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Quantification of traces - pushing the limits with laboratory instrumentation

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Quantification of traces

- Pushing the limits in QPA - some examples
  - Introducing preferred orientation
  - Limiting used wavelength range (monochromatization)
  - Reducing axial divergence
  - Transmission geometry
- Analysis of formulations and (blister packed) tablets

Introducing preferred orientation

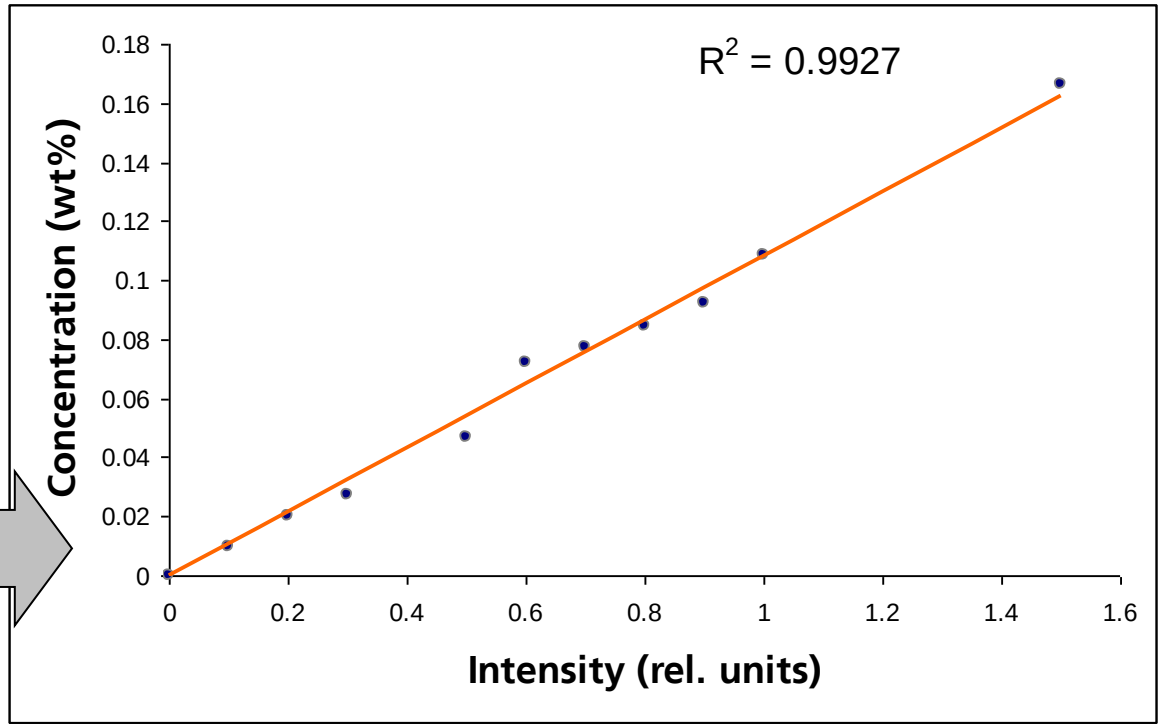
- For a typical XRD analysis an ideal sample should be free of preferred orientation.
- Especially a strongly varying texture makes a quantitative analysis very challenging and sometimes a single peak QPA impossible
- But if the preferred orientation is reproducible it can also improve LoDs and LoQs (induced preferred orientation e.g. with a zero background holder)

Polymorphic impurity quantification

Example of an at-line crystallization control:

- API powder taken from dryer
- Integrated intensity of one reflection of the polymorphic impurity

Down to very low detection and quantification limits

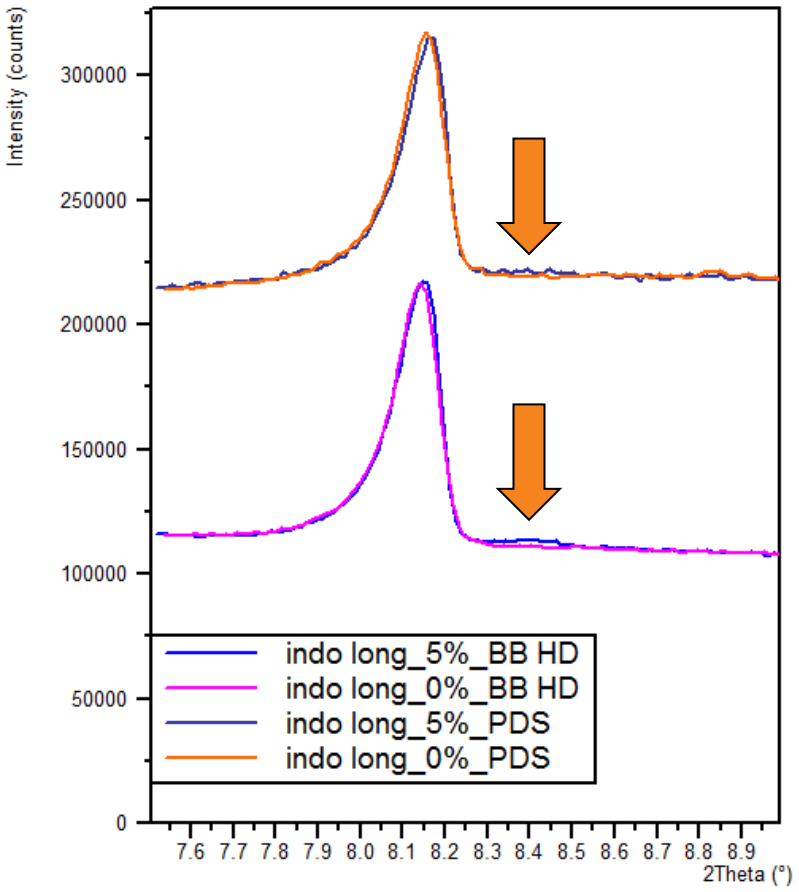


Limiting used wavelength range

- Monochromatization typically costs intensity and therefore worsens the counting statistics
- But background reduction may over-compensate that effect (not only in case of fluorescent samples)
- Some monochromatization is even possible without cost of intensity

Limiting used wavelength range

Improved detection limits



Sample with 0.25% α-Indometacin

Pharma sample:

- 95% excipients,
- 5% API (indometacin)

5% α- / 95% γ – indometacin

Detection limits for α-indometacin:

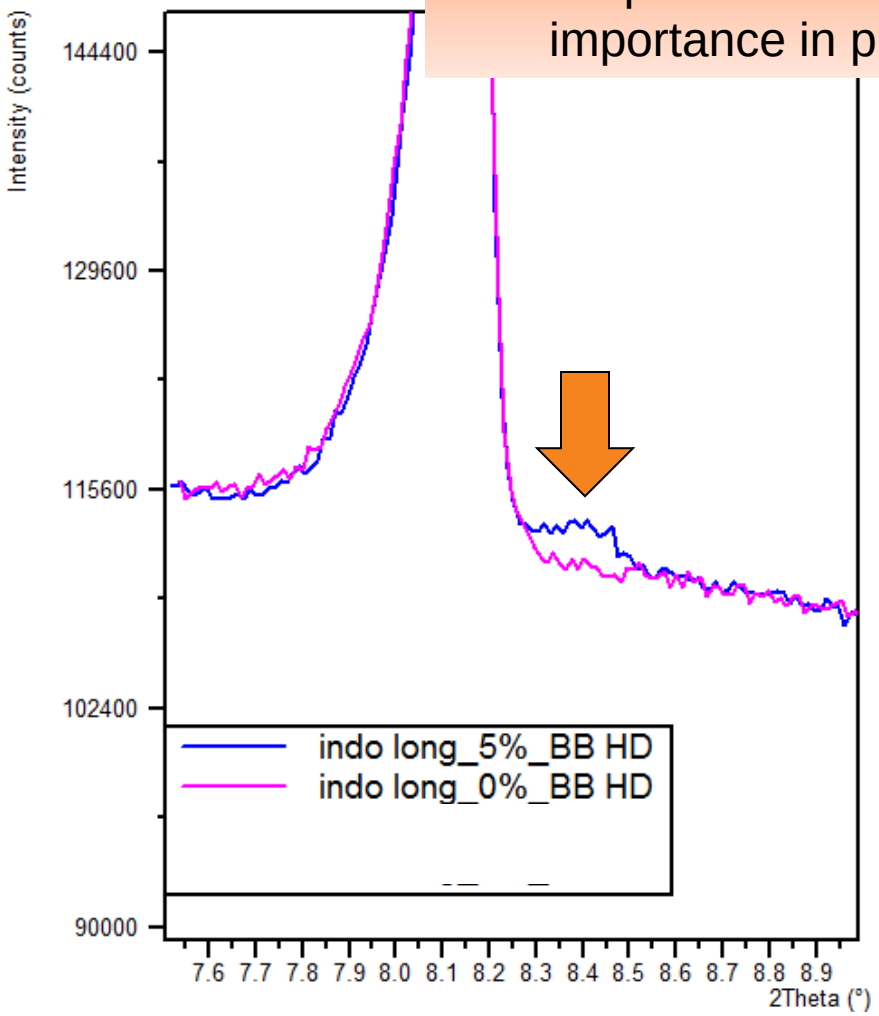
PDS: **LoD = 0.25%** (as measured)

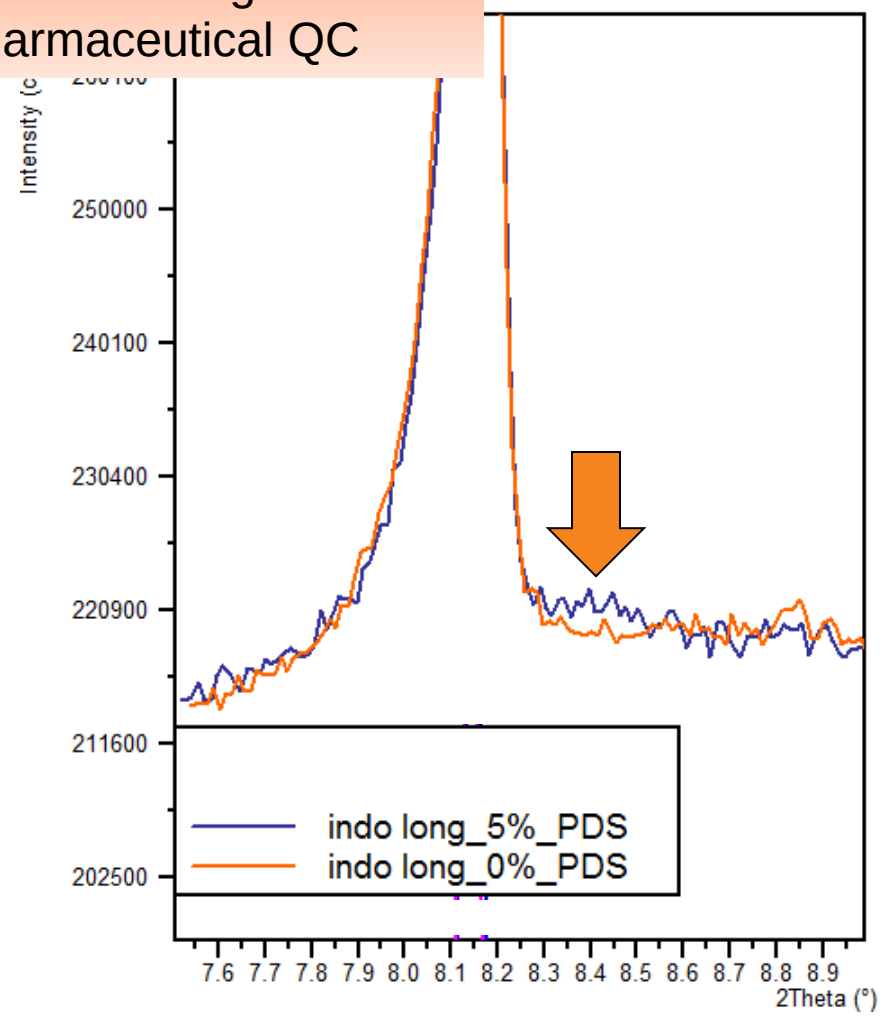
PDS: **LoD = 0.20%** (corrected to the same irradiated area)

Bragg-Brentano^{HD}: **LoD = 0.12%**

Limiting used wavelength range

An improved LoD can be of significant importance in pharmaceutical QC



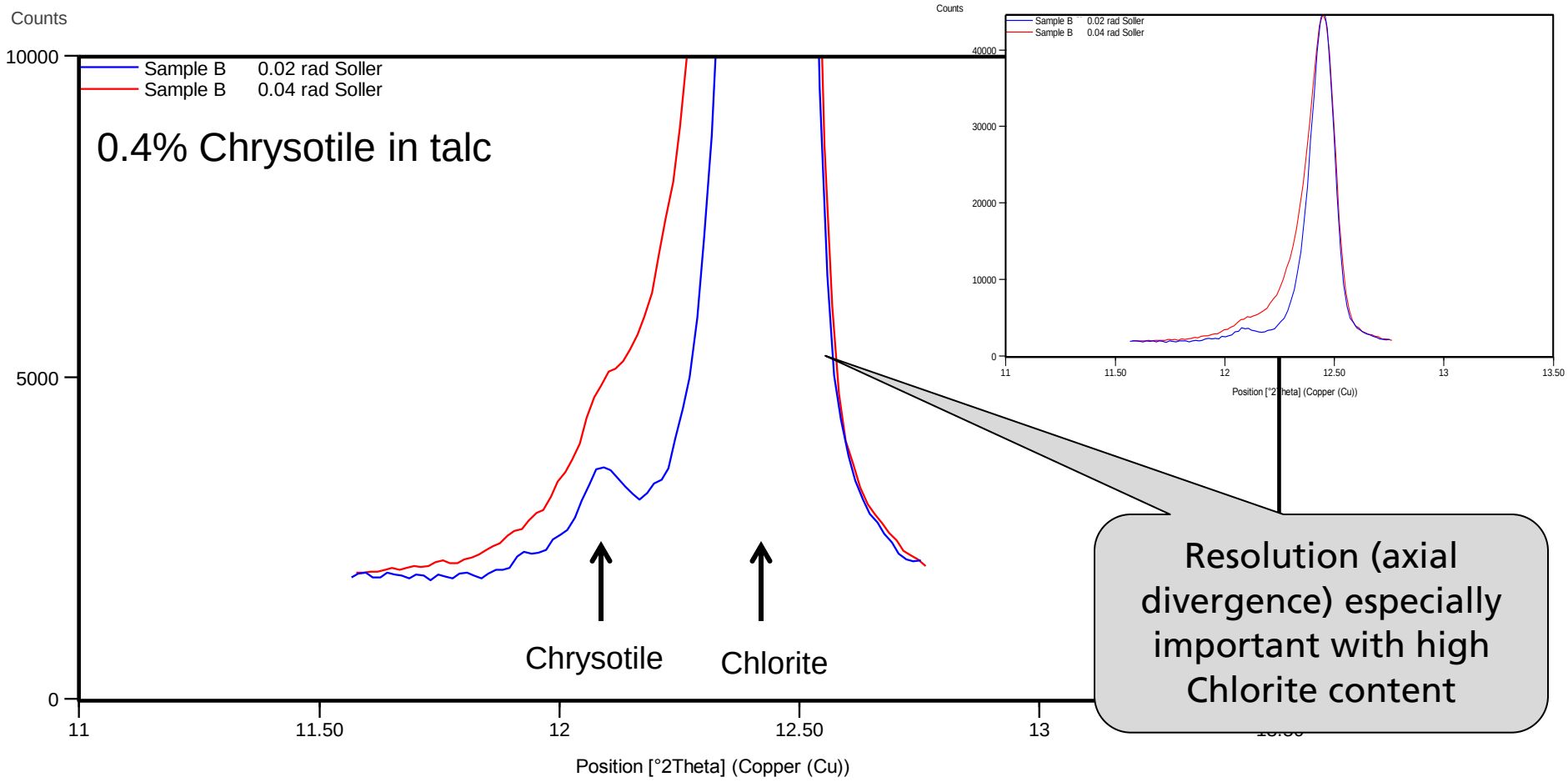


Reducing axial divergence

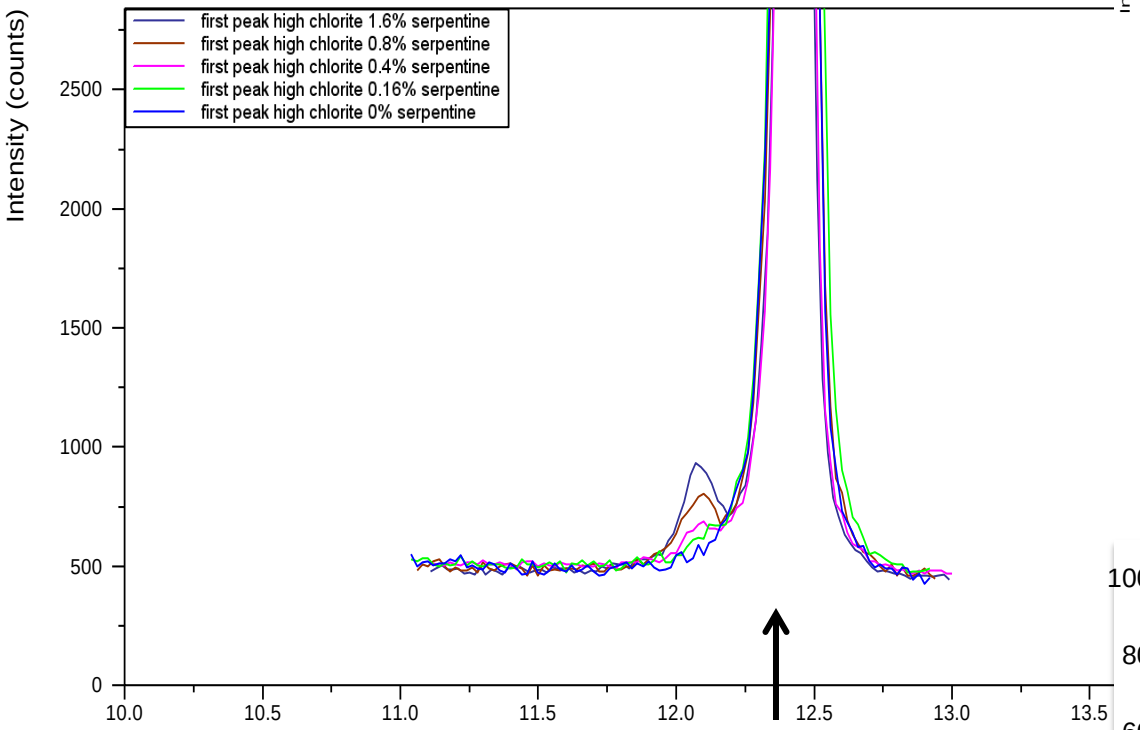
- The reduction of the axial divergence in a diffraction experiment costs intensity
- But the detection of impurity peaks in close proximity to other strong reflection might significantly improve
- Sample transparency also causes peak asymmetry
- Alternative: sample holder with thin sample (less asymmetry due to reduced sample transparency)

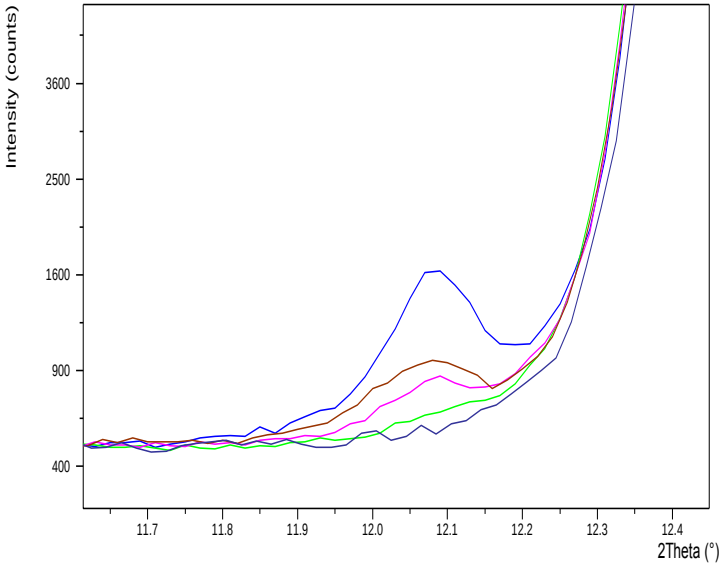
Reduced axial divergence

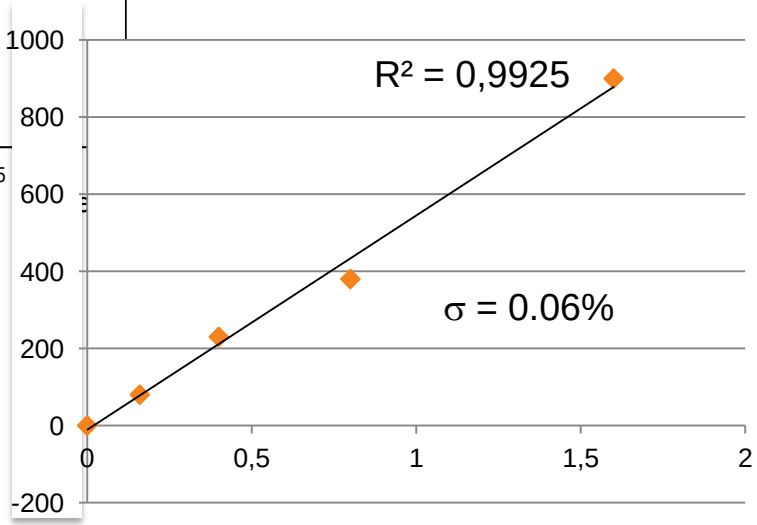
Talc (high Chlorite content) spiked with Chrysotile (white asbestos)



Reduced axial divergence

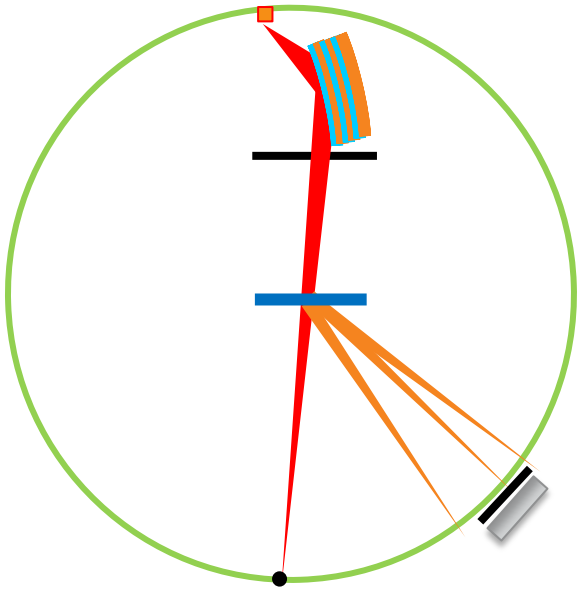






Transmission geometry

- At very low concentrations of impurities only very few crystallites contribute to the measurement signal. Therefore often particle statistics limit the achievable LoD / LoQ level (reproducibility of calibration standards).
- Transmission geometry offers more possibilities for sample/beam manipulation (e.g. wobble) than traditional Bragg-Brentano geometry. This may reduce particle statistic problems and finally may lead to improved LoDs and LoQs
- Transmission geometry is also preferable for tablet analysis (volume vs surface sensitive)



Formulation stages

Formulation

Tablets

Blister card

Challenges:

- API - excipients interference

Challenges:

- Process sensitivity (pressure)
- Functional design
- Analytically: tablet - coating interferences / geometrical aberrations / transparency

Tablet analysis - reflection vs. transmission

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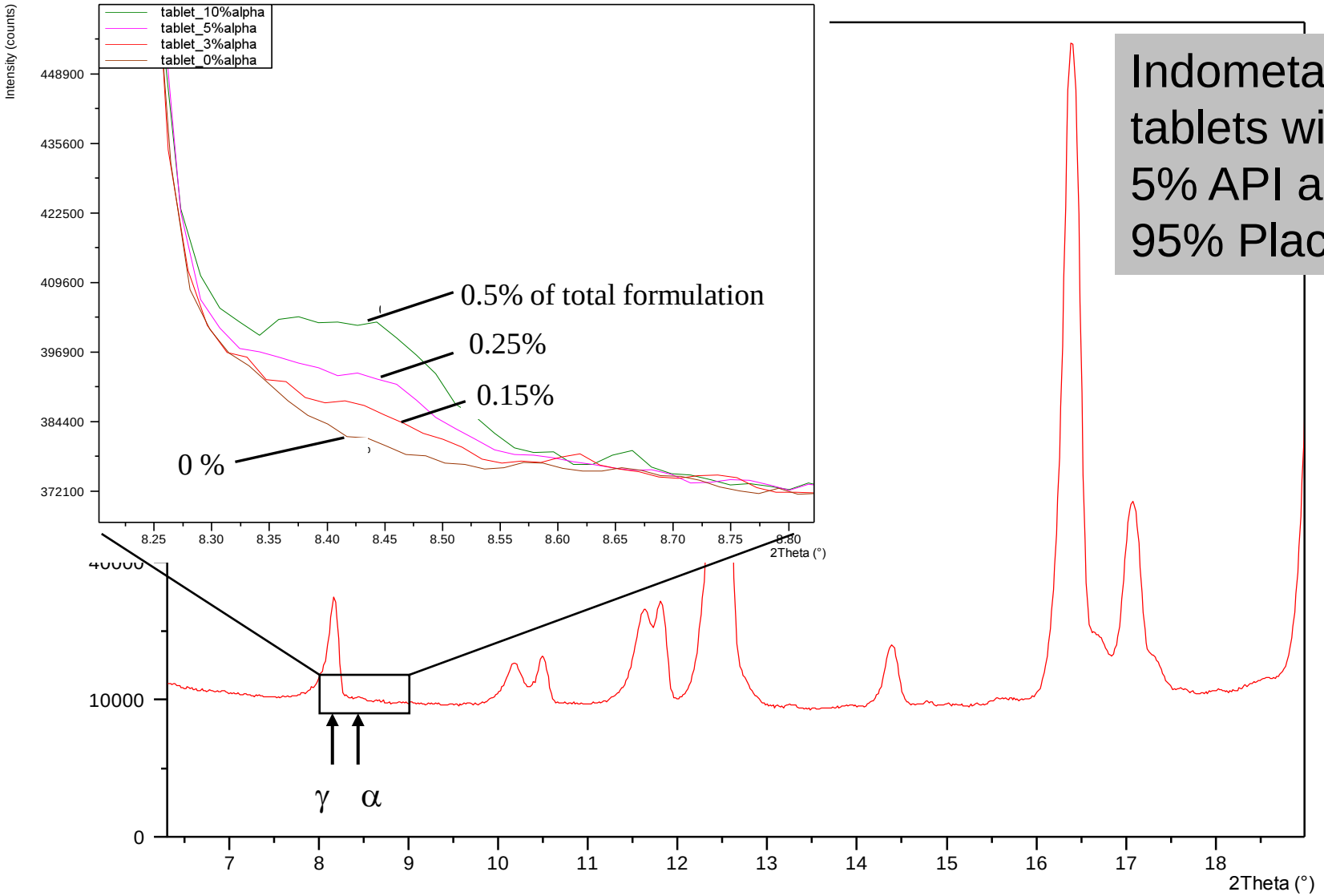
Limitations:

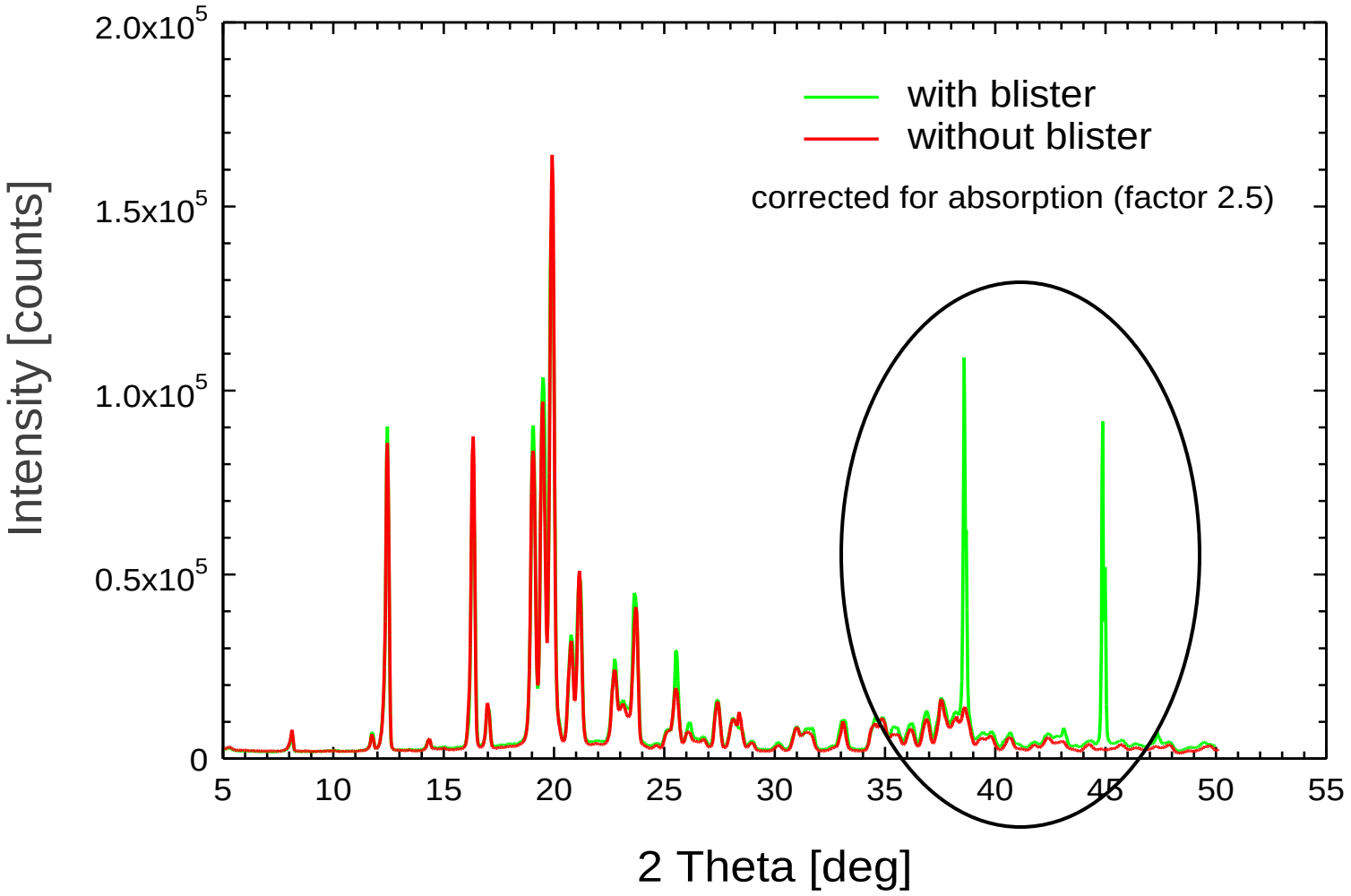
- Reflection:
  - Only probing upper part of tablets (more sensitive to coating)
  - Geometrical aberrations due to tablet curvature (alternative: parallel beam)
- Transmission:
  - Limited by absorption
  - Peak broadening at higher 2Theta angles

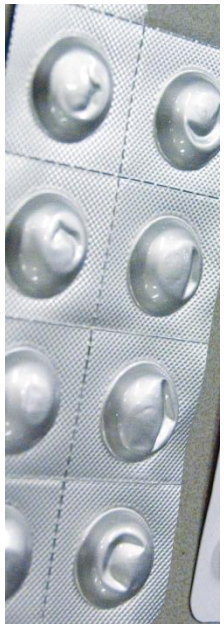
Polymorph detection in tablets (transmission geometry)



Indometacin tablets with 5% API and 95% Placebo

Tablet measurement with and without blister





Polymorph differentiation in blister-packed test tablets

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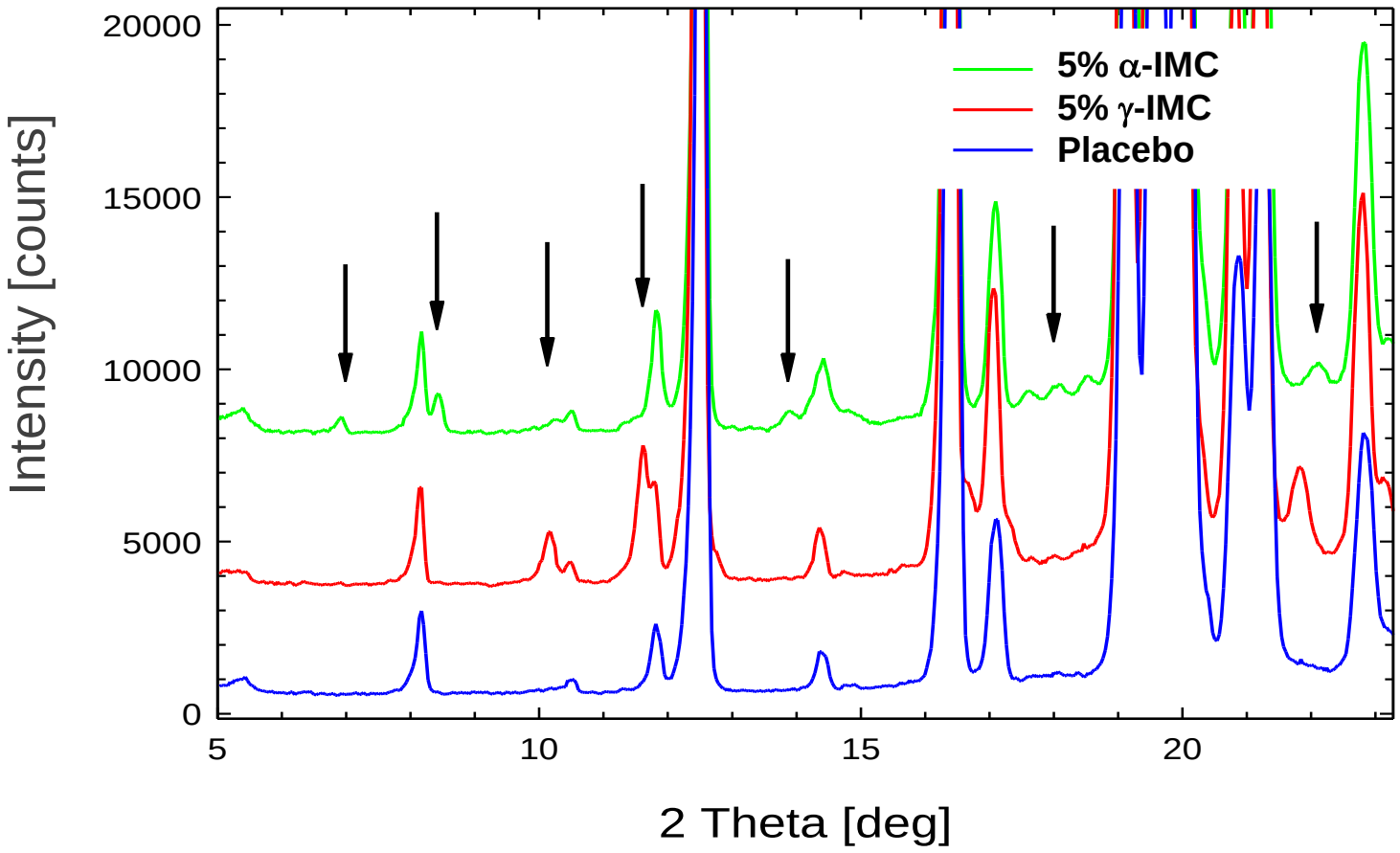
XRD allows to clearly differentiate the API polymorph



Scanning of 2x5 blister – batch uniformity

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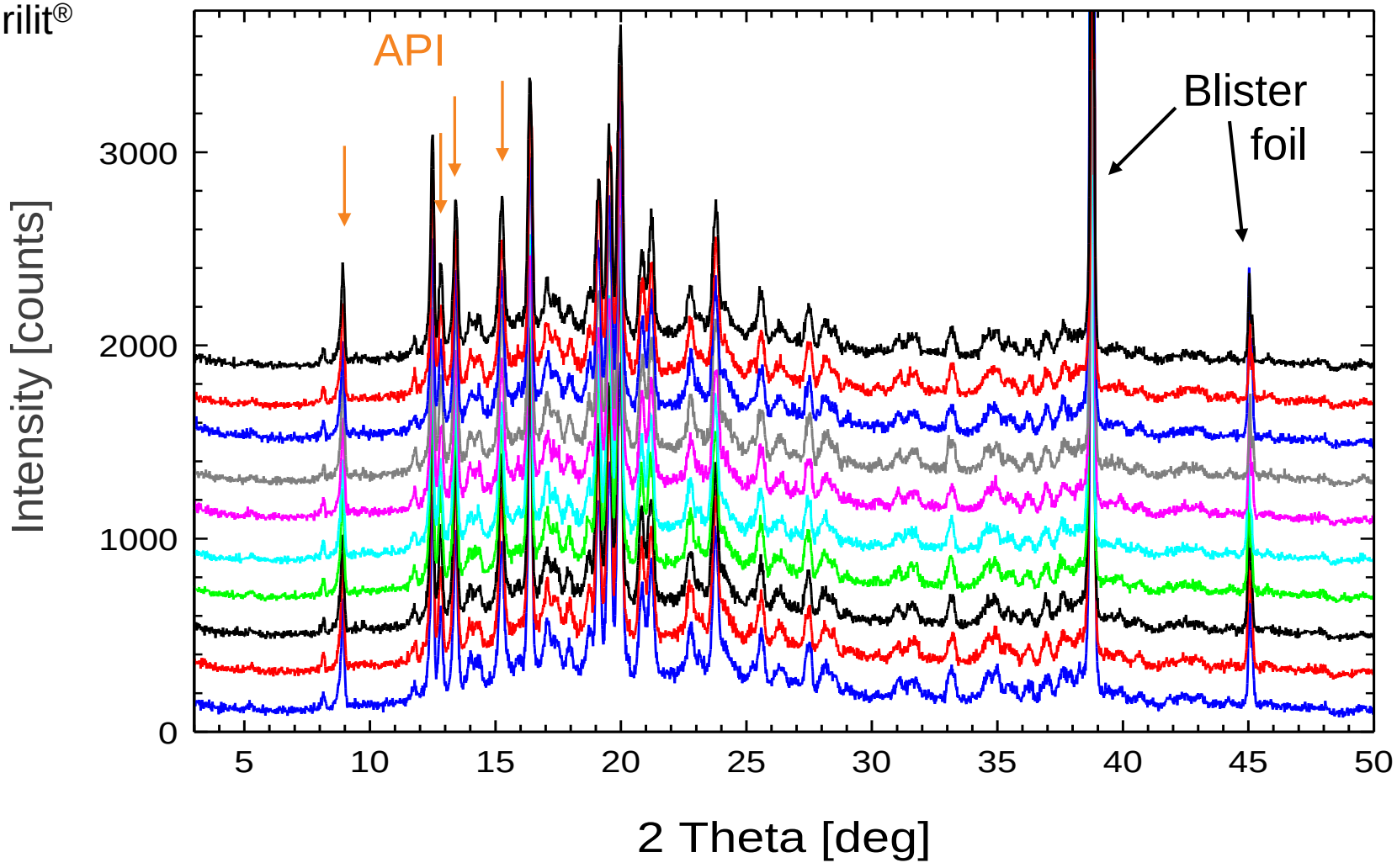
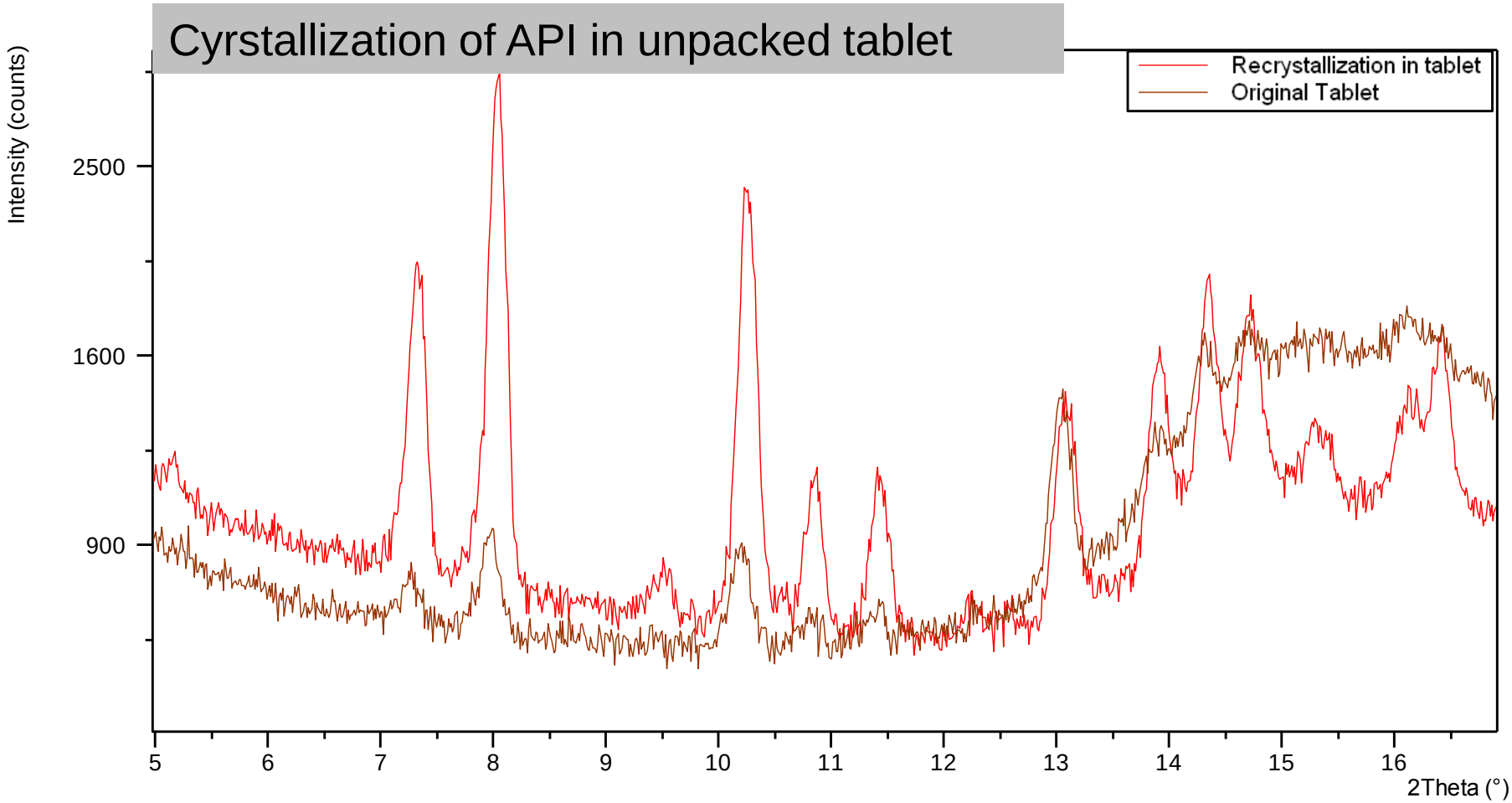
Virilit®



Crystallinity change after tablet stress (T / rH)



Thick tablets – sample transparency

- While analyzing thick tablets, sample transparency is an issue:
  - With Cu radiation a maximum thickness of ~ 3-4 mm can be analyzed with reasonable measurement times
  - Thicker tablets can be analyzed by higher energy radiation (e.g. Mo)

Cu radiation: pattern dependent on measurement position on tablet (variation of transparency)

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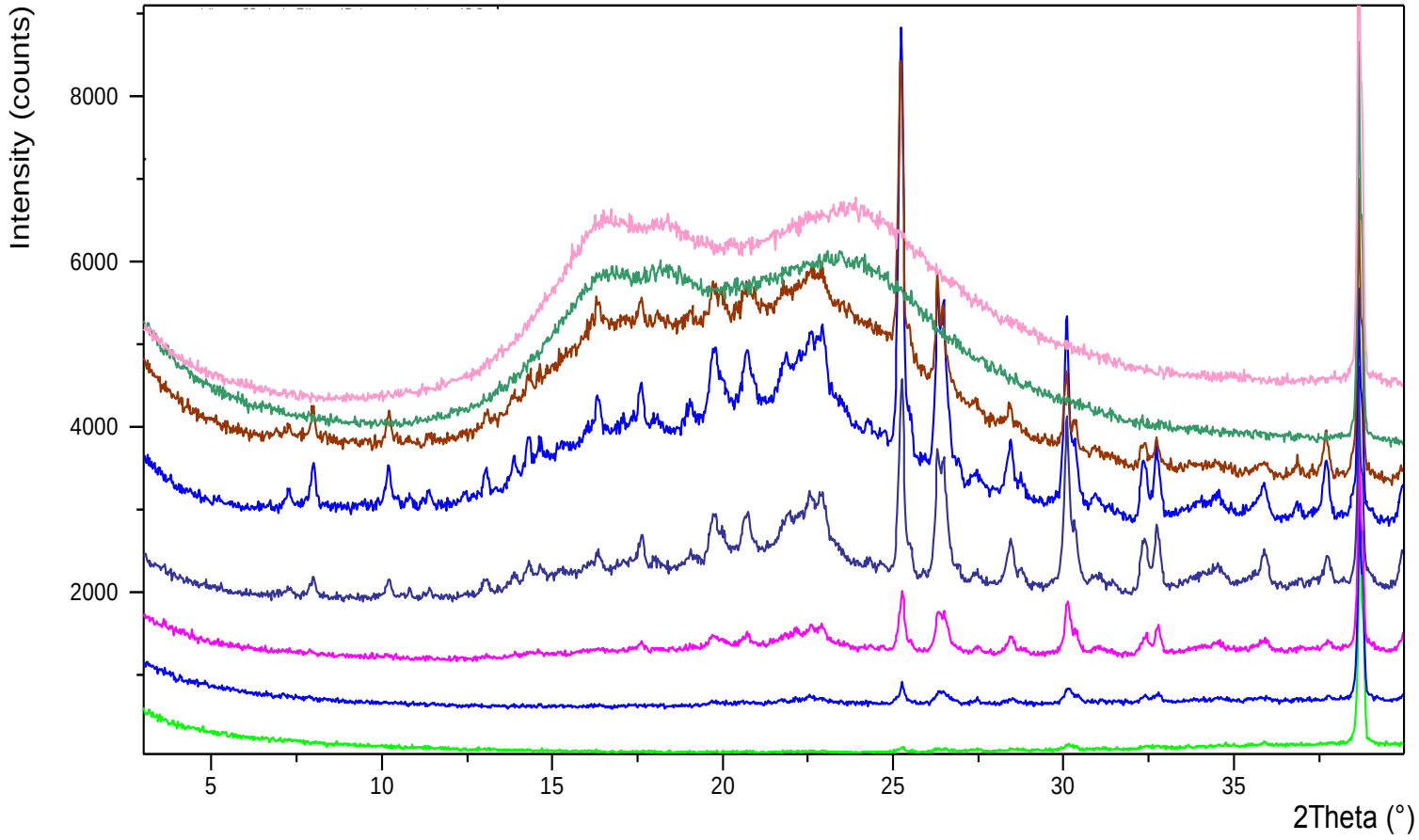
Measurement position shifted in steps of 300 mμ (patterns shifted vertically for better visibility)



Thick tablets require accurate/reproducible positioning

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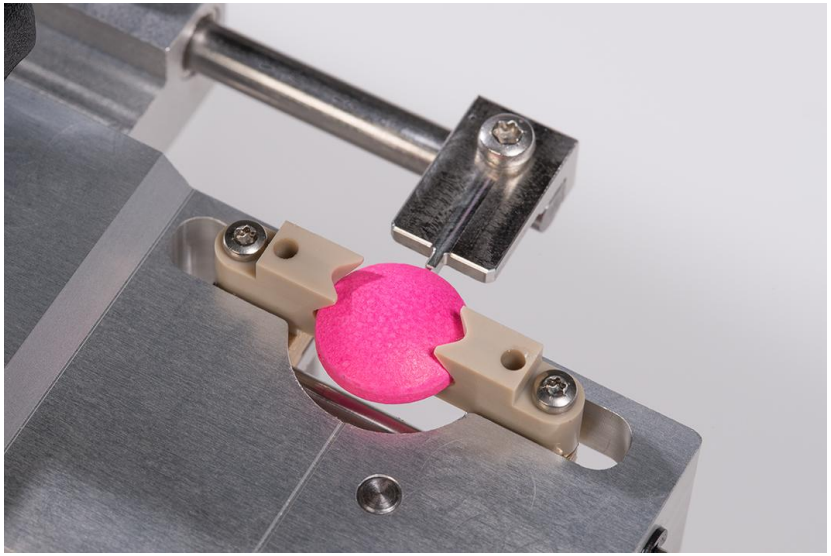
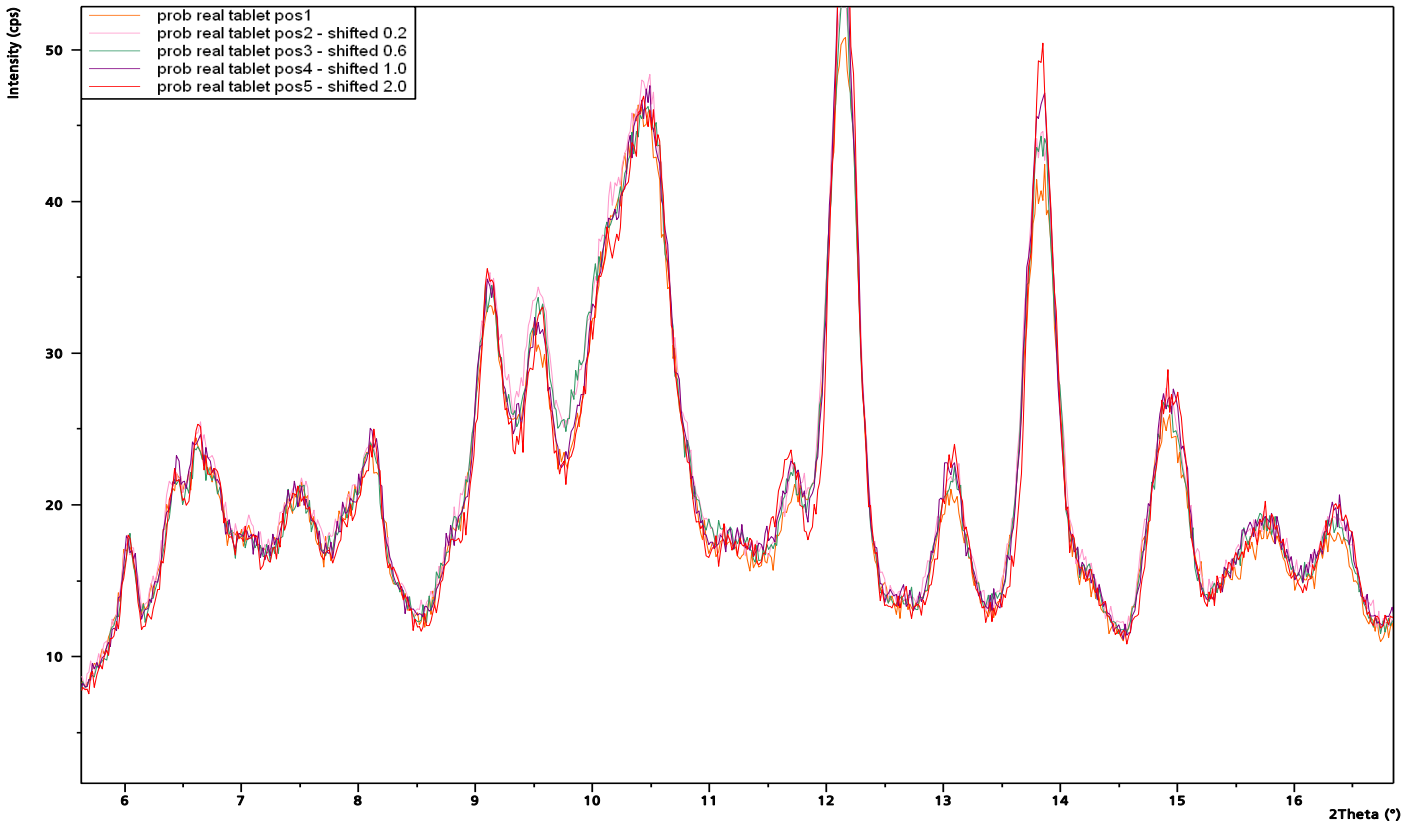
- Automatic / reproducible positioning and height adjustment of tablet
- Formulation analysis for quality control or fake drug detection



Mo radiation: pattern independent from sample positioning



Comparison: genuine vs. counterfeit products

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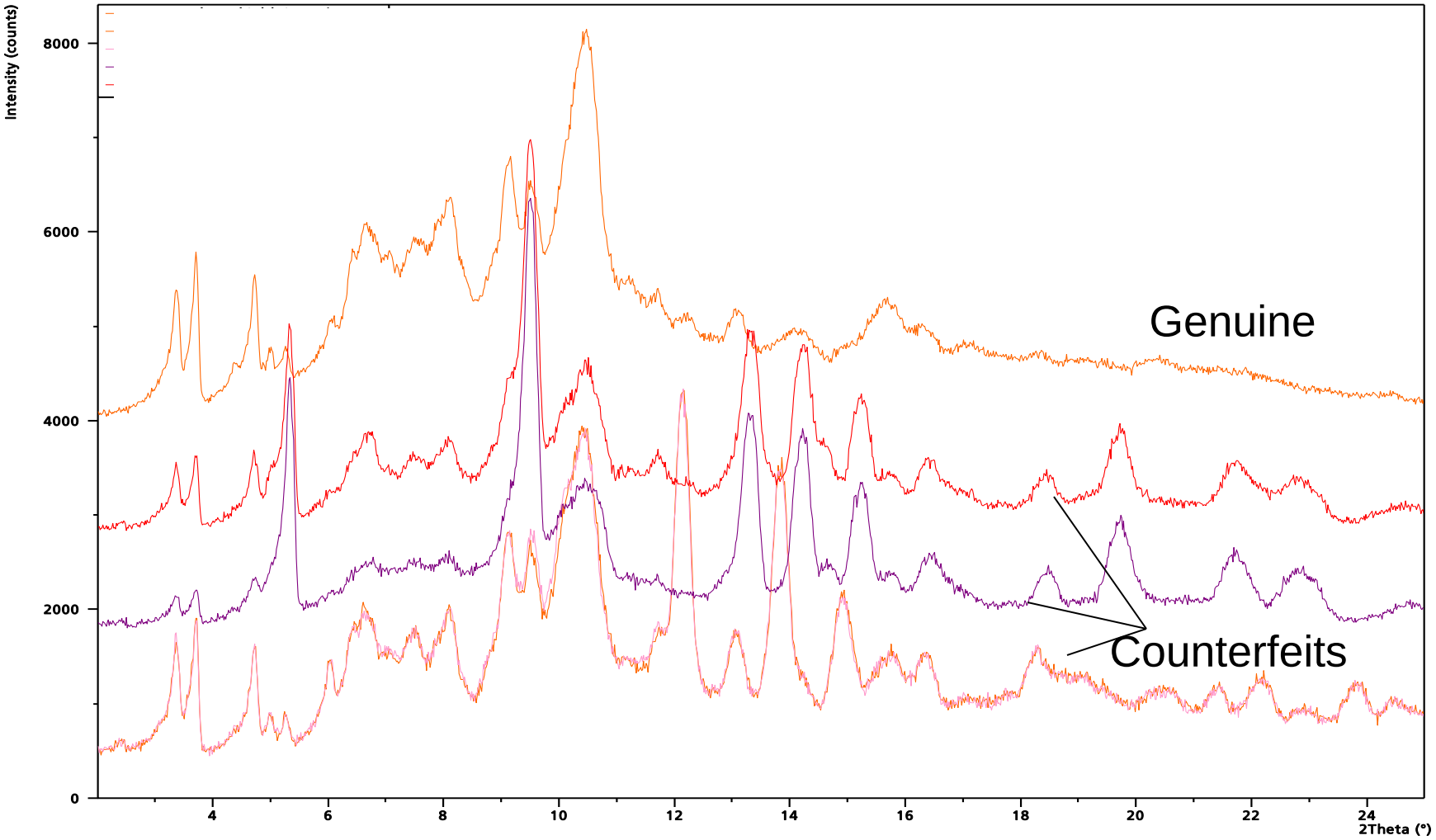

Conclusion

- Lab systems offer a lot of possibilities to achieve low LoDs and LoQs and to optimize a method
- Often the sample preparation possibilities dictate the achievable limits