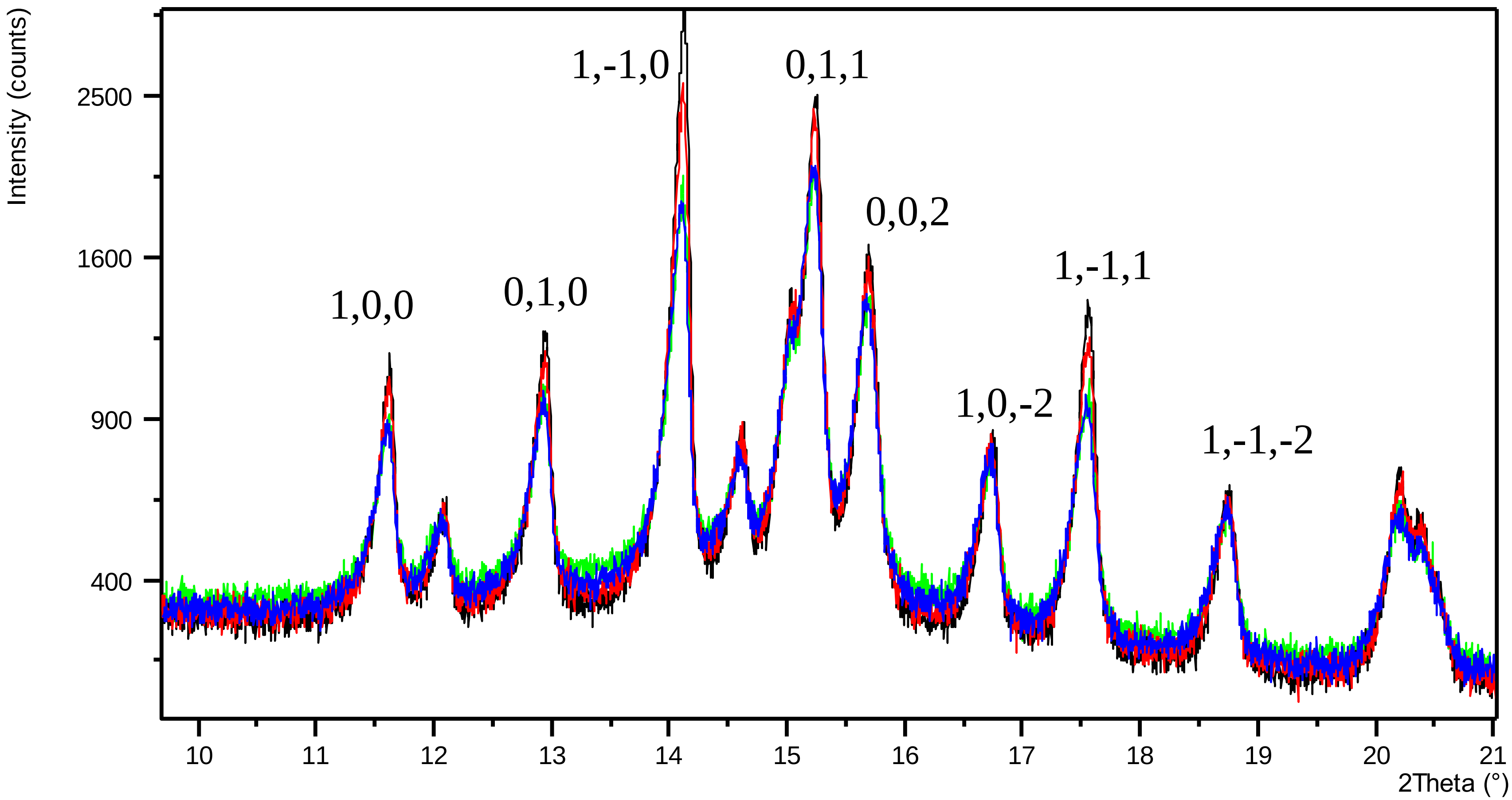
4 milling cycles



Milling effects

1,0,0 Perpendicular to water channels

0,1,0 Parallel to water channels



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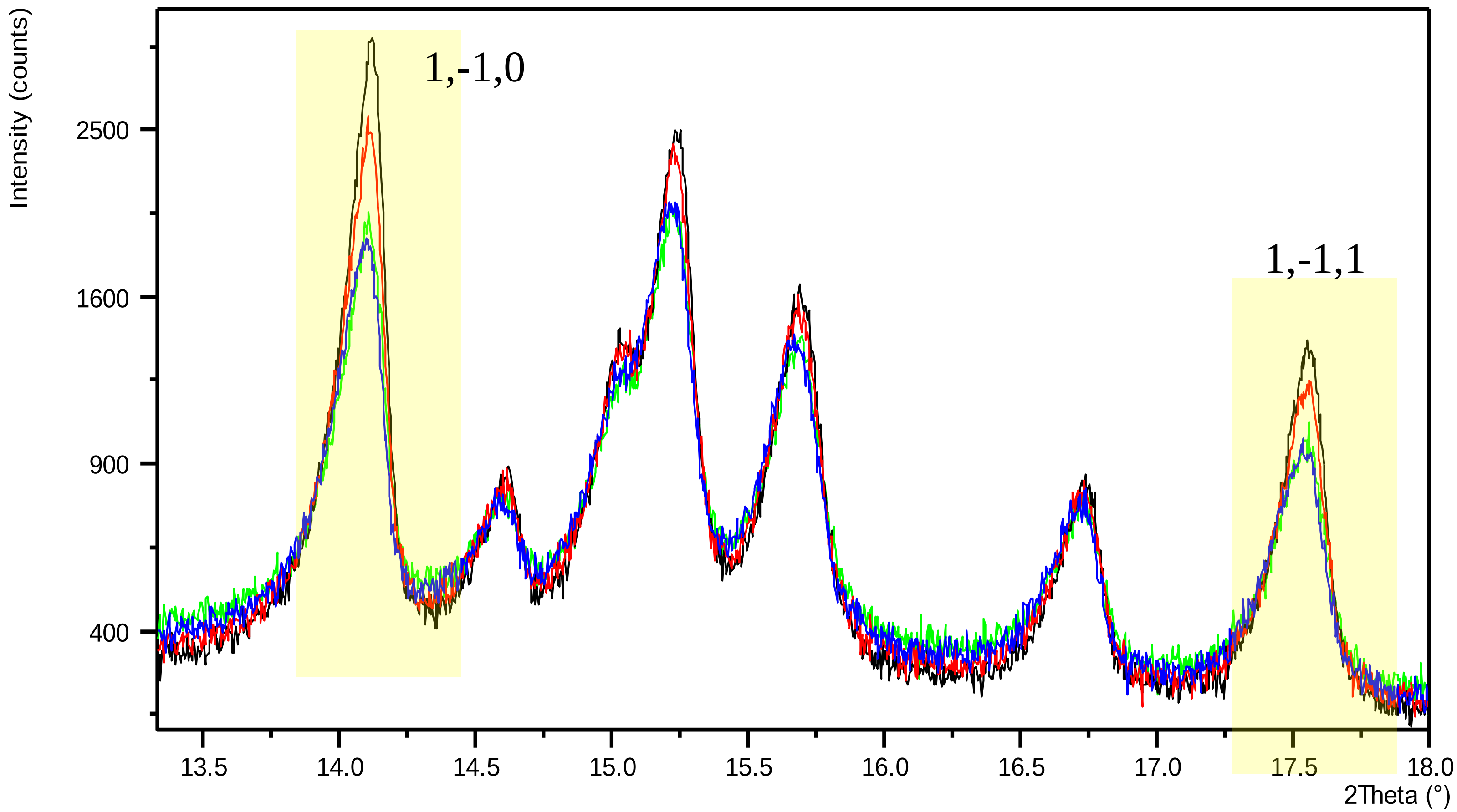
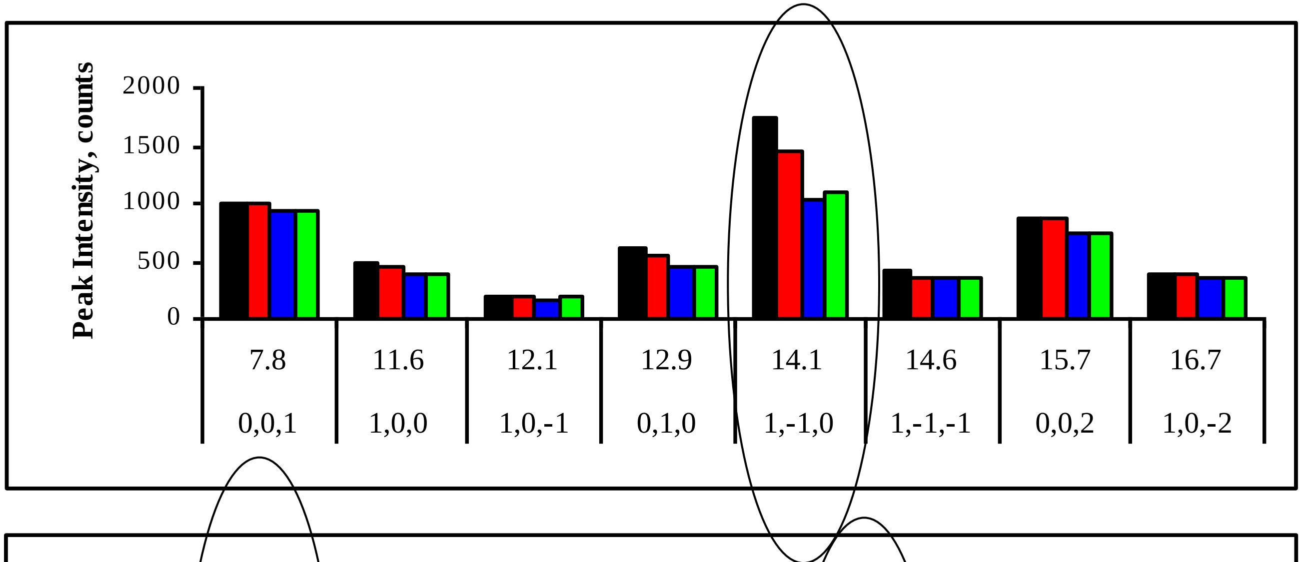
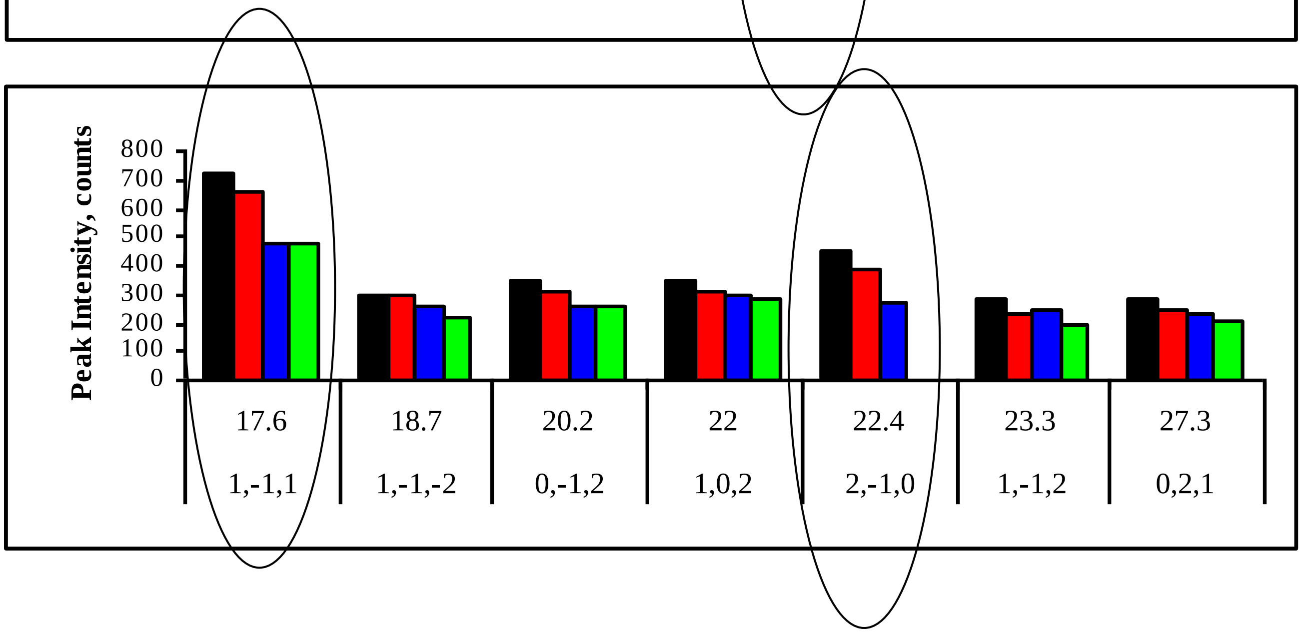
Effect of milling on crystallinity



Effect of milling on different crystallographic planes



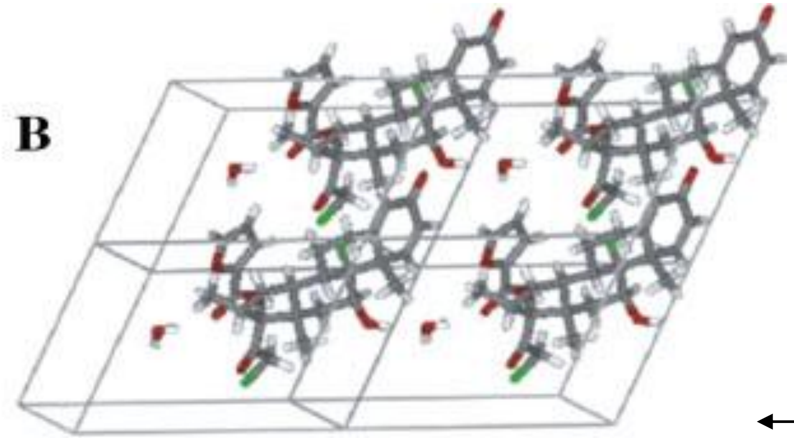


Milling cycles	Size after milling, D(V,0.9) µm
1	**7.8**
2	**5.1**
3	**3.4**
4	**3.0**

Correlating milling and structure

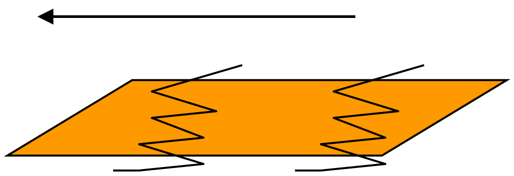
View from 1,0,0 direction

(α axis, parallel to water channels)



major face

0,0,1 direction,, perpendicular to water channels



1st milling cycle

*Three hydrogen bonds with adjacent molecules

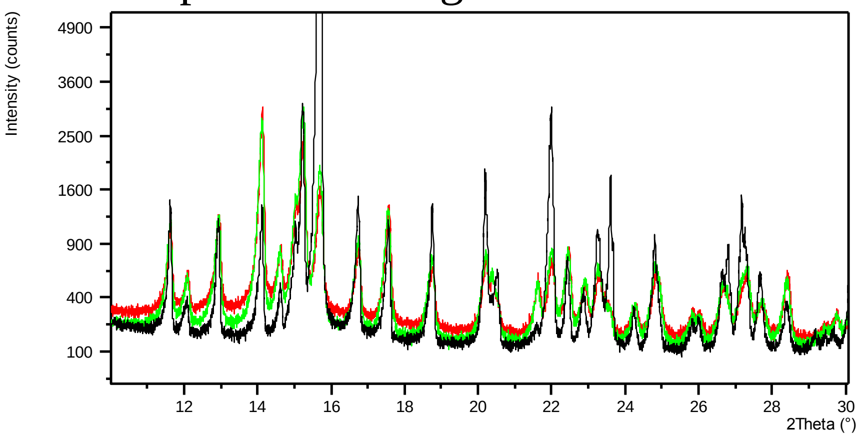
Chen et al. J. Pharm. Sci. 94(11) 2005

Is it all about size?

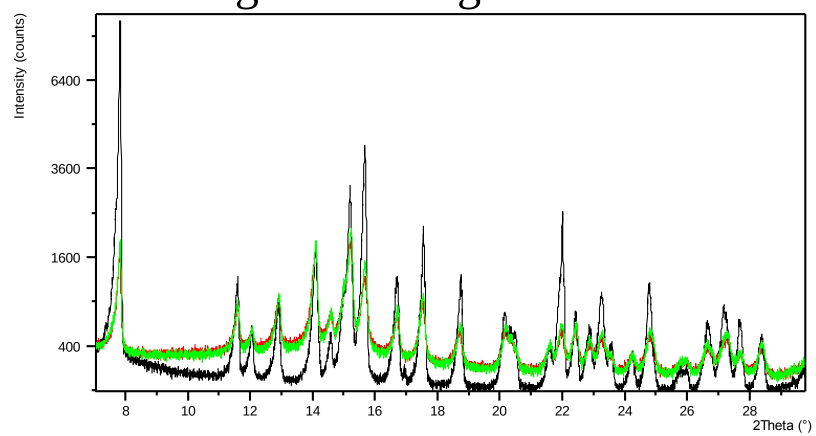
Structural evaluation of the milling process allowed process improvement.

In the new process, significant improvement in crystallinity and water content observed during re-hydration, leading to material with >3.1% water (KF)

Improved milling



Original milling



Black - before milling

Red – After milling

Green – After re-hydration

Conclusions

1. Structural parameters should be used to evaluate and control milling processes
2. The degree of crystallinity of jet-milled products can be controlled and improved.
3. Hydrates can be milled while maintaining their unique structural properties and water content
4. Sequential milling should be avoided in order to prevent excess structural damage.

Acknowledgements

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Orna Kurlat

Carmen Iustain

Yuri Futerman

Guardian of the Negev by Emilio Mogilner

Protect the environment

5 storey high, 450 tons, located opposite Ramat-Hovav industrial zone