QPA of crystalline and amorphous phase abundance with XRPD techniques: bases and methods

Fabia Gozzo

Excelsus Structural Solutions sprl, Brussels, Belgium

Excelsus Structural Solutions (Swiss) AG, Switzerland

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QPA literature: a selection

Books

- *Elements of X-Ray Diffraction*, Cullity, 1959, Addison-Wesley Publishing Company, Inc.
- *Modern Powder Diffraction*, Bish & Post Editors, Reviews in Mineralogy, Vol.20, 1989.
- *Introduction to X-Ray Powder Diffractometry*, Jenkins & Snyder,. Publisher, Wiley 1996.
- *Quantitative X-Ray Diffractometry*, Zevin & Kimmel, Springer-Verlag, New York, 1996.
- *Industrial of X-Ray Diffraction*, Chung & Smith, Marcel Dekker, New York, 2000.
- *Structure Determination from Powder Diffraction Data*, David, Shankland, McCusker & Baerlocher Editors, Oxford University Press, New York, 2002.
- *Fundamentals of Powder Diffraction and Structural Characterization of Materials*, Pecharsky & Zavalij, 2009, Springer.
- *Powder Diffraction* – Theory and Practice, Dinnebier & Billinge Editors, 2009, RSC Pub (QPA: Ch.11).
- *Modern Diffraction Methods*, Mittemeijer & Welzel Edts, 2013 (QPA: Ch.10).

Articles & Reviews

R. J. Hill, *Expanded use of the Rietveld method in studies of phase mixtures*, Powder Diffr., 1991. **6**, 74-77.

B.H. O'Connor & M.D. Raven, *Application of the Rietveld refinement procedure in assaying powdered mixtures*, Powder Diffr. 1988. **3**, 2-6

D.L. Bish & S.A. Howard, *Quantitative phase analysis using the Rietveld method*, J. Appl. Cryst. 1988. **21**, 86-91.

R.J. Hill & C. J. Howard, *Quantitative phase analysis from neutron powder diffraction data using the Rietveld method*, J. Appl. Cryst. 1987. **20**, 467-474.

N.V.Y. Scarlett & I. C. Madsen, *Quantification of phases with **P**artial **O**r **N**o **K**nown **C**rystal **S**tructure*, Powder Diffr. 2006. **21**, 278-284.

C. Giannini, A. Guagliardi & Millini *Quantitative phase analysis by combining the Rietveld and the whole-pattern decomposition methods*, J.Appl.Cryst (2002). **35**, 481

QPA of amorphous phases, a small selection:

I.C. Madsen, N.V.Y. Scarlett & A. Kern, *Description and survey of methodologies for the determination of amorphous content via X-ray powder diffraction, Z. Kristallogr.* 226 (2011) 944-955.

X. Chen, S. Bates & K.R. Morris, *Quantifying amorphous content of lactose using parallel beam X-ray powder diffraction and whole pattern fitting*, J. Pharm. Biomed Anal. 26 (2001) 63-72.

S. Thakral, M.W. Terban, N. K. Thakral & R. Suryanarayanan, *Recent advances in the characterization of amorphous pharmaceuticals by X-ray diffractometry*, Adv. Drug Deliv. Rev. (2015), http://dx.doi.org/10.1016/j.addr.2015.12.013

Outlook

I. Defining the QPA problem

II. Mathematical background

III. Diffraction methods as a DIRECT method for QPA

IV. Single-peak (or single-line) QPA methods

V. Whole patterns QPA methods →Rietveld and Rietveld-like methods

VI. Quantification methods for amorphous phases

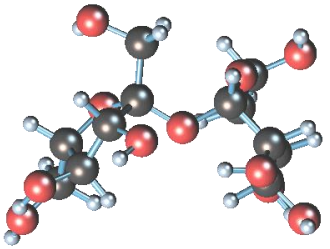
Qualitative *versus* Quantitative phase analysis

Principal use of powder diffraction technique is the identification of crystalline or disordered structures (or phases)

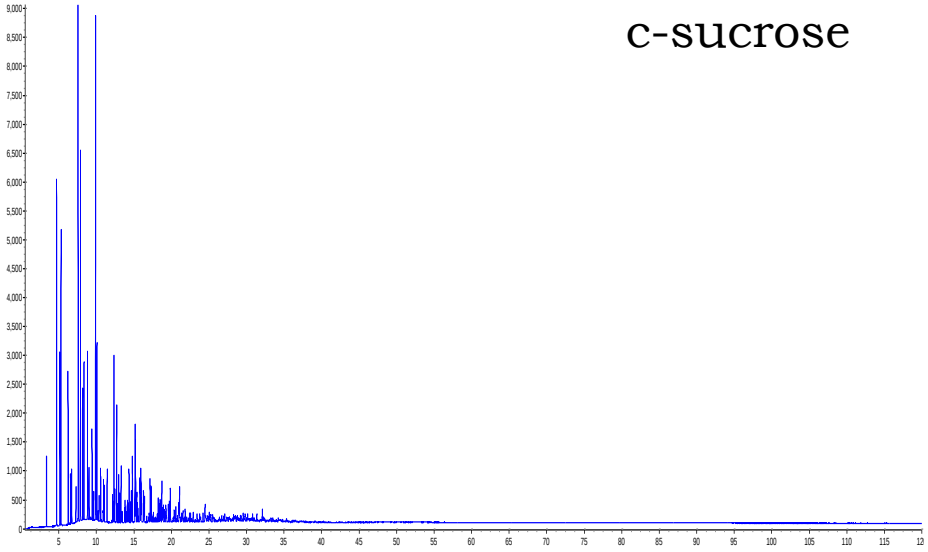
Why?

A powder pattern is DIRECTLY produced by the structure of the component phases and can, therefore, fingerprint them

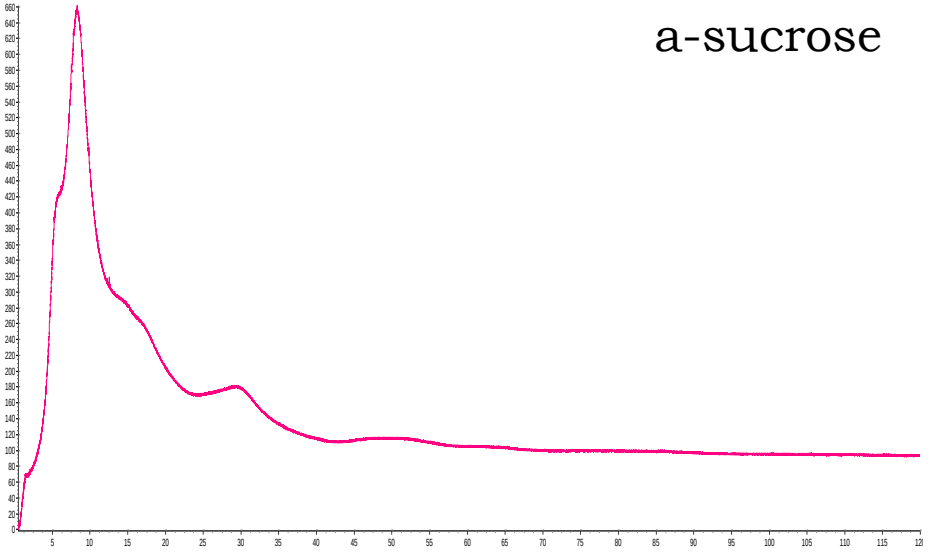
Sucrose: $C_{12}H_{22}O_{11}$



c-sucrose

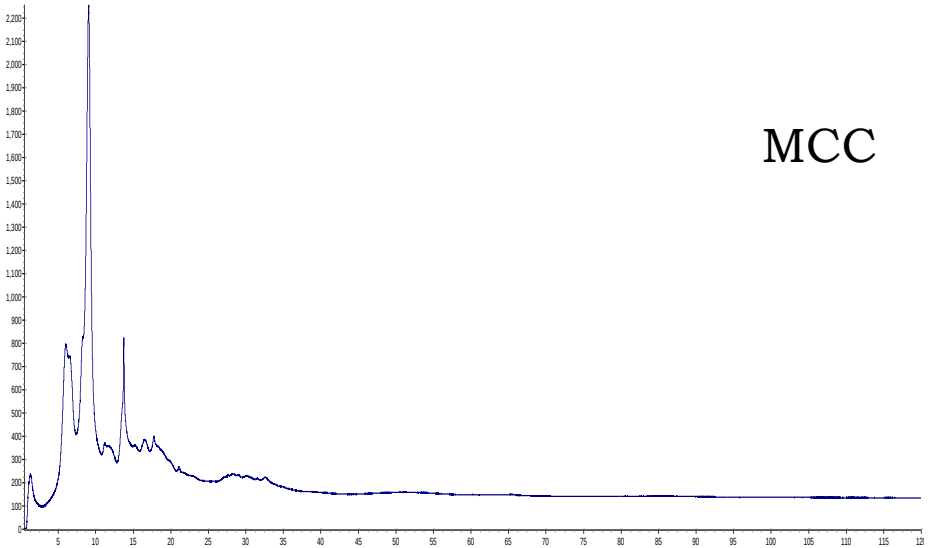


a-sucrose

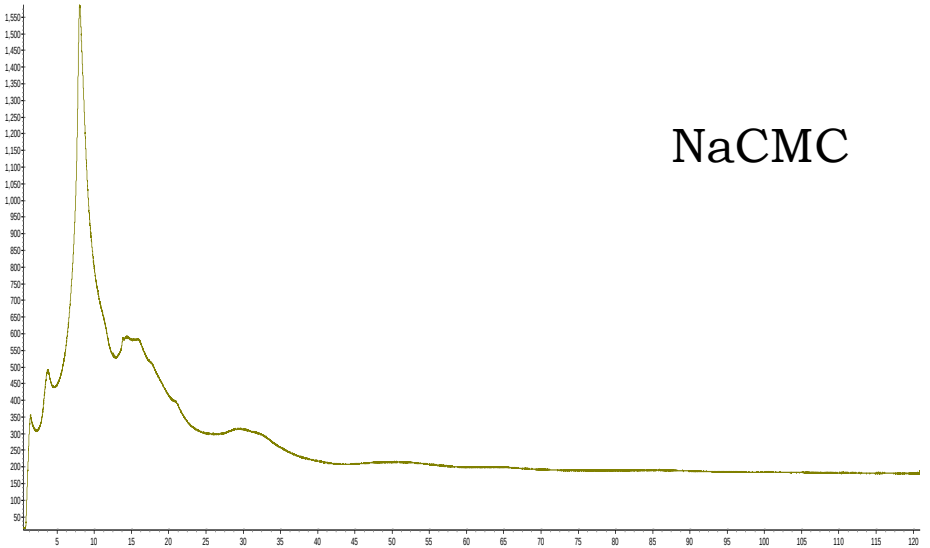


I. Defining the QPA problem

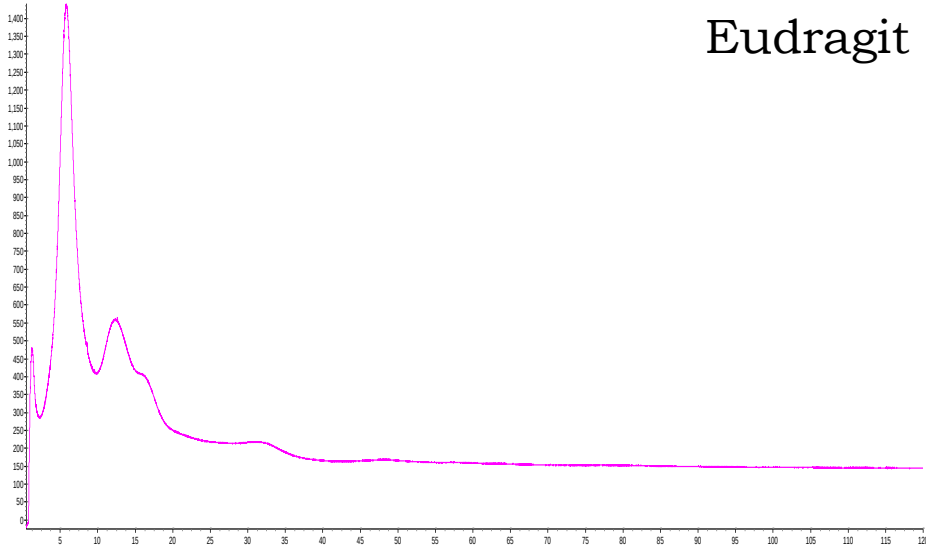
MCC



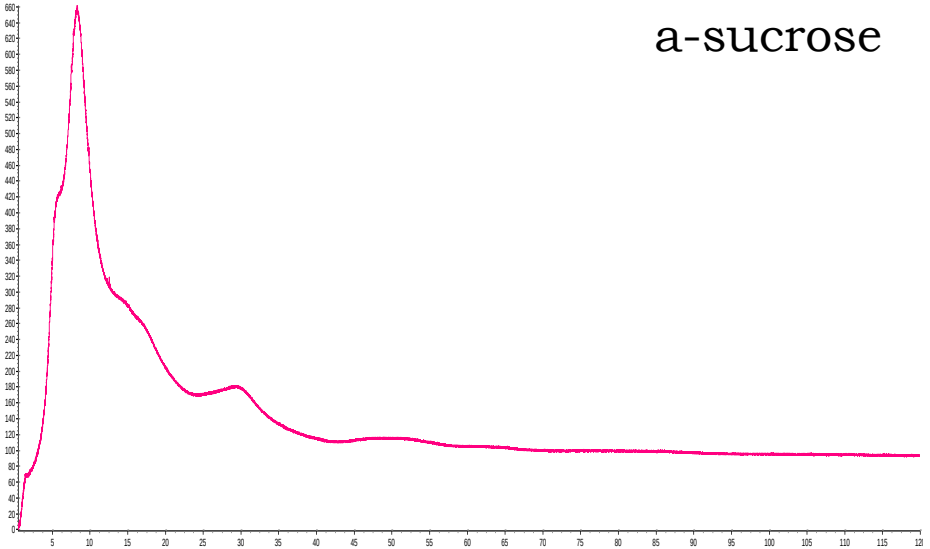
NaCMC



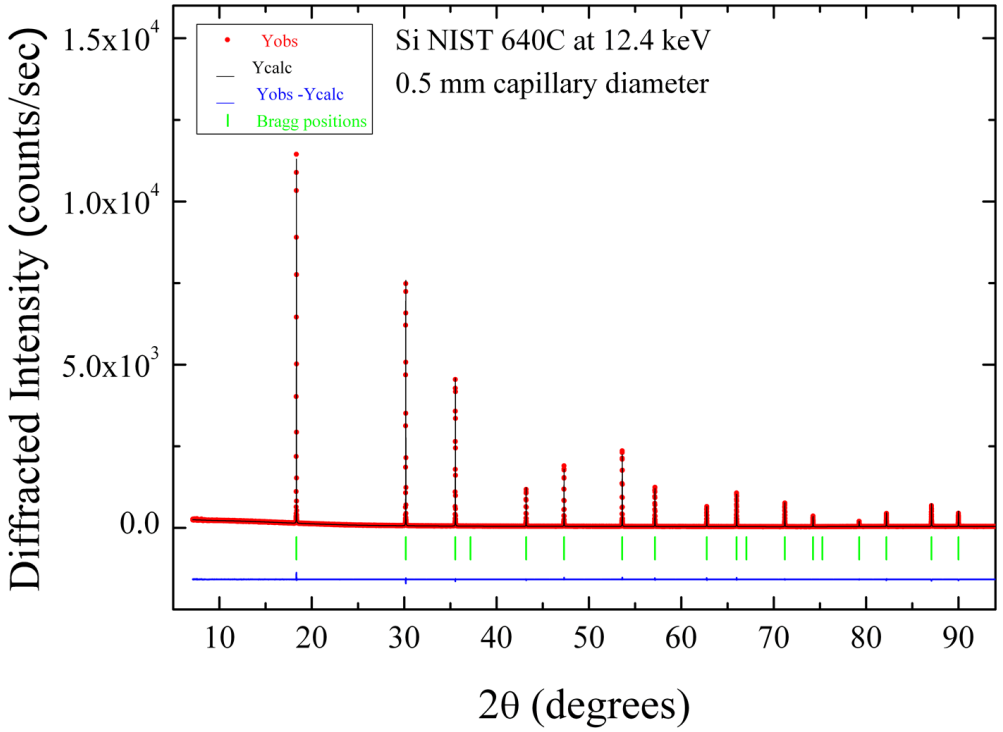
Eudragit



a-sucrose



What do we learn from a powder pattern of a crystalline structure?

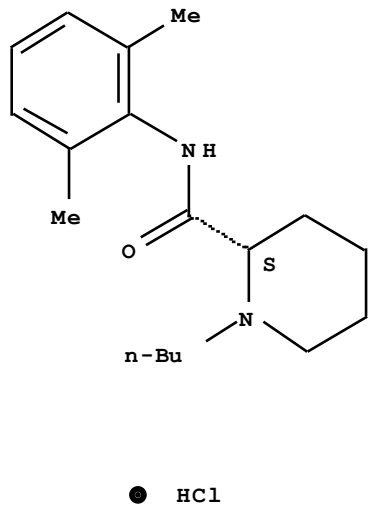


- Position of the diffracted peaks → size and dimension of the unit cell
- Intensity ratios of the diffracted peaks → type and location of atoms in the unit cell
- Full Width at Half Maximum (FWHM) of the diffracted peaks → intrinsic properties of the materials (i.e. microstructural analysis)

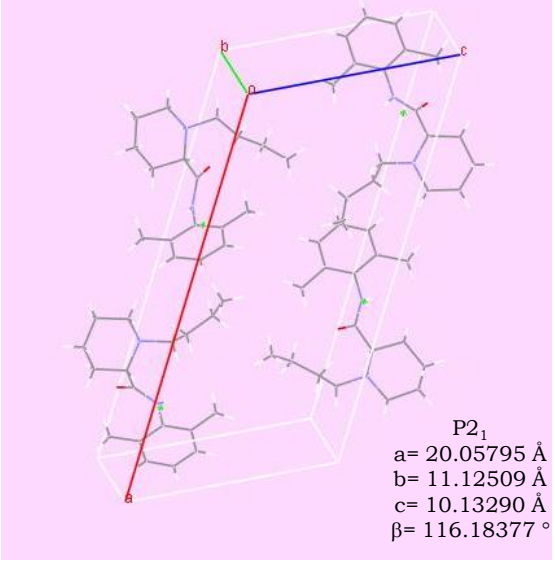
Polymorphism of drugs

Polymorphism is the ability of substances with **identical chemical composition** to crystallize in solid state phases according to different arrangements or conformations of the basic molecule(s) in the crystal lattice

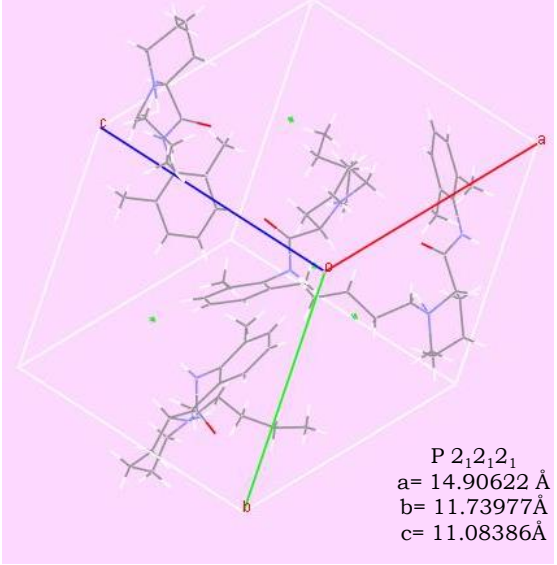
Example of
Bupivacaine Hydrochloride



Form B at 112 °C, monoclinic



Form D at 20 °C, orthorhombic



Gozzo, Masciocchi , Griesser, Niederwanger, 2010

Forms B and D share the same chemical composition, but have different solid forms

→ They are different polymorphs!

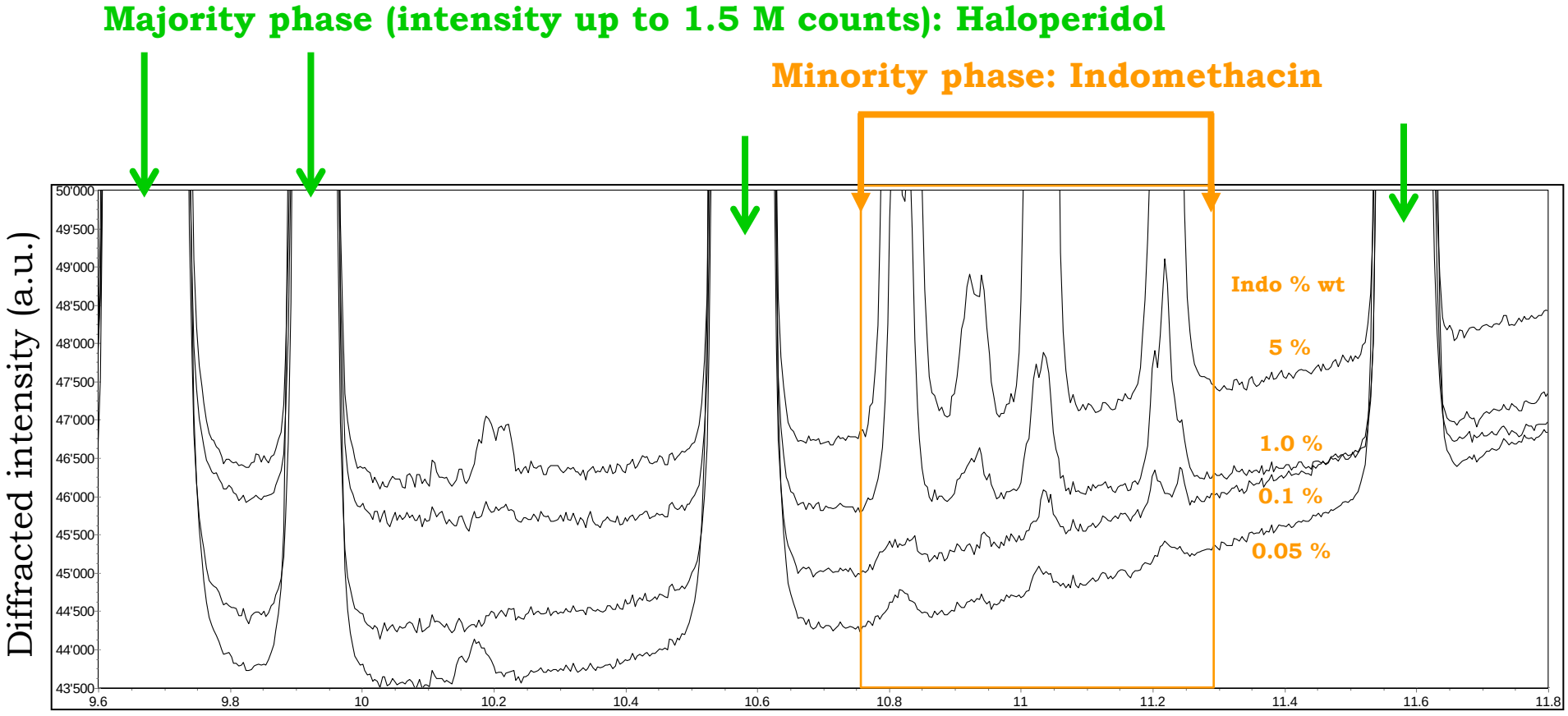
Quantitative Phase Analysis (QPA)

QPA refers to the ability of quantitatively state the abundance of the different phases that constitute a mixture.

Why is this relevant?

- Polymorphic purity: detect and quantify unwanted polymorphic forms in both drug substance and drug product
  - Level of Detection (LoD)
  - Level of Quantitation (LoQ)
- Assess the polymorphic composition in drug substance and product
- In formulated materials, the API/excipients relative proportion is important and needs to be kept under control
- Degree of Crystallinity in amorphous/crystalline mixtures

QPA of a binary API physical mixtures with fast SR-XRPD



F. Gozzo, 2012,
private communication

QPA analytical methods

Several are the analytical methods used to obtain quantitative phase related information:

- Based on chemical composition (so-called *normative calculation*)
- Based on properties specific to the phases of interest (e.g. magnetism, selective dissolution, density)
- Spectroscopic methods (e.g. Raman and Infrared spectroscopy, Mass spectroscopy, Nuclear Magnetic Resonance spectroscopy)
- Thermal Methods (e.g. Differential Scanning Calorimetry, ThermoGravimetric Analysis)
- Diffraction Methods → XRPD **Direct method**

Information is directly produced by the crystal structure of the component phases in the mixture

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- Scattering Methods → XRPD **Direct method**

Information is directly produced by the structure of the component phases in the mixture

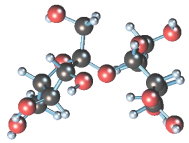
QPA ⟺ determining the contribution (typically in % weight) of each component phase in a mixture

Do the phases in the mixture need to be crystalline to perform their quantitative phase analysis?

Vainshtein's law:

within identical regions of reciprocal space, the scattered intensities from a material are independent of its state of order

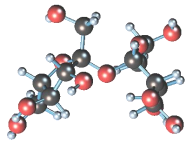
sucrose



Synchrotron-XRPD patterns of **c- & a-sucrose** at λ~0.62 Å; transmission geometry in capillary; data are corrected to:

- **air scattering** & **empty capillary contribution**
- **flat field corrected**
- **normalized to I0 current**

Quantification methods developed for crystalline phases can, therefore, often be also used for the indirect or direct quantification of amorphous phases



sucrose

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DIFFRACTION-BASED QPA METHODS

Single-peak methods:

- Intensity ratio $I_{unknown}/I_{standard}$ of one or more reflections
- No need of structural information but prone to systematic errors (e.g. caused by preferential orientation and peak overlapping)
- Need *ad-hoc* mixtures for calibration curves

Rietveld-based methods:

- Use of full diffraction patterns
- Minimization of systematic errors (e.g. due to peak overlap)
- Preferential Orientation (PO) can be modeled
- Accuracy close to X-Ray fluorescence elemental analysis, with the advantage of being sensitive to structural differences → direct QPA of polymorphs

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(adapted from Cullity, *Elements of X-Ray Diffraction*)

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(adapted from Madsen & Scarlett in *Powder Diffraction-Theory and Practice*)

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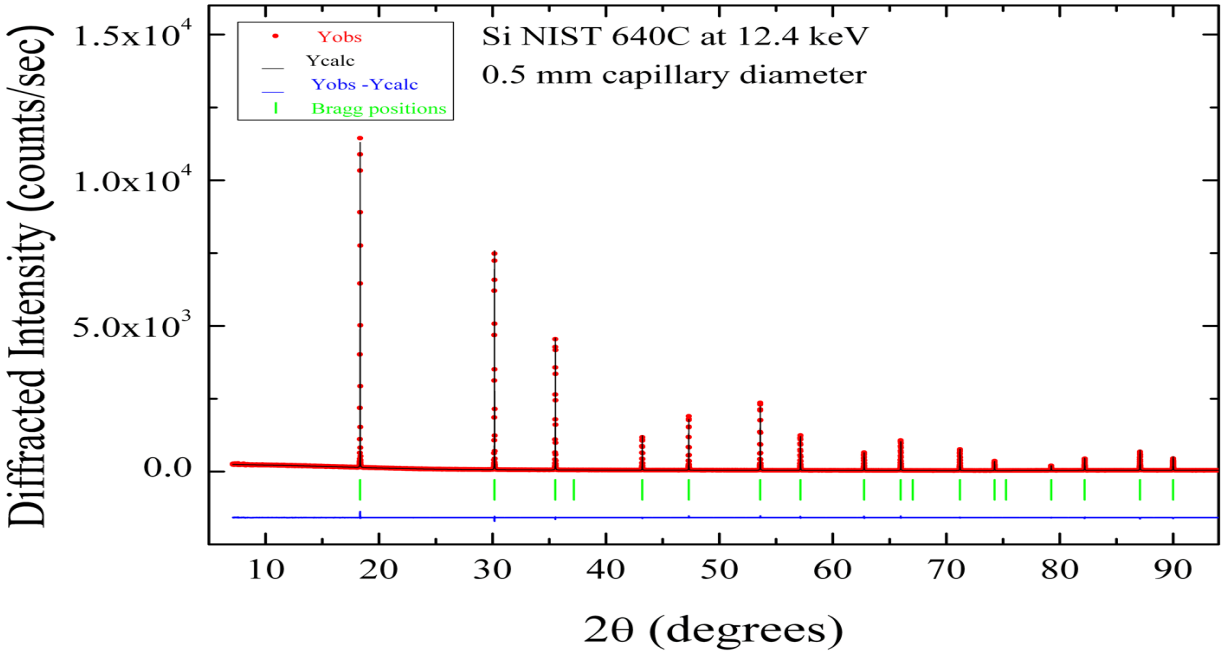
QPA with diffraction methods: math background



The diffracted intensity distribution is defined by:

Structural factors → crystal structure

Specimen factors → preferential orientation, grain size, shape and distribution, microstructure

Instrumental factors → properties of radiation, optics geometry, properties of detectors, slits and/or monochromator

For a powder diffraction pattern of a **pure crystalline phase** we can write:

$$I_{hkl} = \mathrm{K} \cdot M_{hkl} \cdot L_\theta \cdot P_\theta \cdot A_\theta \cdot PO_{hkl} \cdot E_{hkl} \cdot \left|F_{(hkl)}\right|^2 \cdot exp\left(-2B\left(\frac{\sin\theta}{\lambda}\right)\right)$$

Integrated intensity of reflection hkl

Scale factor

Multiplicity factor

Lorentz factor for powders $= \frac{1}{sin^2\theta \cdot cos\theta}$

Polarization factor $= \begin{cases} 1 & \text{Synchrotron: vertical scattering plane} \\ \cos^2 2\theta & \text{Synchrotron: horizontal scattering plane} \\ \frac{1+\cos^2 2\theta}{2} & \text{Unpolarized/unmonochromatized source} \end{cases}$

Absorption multiplier factor: experimental geometry dependent (see: Ch.8 in Pechasky & Zavalij; Ch.11 in Dinnebier &Billinge)

Preferential Orientation factor

Extinction factor

Structure factor (or amplitude)

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Lorentz-Polarization factor for powders $= \frac{1+\cos^2 2\theta \cos^2 2\theta_M}{sin^2\theta \cdot cos\theta}$

Lab XRPD:
$2\theta_M$ is the Bragg angle of the reflection from a monochromator, $2\theta_M$=0 for unpolarized unmonochromatized source , $2\theta_M \neq 0$ ($e.g.$ 26.5° graphite mono +CuKα radiation)
Synchrotron XRPD:
$2\theta_M$ is the angle between the scattering direction (where we place our detector!) and the direction of acceleration of the electron (e.g. the direction of the electric field of the synchrotron e.m. radiation). In the vertical plane this is always 90°.

For a powder diffraction pattern of a **pure crystalline phase** we can write:

$$I_{hkl} = \mathrm{K} \cdot M_{hkl} \cdot L_\theta \cdot P_\theta \cdot A_\theta \cdot PO_{hkl} \cdot E_{hkl} \cdot \left|F_{(hkl)}\right|^2 \cdot exp\left(-2B\left(\frac{\sin\theta}{\lambda}\right)\right)$$

negligible

Under the hypothesis of A, PO and E negligible, transmission (Debye-Scherrer) geometry, synchrotron radiation with vertical diffraction plane (as at the SLS-MS-PD), with powders loaded in capillaries and a 1D display detector (e.g. Mythen II):

$$I_{hkl} = \left[\frac{I_0 \lambda^3}{32\,\pi\, r} \cdot \frac{\sigma\, e^4}{m_e{}^2\, c^4}\right] \cdot \left[\frac{M_{hkl}}{V^2} \cdot \left|F_{(hkl)}\right|^2 \cdot \left(\frac{1}{sin^2\theta \cdot cos\theta}\right)\right] \cdot exp\left(-2B\left(\frac{\sin\theta}{\lambda}\right)\right) \cdot \left[\frac{1}{\mu}\right]$$

I_0	incident beam intensity
λ	photon beam wavelength
σ	cross sectional area of incident beam
e	charge of the electron
m_e	mass of the electron
c	speed of light
V	unit cell volume

$\mu = \rho\, \mu^*$	linear absorption (attenuation) coefficient of the pure phase
with ρ and μ^*	density of the pure phase and its mass absorption coefficient
$\exp(-2B\left(\frac{\sin\theta}{\lambda}\right)$	thermal factor, B is the mean Atomic Displacement Parameter (ADP)

For a powder diffraction pattern of a **mixture** (e.g. binary α+β mixture), for a hkl intensity line of phase α, we can write:

$$I_{(hkl)\alpha}=\left[\frac{I_0\lambda^3}{32\,\pi\,r}\cdot\frac{\sigma\,e^4}{{m_e}^2\,c^4}\right]\cdot\left[\frac{M_{hkl}}{{V_\alpha}^2}\cdot{|F_{hkl}|_\alpha}^2\left(\frac{1}{sin^2\theta\cdot cos\theta}\right)\right]\cdot exp\left(-2B_\alpha\left(\frac{\sin\theta}{\lambda}\right)\right)\cdot\left[\frac{c_\alpha}{\mu_m}\right]$$

I_0	incident beam intensity
λ	photon beam wavelength
σ	cross sectional area of incident beam
e	charge of the electron
m_e	mass of the electron
c	speed of light
r	distance scattering electron-detector
V_α	unit cell volume of phase α

c_α	volume fraction of phase α
$\mu_m = \rho_m \cdot {\mu_m}^*$	linear absorption (attenuation) coefficient of the entire mixture
with ρ_m *and* ${\mu_m}^*$	density of the entire mixture and its mass absorption coefficient
$exp(-2B\left(\frac{\sin\theta}{\lambda}\right)$	thermal factor, with B mean Atomic Displacement Parameter (ADP)

And similarly, for a h'k'l' line of phase β, we can write:

$$I_{(h'k'l')\beta}=\left[\frac{I_0\lambda^3}{32\,\pi\,r}\cdot\frac{\sigma\,e^4}{{m_e}^2\,c^4}\right]\cdot\left[\frac{M_{hkl}}{{V_\beta}^2}\cdot{\left|F_{(h'k'l')}\right|_\beta}^2\cdot\left(\frac{1}{sin^2\theta\cdot cos\theta}\right)\right]\cdot exp\left(-2B_\beta\left(\frac{\sin\theta}{\lambda}\right)\right)\cdot\left[\frac{c_\beta}{\mu_m}\right]$$

For a powder diffraction pattern of a **mixture** (e.g. binary α+β mixture), for a hkl intensity line of phase α, we can write:

$$I_{(hkl)\alpha} = \left[\frac{I_0 \lambda^3}{32\,\pi\, r} \cdot \frac{\sigma\, e^4}{m_e{}^2\, c^4}\right] \cdot \left[\frac{M_{hkl}}{V_\alpha{}^2} \cdot |F_{hkl}|_\alpha{}^2 \left(\frac{1}{sin^2\theta \cdot cos\theta}\right)\right] \cdot exp\left(-2B_\alpha \left(\frac{\sin\theta}{\lambda}\right)\right) \cdot \left[\frac{c_\alpha}{\mu_m}\right]$$

All factors are constant and independent of the concentration of the α phase with the exception of c_α and μ_m

$$I_{(hkl)\alpha} = \frac{K_{1,\alpha} \cdot c_\alpha}{\mu_m} \qquad \text{and equivalently:} \quad I_{(hkl)\beta} = \frac{K_{1,\beta} \cdot c_\beta}{\mu_m}$$

The simplified expression: $I_{(hkl)\alpha} = \frac{K_{1,\alpha} \cdot c_\alpha}{\mu_m}$ can also be written in terms of weight fractions w_α (and w_β):

$$I_{(hkl)\alpha} = \frac{K_{1,\alpha} \cdot w_\alpha \cdot \rho_m}{\mu_m \cdot \rho_\alpha} = \frac{K_{1,\alpha} \cdot w_\alpha}{\rho_\alpha \frac{\mu_m}{\rho_m}} = \frac{K_{1,\alpha} \cdot w_\alpha}{\rho_\alpha \mu_m *}$$

with ρ_α the density of phase α and $\mu_m *$ the mass absorption coefficient ($= \frac{\mu_m}{\rho_m}$) of the entire mixture.

DEMO:
Assuming a unit volume of mixture (V_m=1): ρ_m=density of mixture=weight of mixture → $w_\alpha\rho_m$ and $w_\beta\rho_m$ represent the weights of the α and β contents in our binary mixture with w_α and w_β the weight fractions → $\rho_\alpha = \frac{w_\alpha \rho_m}{c_\alpha} \rightarrow c_\alpha = \frac{w_\alpha \rho_m}{\rho_\alpha}$ and equivalently $c_\beta = \frac{w_\beta \rho_m}{\rho_\beta} \rightarrow \frac{c_\alpha}{\mu_m} = \frac{w_\alpha \rho_m}{\rho_\alpha \mu_m} = \frac{w_\alpha}{\rho_\alpha} \cdot \frac{1}{\mu_m *}$ with μ_m linear absorption (or attenuation) coefficient and μ_m* mass absorption coefficient.

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If we can access a powder sample of pure phase α: $I_{(hkl)\alpha,pure} = \frac{K_{1,\alpha}}{\rho_\alpha \mu_\alpha *} = \frac{K_{1,\alpha}}{\mu_\alpha}$

and we can write: $\frac{I_{(hkl)\alpha}}{I_{(hkl)\alpha,pure}} = \frac{K_{1,\alpha} \cdot w_\alpha}{\rho_\alpha \frac{\mu_m}{\rho_m}} \cdot \frac{\mu_\alpha}{K_{1,\alpha}} = \frac{w_\alpha \left(\mu_\alpha / \rho_\alpha\right)}{\left(\mu_m / \rho_m\right)} = \frac{w_\alpha \left(\mu_\alpha / \rho_\alpha\right)}{w_\alpha \left(\mu_\alpha / \rho_\alpha - \mu_\beta / \rho_\beta\right) + \mu_\beta / \rho_\beta}$

[demo p.389-390 Cullity]

$$\frac{I_{(hkl)\alpha}}{I_{(hkl)\alpha,pure}} = \frac{w_\alpha \left(\mu\alpha/\rho_\alpha\right)}{w_\alpha\left(\mu\alpha/\rho_\alpha - \mu\beta/\rho_\beta\right) + \mu\beta/\rho_\beta}$$

QPA of a binary mixture can, therefore be performed provided that we can access:

- the mass absorption coefficients of the two phases (if not, a calibration curve can be prepared using mixtures of known composition)
- one pure phase (or a mixture with a known amount of that phase)
- No need of structural information, $K_{1,\alpha}$ cancels out

What can we observe?

$$\frac{I_{(hkl)\alpha}}{I_{(hkl)\alpha,pure}} = \frac{w_\alpha\left(\mu\alpha/\rho_\alpha\right)}{w_\alpha\left(\mu\alpha/\rho_\alpha - \mu\beta/\rho_\beta\right) + \mu\beta/\rho_\beta}$$

- The intensity of a particular diffraction line depends on the mass absorption coefficient of the other phase
- For binary mixtures of phases with the same mass absorption coefficient:

$$\frac{I_{(hkl)\alpha}}{I_{(hkl)\alpha,pure}} = w_\alpha$$

The binary mixture case that we have worked out together is an example of the so-called ***single-line*** or ***single-peak methods of QPA***, for which *the measurement of the weight fraction of phase in a mixture depends on the measurement of the ratio of the intensity of a diffraction line from that phase to the intensity of some standard reference line*!

In the case discussed, the reference standard is the pure phase α!

DIRECT COMPARISON METHOD

INTERNAL STANDARD METHOD

DIRECT COMPARISON METHOD

Let us again consider a α+β binary mixture:

$$I_{(hkl)\alpha} = \frac{K_{1,\alpha} \cdot c_\alpha}{\mu_m} = \frac{K_{1,\alpha} \cdot w_\alpha}{\rho_\alpha \mu_m *} \qquad I_{(h\prime k\prime l\prime)\beta} = \frac{K_{1,\beta} \cdot c_\beta}{\mu_m} = \frac{K_{1,\beta} \cdot w_\beta}{\rho_\beta \mu_m *}$$

Let us separate in $K_{1,\alpha}$ the phase-dependent from the phase-independent part:

$K_{1,\alpha} = K_2 \cdot R_\alpha$ K_2 is a constant independent of the kind and amount of diffracting substance; R depends on θ, hkl, kind of substance

$$I_{(hkl)\alpha} = \frac{K_2 \cdot R_\alpha \cdot c_\alpha}{\mu_m} \qquad I_{(h\prime k\prime l\prime)\beta} = \frac{K_2 \cdot R_\beta \cdot c_\beta}{\mu_m}$$

$$\Rightarrow \quad \frac{I_{(hkl)\alpha}}{I_{(h\prime k\prime l\prime)\beta}} = \frac{R_\alpha \cdot c_\alpha}{R_\beta \cdot c_\beta} \quad \Rightarrow \quad \frac{c_\alpha}{c_\beta} = \frac{I_{(hkl)\alpha}}{I_{(h\prime k\prime l\prime)\beta}} \cdot \frac{R_\beta}{R_\alpha}$$

Details here: $K_2 = \frac{I_0 \lambda^3}{32\,\pi\, r} \cdot \frac{\sigma\, e^4}{{m_e}^2\, c^4}$ *and* $R_\alpha = \left[\frac{M_{hkl}}{{V_\alpha}^2} \cdot {\left|F_{(hkl)}\right|_\alpha}^2 \cdot \left(\frac{1+\cos^2 2\theta}{2}\right)\right] \cdot exp\left(-2B_\alpha \left(\frac{\sin\theta}{\lambda}\right)\right)$

DIRECT COMPARISON METHOD

Let us again consider a α+β binary mixture:

$$I_{(hkl)\alpha} = \frac{K_{1,\alpha} \cdot c_\alpha}{\mu_m} = \frac{K_{1,\alpha} \cdot w_\alpha}{\rho_\alpha \mu_m *} \qquad I_{(h\prime k\prime l\prime)\beta} = \frac{K_{1,\beta} \cdot c_\beta}{\mu_m} = \frac{K_{1,\beta} \cdot w_\beta}{\rho_\beta \mu_m *}$$

Let us separate in $K_{1,\alpha}$ the phase-dependent from the phase-independent part:

$K_{1,\alpha} = K_2 \cdot R_\alpha$ K_2 is a constant independent of the kind and amount of diffracting substance; R depends on θ, hkl, kind of substance

$$I_{(hkl)\alpha} = \frac{K_2 \cdot R_\alpha \cdot c_\alpha}{\mu_m} \qquad I_{(h\prime k\prime l\prime)\beta} = \frac{K_2 \cdot R_\beta \cdot c_\beta}{\mu_m}$$

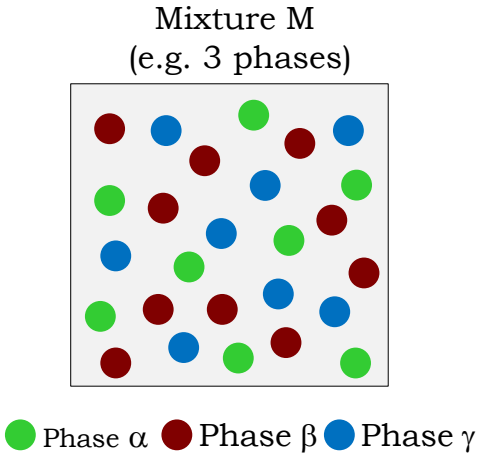
$$\rightarrow \quad \frac{I_{(hkl)\alpha}}{I_{(h\prime k\prime l\prime)\beta}} = \frac{R_\alpha \cdot c_\alpha}{R_\beta \cdot c_\beta} \quad \rightarrow \quad \frac{w_\alpha}{w_\beta} = \frac{I_{(hkl)\alpha}}{I_{(h\prime k\prime l\prime)\beta}} \cdot \frac{\rho_\alpha \cdot R_\beta}{\rho_\beta \cdot R_\alpha}$$

Details here: $K_2 = \frac{I_0 \lambda^3}{32\,\pi\, r} \cdot \frac{\sigma\, e^4}{{m_e}^2\, c^4}$ *and* $R_\alpha = \left[\frac{M_{hkl}}{{V_\alpha}^2} \cdot \left|F_{(hkl)}\right|_\alpha^{\,2} \cdot \left(\frac{1+\cos^2 2\theta}{2}\right)\right] \cdot exp\left(-2B_\alpha\left(\frac{\sin\theta}{\lambda}\right)\right)$

INTERNAL STANDARD METHOD

A diffraction line from the phase that we need to quantify in a given mixture (e.g. $I_{hkl,\alpha}$) is compared with a line from a standard (e.g. $I_{h'k'l',Std}$) mixed with our original mixture in known proportion → the ISM method is only applicable to powders!

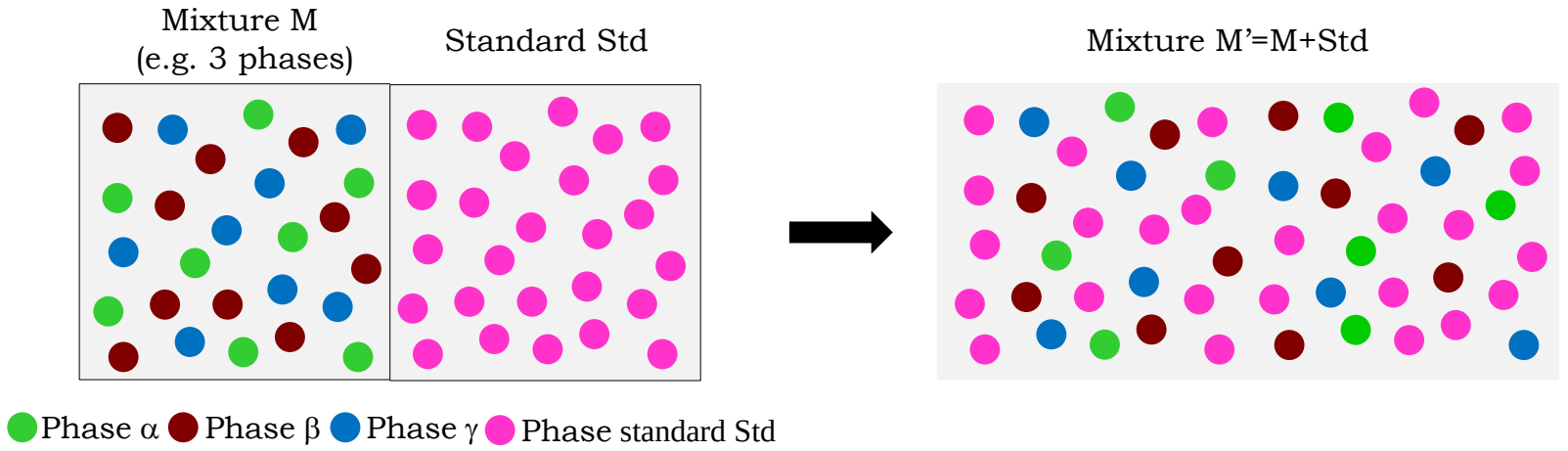
Let us consider a mixture M of n phases α, β, γ …



We need to quantify the **amount of phase** α in a series of mixtures of type M in which the relative proportion of the other phases β, γ …might change from mixture to mixture.

INTERNAL STANDARD METHOD: how does it work?

i. We mix a known amount of original mixture **M** with a known amount of a known standard **Std** and form a new mixture **M'=M+Std** (e.g. 50% M + 50% Std)



ii. Let $\mathbf{c}_{\alpha}$ and $\mathbf{c'}_{\alpha}$ the volume fractions of phase α in M and M' (both unknown!) and $\mathbf{c}_{\mathbf{Std}}$ the volume fraction of the standard Std (that we know!)

INTERNAL STANDARD METHOD: how does it work?

i. We mix a known amount of original mixture **M** with a known amount of a known standard **Std** and form a new mixture **M'=M+Std** (e.g. 50% M + 50% Std)

ii. Let $\mathbf{c}_\alpha$ and $\mathbf{c'}_\alpha$ the volume fractions of phase α in M and M' (both unknown!) and $\mathbf{c}_{\mathbf{Std}}$ the volume fraction of the standard Std (that we know!)

iii. From a powder diffraction pattern recorded on the new mixture M', we obtain:

$$I_{(hkl)\alpha} = I_\alpha = \frac{K_{1,\alpha} \cdot c_\alpha{}'}{\mu_m}$$ and similarly: $$I_{(h'k'l')Std} = I_{Std} = \frac{K_{1,Std} \cdot c_{Std}}{\mu_m}$$

Note that μ_m **cancels out**!

$$\longrightarrow \quad \frac{I_\alpha}{I_{Std}} = \frac{K_{1,\alpha} \cdot c_\alpha{}'}{K_{1,Std} \cdot c_{Std}}$$

It physically means that the variation of absorption due to the variation of the relative amounts of the other phases present in the original mixture (β, γ, …) does not affect the $\mathbf{I_\alpha/I_{Std}}$ ratio since such variations equivalently affects $\mathbf{I_\alpha}$ and $\mathbf{I_{Std}}$!

INTERNAL STANDARD METHOD: how does it work?

i. We mix a known amount of original mixture **M** with a known amount of a known standard **Std** and form a new mixture **M'=M+Std** (e.g. 50% M + 50% Std)

ii. Let $\mathbf{c}_\alpha$ and $\mathbf{c'}_\alpha$ the volume fractions of phase α in M and M' (both unknown!) and $\mathbf{c}_{\mathbf{Std}}$ the volume fraction of the standard Std (that we know!)

iii. From a powder diffraction pattern recorded on the new mixture M', we obtain:

$$\frac{I_\alpha}{I_{Std}} = \frac{K_{1,\alpha} \cdot c'_\alpha}{K_{1,Std} \cdot c_{Std}} \longrightarrow with \quad \frac{c'_\alpha}{c_{Std}} = \frac{w'_\alpha \cdot \rho_{Std}}{\rho_\alpha \cdot w_{Std}} \longrightarrow \quad \frac{I_\alpha}{I_{Std}} = \frac{K_{1,\alpha}}{K_{1,Std}} \cdot \frac{w'_\alpha \cdot \rho_{Std}}{\rho_\alpha \cdot w_{Std}}$$

If w_{Std} is kept <u>constant</u> in all mixtures of type M', then $\frac{K_{1,\alpha}}{K_{1,Std}} \cdot \frac{\rho_{Std}}{\rho_\alpha \cdot w_{Std}} \overset{\text{def}}{=} K_3$

$$\longrightarrow \frac{I_\alpha}{I_{Std}} = K_3 \cdot w'_\alpha \longrightarrow \frac{I_\alpha}{I_{Std}} = K_4 \cdot w_\alpha \quad \text{being:} \quad w'_\alpha = w_\alpha(1 - w_{Std})$$

INTERNAL STANDARD METHOD: how does it work?

i. We mix a known amount of original mixture **M** with a known amount of a known standard **Std** and form a new mixture **M'=M+Std** (e.g. 50% M + 50% Std)

ii. Let $\mathbf{c}_\alpha$ and $\mathbf{c'}_\alpha$ the volume fractions of phase α in M and M' (both unknown!) and $\mathbf{c}_{\mathbf{Std}}$ the volume fraction of the standard Std (that we know!)

iii. From a powder diffraction pattern recorded on the new mixture M', we obtain:

$$\frac{I_\alpha}{I_{Std}} = K_4 \cdot w_\alpha$$

Slope of the straight line

- The intensity ratio $\frac{I_\alpha}{I_{Std}}$ is therefore a **linear function** of the weight fraction w_α of phase α.
- A calibration curve can be prepared from XRPD measurements on a set of *ad-hoc* synthetic samples containing **known** concentrations of phase α and a **constant** concentration w_{Std} of a suitable standard
- The concentration of α in an unknown mixture is obtained by measuring the ratio $\frac{I_\alpha}{I_{Std}}$ in a mixture of type M' (so-called ***spiked*** sample) containing the unknown original mixture and the standard in the same proportion as used to build up the calibration curve.

Generalization of the Internal Standard Method →

→The Reference Intensity Ratio (RIR)

$$\frac{I_\alpha}{I_{Std}} = K_4 \cdot w_\alpha$$

The calibration constant K_4 depends on: α, Std, $(hkl)_\alpha$, $(h'k'l')_{Std}$ and w_{Std}

(remember: $I_\alpha = I_{(hkl)\alpha}$ and $I_{Std} = I_{(h'k'l')S}$)

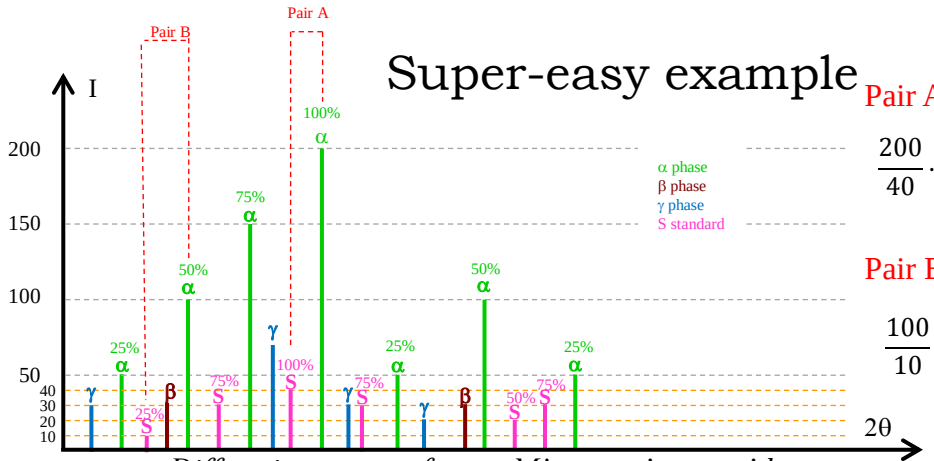
For a more reliable quantification, the use of several analyte-line/internal standard-line pair is preferable → each pair requires a calibration constant!

The use of ***relative intensities I^{rel}*** and so-called ***Relative Intensity Ratio (RIR)*** allows us to use multiple analyte/standard reflection pairs without the need of multiple reference standards:

Hubbard & Snyder, (1988) Powder Diffraction 3, 74-78.

$$\frac{I_{i\alpha}}{I_{jS}} \cdot \frac{I_{jS}^{rel}}{I_{i\alpha}^{rel}} \cdot \frac{w_S}{w_\alpha} = K = RIR_{\alpha,S}$$

i denotes one hkl reflection of α phase
j denotes one h'k'l' reflection of the internal standard



Diffraction pattern from a M'-type mixture with 50% standard and (for example) 20% α-phase

Pair A:

$$\frac{200}{40} \cdot \frac{100}{100} \cdot \frac{0.5}{0.2} = 12.5 = K = RIR_{\alpha,S}$$

Pair B:

$$\frac{100}{10} \cdot \frac{25}{50} \cdot \frac{0.5}{0.2} = 12.5 = K = RIR_{\alpha,S}$$

The Reference Intensity Ratio (RIR)

$$K = RIR_{\alpha,S} = \frac{I_{i\alpha}}{I_{jS}} \cdot \frac{I_{jS}^{rel}}{I_{i\alpha}^{rel}} \cdot \frac{w_S}{w_\alpha}$$

Universal calibration constant relating the scattering power of phase α to that of the standard Std

→ *So-called* ***Reference Intensity Ratio*** or ***RIR***

Standard Std → NIST Corundum → RIR=I/I_C

The Powder Diffraction File (PDF) contains I/I_C ratios for more than 2500 phases!

Quantitative Phase Analysis with I/I_C (RIR or Chung Method)

$$w_\alpha = \frac{I_{i\alpha}}{I_{jC}} \cdot \frac{I_{jC}^{rel}}{I_{i\alpha}^{rel}} \cdot \frac{w_S}{RIR_{\alpha,C}} = \frac{I_{i\alpha}}{I_{jC}} \cdot \frac{I_{jC}^{rel}}{I_{i\alpha}^{rel}} \cdot \frac{w_S}{(I/I_C)_\alpha}$$

With the addition of a known %wt of corundum, no calibration curves needed!

Or **standardless QPA**, if all phases in the mixture are crystalline, identified, and the RIR values known for each of them!

DIFFRACTION-BASED QPA METHODS

Single-peak methods:

(adapted from Cullity, *Elements of X-Ray Diffraction*)

- Intensity ratio $I_{unknown}/I_{standard}$ of one or more reflections
- No need of structural information but prone to systematic errors (e.g. caused by preferential orientation and peak overlapping)
- Need *ad-hoc* mixtures for calibration curves

Rietveld-based methods:

(adapted from Madsen & Scarlett in *Powder Diffraction-Theory and Practice*)

- Use of full diffraction patterns
- Minimization of systematic errors (e.g. due to peak overlap)
- Preferential Orientation (PO) can be modeled
- Accuracy close to X-Ray fluorescence elemental analysis, with the advantage of being sensitive to structural differences → direct QPA of polymorphs

Rietveld QPA METHOD

"The Rietveld method uses a model to calculate a diffraction pattern which is then compared with observed data. The difference between the two patters is then reduced through least square minimization. ***The refinable parameters used in the models provide the analyst with information regarding*** *the crystal structure of the component phases, the crystalline size and strain and, importantly,* ***their relative proportions****. The* ***Rietveld scale factor S****, which is a multiplier for each components' contribution to the pattern, is related to the relative abundance of that phase and can be used in the quantification of phases."*

(textual citation from ***Quantitative Phase Analysis using the Rietveld Method***, Madsen, Scarlett, Riley & Raven, Ch.10 in Modern Diffraction Methods, Mittemeijer & Welzel Edts, 2013)

Rietveld QPA METHOD

$$I_{(hkl)\alpha}=\left[\frac{I_0\lambda^3}{32\,\pi\,r}\cdot\frac{\sigma\,e^4}{{m_e}^2\,c^4}\right]\cdot\left[\frac{M_{hkl}}{{V_\alpha}^2}\cdot{|F_{hkl}|_\alpha}^2\left(\frac{1}{sin^2\theta\cdot cos\theta}\right)\right]\cdot exp\left(-2B_\alpha\left(\frac{\sin\theta}{\lambda}\right)\right)\cdot\left[\frac{c_\alpha}{\mu_m}\right]$$

D-S geometry with capillary, assuming absorption, PO and extinction negligible

Rietveld QPA METHOD

$$I_{(hkl)\alpha}=\left[\frac{I_0\lambda^3}{32\,\pi\,r}\cdot\frac{\sigma\,e^4}{m_e{}^2\,c^4}\right]\cdot\left[\frac{M_{hkl}}{V_\alpha{}^2}\cdot|F_{hkl}|_\alpha{}^2\left(\frac{1}{sin^2\theta\cdot cos\theta}\right)\right]\cdot exp\left(-2B_\alpha\left(\frac{\sin\theta}{\lambda}\right)\right)\cdot\left[\frac{w_\alpha}{\rho_\alpha\mu_m^*}\right]$$

D-S geometry with capillary, assuming absorption, PO and extinction negligible

$$I_{(hkl)\alpha}=\frac{K_{1,\alpha}\cdot w_\alpha}{\rho_\alpha\cdot\mu_m^*}\longrightarrow\quad w_\alpha=\frac{I_\alpha\cdot\rho_\alpha\cdot\mu_m^*}{K_{1,\alpha}}=\frac{S_\alpha\cdot(ZMV)_\alpha\cdot\mu_m^*}{K}$$

$$K_{1,\alpha}\propto\frac{1}{V_\alpha^2}$$

$$I_\alpha\propto S_\alpha$$

R. J. Hill, Powder Diffr. 1991, **6**, 74-77

$$\rho_\alpha=1.6604\cdot\frac{ZM_\alpha}{V_\alpha}$$

Z=number of formula units
M=molecular mass of the formula unit

Rietveld QPA METHOD

$$I_{(hkl)\alpha}=\left[\frac{I_0\lambda^3}{32\,\pi\,r}\cdot\frac{\sigma\,e^4}{{m_e}^2\,c^4}\right]\cdot\left[\frac{M_{hkl}}{{V_\alpha}^2}\cdot{|F_{hkl}|_\alpha}^2\left(\frac{1}{sin^2\theta\cdot cos\theta}\right)\right]\cdot exp\left(-2B_\alpha\left(\frac{\sin\theta}{\lambda}\right)\right)\cdot\left[\frac{w_\alpha}{\rho_\alpha\mu_m^*}\right]$$

D-S geometry with capillary, assuming absorption, PO and extinction negligible

$$w_\alpha=\frac{S_\alpha\cdot(ZMV)_\alpha\cdot\mu_m^*}{K}$$

★ IMPORTANT RELATION

In 1988, O'Connor & Raven demonstrated that the scaling factor K is independent of individual phases and overall sample-related parameters (Powder Diffr. **3**, 2-6) .

This implies that K only needs to be estimated once for a given instrumental configuration and using an appropriate standard

→ **EXTERNAL STANDARD METHOD** for absolute QPA analysis

Warning: the term "*instrumental configuration*" really refers to all experimental details →

→ in DS geometry with powders in capillaries it would imply also the same powder packing!

Rietveld QPA METHOD

$$I_{(hkl)\alpha}=\left[\frac{I_0\lambda^3}{32\,\pi\,r}\cdot\frac{\sigma\,e^4}{{m_e}^2\,c^4}\right]\cdot\left[\frac{M_{hkl}}{{V_\alpha}^2}\cdot{|F_{hkl}|_\alpha}^2\left(\frac{1}{sin^2\theta\cdot cos\theta}\right)\right]\cdot exp\left(-2B_\alpha\left(\frac{\sin\theta}{\lambda}\right)\right)\cdot\left[\frac{w_\alpha}{\rho_\alpha\mu_m^*}\right]$$

D-S geometry with capillary, assuming absorption, PO and extinction negligible

$$w_\alpha=\frac{S_\alpha\cdot(ZMV)_\alpha\cdot\mu_m^*}{K}$$

★ IMPORTANT RELATION

$(ZMV)_\alpha$ is the so-called ***calibration constant*** for phase α that can be calculated from the structural model (either from crystallographic database or the refinement of the pure α phase)

Absolute QPA analysis can, then, be obtained provided we correctly estimate K and μ_m^* for all our mixtures and calibration standards (the latter for K determination)

Rietveld QPA METHOD: Q&A

$$w_\alpha = \frac{S_\alpha \cdot (ZMV)_\alpha \cdot \mu_m^*}{K}$$ ★

Q_1: Can we still perform **absolute QPA** analyses without estimating K and μ_m^*?

A_1: Yes, we can, if we "spike" our unknown mixture with a known amount w_S of an appropriate reference standard Std of well known crystallographic structure (**INTERNAL STANDARD METHOD**)

$$w'_\alpha = \frac{S_\alpha \cdot (ZMV)_\alpha \cdot \mu_m^*}{K}$$

★ For α and Std

$$w_{Std} = \frac{S_{Std} \cdot (ZMV)_{Std} \cdot \mu_m^*}{K}$$

➡

$$w'_\alpha = w_{Std} \cdot \frac{S_\alpha \cdot (ZMV)_\alpha}{S_{Std} \cdot (ZMV)_{Std}}$$ ★★

$$w'_\alpha = w_\alpha (1 - w_{Std})$$

Remark: note that there is no need of a calibration curve as for the Internal Standard Method as implemented in the single-line diffraction method in virtue of performing here a Rietveld refinement!

Rietveld QPA METHOD: Q&A

$$w_\alpha = \frac{S_\alpha \cdot (ZMV)_\alpha \cdot \mu_m^*}{K}$$ ★

$$w'_\alpha = w_{Std} \cdot \frac{S_\alpha \cdot (ZMV)_\alpha}{S_{Std} \cdot (ZMV)_{Std}}$$ ★★

$$w'_\alpha = w_\alpha (1 - w_{Std})$$

Q_2: What if we **do NOT** dispose of the whole composition of the unknown mixture?

A_2: We have 2 possibilities:

- if we can reasonably estimate K and μ_m^*, we apply ★ , that is the External Standard Method.
- we spike the sample with a known amount of a known standard and apply the ★★ (Internal Standard Method)

Rietveld QPA METHOD: Q&A

$$w_\alpha = \frac{S_\alpha \cdot (ZMV)_\alpha \cdot \mu_m^*}{K}$$ ★

$$w'_\alpha = w_{Std} \cdot \frac{S_\alpha \cdot (ZMV)_\alpha}{S_{Std} \cdot (ZMV)_{Std}}$$ ★★

$$w'_\alpha = w_\alpha (1 - w_{Std})$$

Q_2: What if we dispose of the whole composition of the unknown mixture?

A_2: For a mixture of n crystalline phases α, β, γ, δ … we can write:

$$w_\alpha + w_\beta + w_\gamma + \cdots = \sum_{i=1}^{n} w_i = 1$$

★★ $$w_\alpha = \frac{w_\alpha}{\sum_{i=1}^{n} w_i} = \frac{S_\alpha \cdot (ZMV)_\alpha}{\sum_{i=1}^{n} S_i \cdot (ZMV)_i}$$ and equivalent expressions for w_β, w_γ …

★ **Hill & Howard** (JAC (1987). 20, 467-474) modification of the Rietveld QPA method, known as the *ZMV approach* inspired by the *Matrix Flushing Method* of **Chung** (JAC, 1974, 7, 519-525 and 526-531)

Rietveld QPA METHOD: Q&A

$$w_\alpha = \frac{S_\alpha \cdot (ZMV)_\alpha \cdot \mu_m^*}{K}$$ ★

External Standard Method

$$w'_\alpha = w_{Std} \cdot \frac{S_\alpha \cdot (ZMV)_\alpha}{S_{Std} \cdot (ZMV)_{Std}}$$ ★★

$$w'_\alpha = w_\alpha (1 - w_{Std})$$

Internal Standard Method

$$w_\alpha + w_\beta + w_\gamma + \cdots = \sum_{i=1}^{n} w_i = 1$$

$$w_\alpha = \frac{w_\alpha}{\sum_{i=1}^{n} w_i} = \frac{S_\alpha \cdot (ZMV)_\alpha}{\sum_{i=1}^{n} S_i \cdot (ZMV)_i}$$ ★★★

Hill & Howard (ZMV) Approach

Warning: the (ZMV) approach assumes that:

- All phases in the mixtures are crystalline!
- We have identified them all!

If our mixture has unknown crystalline phases or amorphous components, a QPA analysis via (ZMV) approach inevitably overestimates the w_i weight fractions

Rietveld QPA METHOD: Q&A

$$w_\alpha = \frac{S_\alpha \cdot (ZMV)_\alpha \cdot \mu_m^*}{K}$$ ★

External Standard Method

$$w'_\alpha = w_S \cdot \frac{S_\alpha \cdot (ZMV)_\alpha}{S_S \cdot (ZMV)_S}$$ ★★

$$w'_\alpha = w_\alpha (1 - w_S)$$

Internal Standard Method

$$w_\alpha + w_\beta + w_\gamma + \cdots = \sum_{i=1}^{n} w_i = 1$$

$$w_\alpha = \frac{w_\alpha}{\sum_{i=1}^{n} w_i} = \frac{S_\alpha \cdot (ZMV)_\alpha}{\sum_{i=1}^{n} S_i \cdot (ZMV)_i}$$ ★★★

Hill & Howard (ZMV) Approach

What do we do in such cases?

We apply the Internal Standard Method:

- We add a known amount of an appropriate standard Std
- We write ★★★ for all identified crystalline phases i and for Std
- For each phase i we can write: $Corrected(W_i) = W_{i,Rietveld} \frac{W_{Std,true}}{W_{Std,Rietveld}}$
- $W_{unknown} = 1.0 - \sum_{k=1}^{n} Corrected(W_k)$

What if a **structural model is NOT available** or if it does not work well with our experimental data?

➢ Partial Or No Known Crystal Structure (PONKCS) Method

Madsen & Scarlett, Powder Diffr. 21(4), 2006, 278-284;
Madsen, Scarlett & Kern, Z. Kristallogr.226 (2011) 944-955

→ implemented in Topas

- *If partial structure available (i.e. unit cell and SG) → real structure factors substituted with empirical values derived from a Pawley or LeBail refinement performed on pure phases → an **hkl_Is phase** in Topas*
- *If partial structure NOT available → real structure factor substituted by fictitious phases consisting each of a series of related peaks with FIXED relative intensities and GROUP-SCALED as a single entity during the QPA analysis → a **x0_Is phase** or **peak-phase** in Topas*
- *Compute empirical ZM or ZMV calibration constants from the refinement of ad-hoc mixtures of pure phases with a known amount of a known standard (e.g. via spiking)→ so-called PONKCS phases.*

$$w_\alpha + w_\beta + w_\gamma + \cdots = \sum_{i=1}^{n} w_i = 1$$

$$w_\alpha = \frac{w_\alpha}{\sum_{i=1}^{n} w_i} = \frac{S_\alpha \cdot (ZMV)_\alpha}{\sum_{i=1}^{n} S_i \cdot (ZMV)_i}$$

➢ **Partial Or No Known Crystal Structure** (**PONKCS**) Method

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- *Compute empirical ZM or ZMV calibration constants from the refinement of ad-hoc mixtures of pure phases with a known amount of a known standard (e.g. via spiking)→ so-called PONKCS phases.*

$$w_\alpha + w_{Std} = \sum_{i=1}^{2} w_i = 1$$

For the PONKCS binary mixtures (phase α + Std); for every a phase we want a PONKCS phase of!

$$w_\alpha = \frac{w_\alpha}{w_\alpha + w_{std}} = \frac{S_\alpha \cdot (ZMV)_\alpha}{S_\alpha \cdot (ZMV)_\alpha + S_{std} \cdot (ZMV)_{std}}$$

… and the same written for the Std

➢ Partial Or No Known Crystal Structure (PONKCS) Method

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- *Compute empirical ZM or ZMV calibration constants from the refinement of ad-hoc mixtures of pure phases with a known amount of a known standard (e.g. via spiking)→ so-called PONKCS phases.*

$$w_\alpha + w_{Std} = \sum_{i=1}^{2} w_i = 1$$

For phase α

$$w_\alpha = \frac{w_\alpha}{w_\alpha + w_{std}} = \frac{S_\alpha \cdot (ZMV)_\alpha}{S_\alpha \cdot (ZMV)_\alpha + S_{std} \cdot (ZMV)_{std}}$$

For standard Std

$$w_{std} = \frac{w_{std}}{w_\alpha + w_{std}} = \frac{S_{std} \cdot (ZMV)_{std}}{S_\alpha \cdot (ZMV)_\alpha + S_{std} \cdot (ZMV)_{std}}$$

➢ Partial Or No Known Crystal Structure (PONKCS) Method

Madsen & Scarlett, Powder Diffr. 21(4), 2006, 278-284;
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- *Compute empirical ZM or ZMV calibration constants from the refinement of ad-hoc mixtures of pure phases with a known amount of a known standard (e.g. via spiking)→ so-called PONKCS phases.*

$$w_\alpha + w_{Std} = \sum_{i=1}^{2} w_i = 1$$

From the ratio:

$$\frac{w_\alpha}{w_{std}} = \frac{S_\alpha \cdot (ZMV)_\alpha}{S_{std} \cdot (ZMV)_{std}} \rightarrow$$

$$\rightarrow \quad (ZM)_\alpha = \frac{w_\alpha}{w_{std}} \cdot \frac{S_{std} \cdot (ZM)_{std} \cdot V_{std}}{S_\alpha \cdot (ZM)_\alpha \cdot V_\alpha}$$

➢ Partial Or No Known Crystal Structure (PONKCS) Method

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Madsen, Scarlett & Kern, Z. Kristallogr.226 (2011) 944-955

→ implemented in Topas

- *If partial structure available (i.e. unit cell and SG) → real structure factors substituted with empirical values derived from a Pawley or LeBail refinement performed on pure phases → an **hkl_Is phase** in Topas*
- *If partial structure NOT available → real structure factor substituted by fictitious phases consisting each of a series of related peaks with FIXED relative intensities and GROUP-SCALED as a single entity during the QPA analysis → a **x0_Is phase** or **peak-phase** in Topas*
- *Compute empirical ZM or ZMV calibration constants from the refinement of ad-hoc mixtures of pure phases with a known amount of a known standard (e.g. via spiking)→ so-called PONKCS phases.*

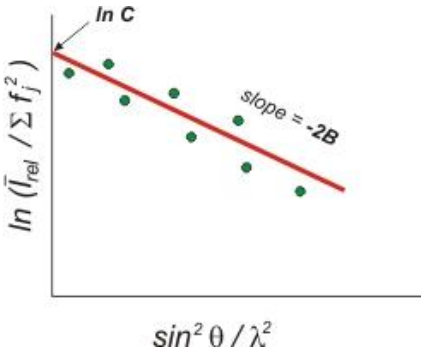
Requirements:

- Pure phases (or pure phases with known impurities) must be available
- *Ad-hoc* mixtures of pure phases with an appropriate standard in known %wt must be available to build the so-called PONKCS phase

Benefits:

- No need of a valid structural model
- PONKCS phases can be "re-used" provided the QPA analyses are conducted at the same photon energy! → Careful with SR-XRPD data!
- PONKCS works for **crystalline** as well as **amorphous phases**

Whole-patterns QPA Methods



➢ QUANTO+

Giannini, Guagliardi & Mililli, JAC (2002). 35, 481-490

- *If partial structure available (i.e. unit cell and SG) → for each phase in the mixture a reflection intensity file is built via whole pattern decomposition (e.g. Le Bail refinement) performed on pure phases*
- *This «external» file is used instead of the calculated structural factors from the model ($|\boldsymbol{Fc}|^2$) for the absolute scaling of the diffracted intensity via a Wilson plot*

Requirements:

- Pure phases must be available
- Partial structure (unit cell and SG) must be known
- Crystalline phases

Benefits:

- No need to have a valid structural model
- No need to prepare *ad-hoc* mixtures with an appropriate standard!

→ implemented in Quanto (CNR-IC)

Quantification of amorphous (X-ray amorphous) phases based on X-ray scattering methods

- Conventional XRD methods
- Total scattering techniques
- Principal Component Analyses

Quantification of amorphous (X-ray amorphous) phases based on X-ray scattering methods

- Conventional XRD methods

- Total scattering techniques

  Both Bragg peaks and diffuse scattering is interpreted: e.g. Pair Distribution Function

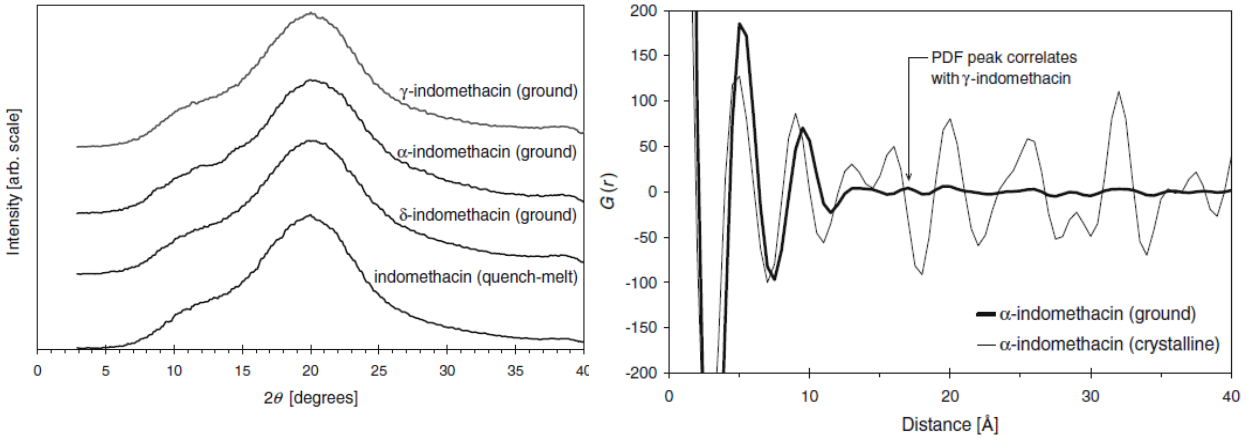
  PDF (so-called G(r) function) is the probability of finding a couple of atoms separated by a distance r

- Principal Component Analyses

Quantification of amorphous (X-ray amorphous) phases based on X-ray scattering methods

- Conventional XRD methods

- Total scattering techniques → Quantification via PDF refinement of mixtures



Billinge et al, CrystEngComm 12, 1366-1368 (2010)

Trakral et al, *Recent advances in the characterization of amorphous pharmaceuticals by X-ray difractometry*, Adv. Drug Deliv. Rev. (2015), http://dx.doi.org/10.1016/j.addr.2015.12.013

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H. Abdi and L. J. Williams, Principal Components Analysis, 2010 John Wiley & Sons, Inc. WIREs Comp Stat 2010 2 433–459 → *for generalities*

K. Chapman, S. Lapidus & P.J. Chupas, Applications of principal components analysis to Pair Distribution Function data, J. Appl. Cryst. (2015). 48, 1619-1626 → *for applications of PCA to PDF*

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Quantification of amorphous (X-ray amorphous) phases based on X-ray scattering methods

❑ Conventional XRD methods

- single peak or whole pattern methods
- Direct or Indirect methods

Implemented or implementable in virtually all XRD software

❑ Total scattering techniques

Both Bragg peaks and diffuse scattering is interpreted: e.g. Pair Distribution Function

PDF (so-called G(r) function) is the probability of finding a couple of atoms separated by a distance r

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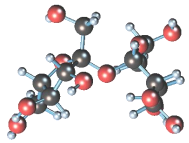
Reminder

Vainshtein's law:

within identical regions of reciprocal space, the scattered intensities from a material are independent of its state of order

sucrose



Synchrotron-XRPD patterns of **c- & a-sucrose** at λ~0.62 Å; data are corrected to:

- **air scattering** &**empty capillary contribution**
- **flat field corrected**
- **normalized to I0 current**

Quantification of amorphous (X-ray amorphous) phases based on X-ray scattering methods

- Conventional XRD methods → **Single peak** approach
- Conventional XRD methods → **Whole pattern** approach

Direct XRD methods:

the contribution of the amorphous component(s) to the pattern is used to obtain an estimate of the amorphous concentration

Indirect XRD methods:

the absolute abundances of the crystalline components are used to estimate the amorphous component by difference

Review article: Madsen, Scarlett & Kern, *Description and survey of methodologies for the determination of amorphous content via X-Ray powder diffraction*, Z. Kristallogr. 226 (2011) 944-955

Direct XRD methods:

- Single peak & Linear Calibration Method (LCM)
- PONKCS (**P**artial **O**r **N**o **K**nown **C**rystal **S**tructure) Method → the same we have seen for crystalline phases!
- DoC (Degree of Crystallinity) Method
- Full Structure Method

Direct XRD methods:

- Single peak & Linear Calibration Method (LCM)
  - Calibration suite of samples needed
  - Amorphous contribution needs to be distinguishable from background
- PONKCS (**P**artial **O**r **N**o **K**nown **C**rystal **S**tructure) Method → the same we have seen for crystalline phases!
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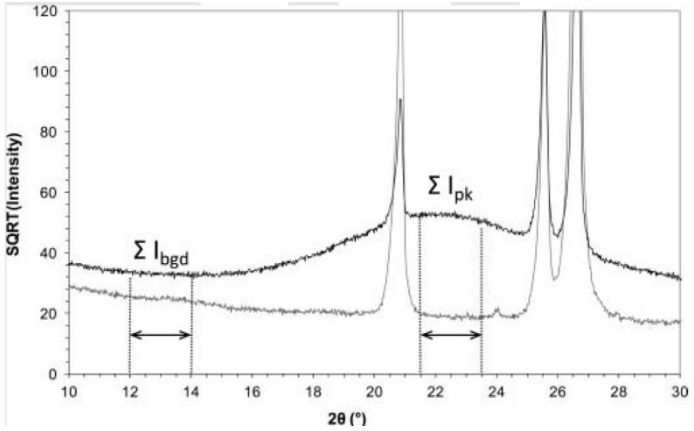

Fig.1 from Madsen, Scarlett & Kern, Z. Krist. 226 (2011) 944-955

← In this example, the authors had available one sample "free" of amorphous phase and used its diffraction pattern to estimate the background under the amorphous broad peak, but bkg determination is in principle not necessary!

$$W_a = A * I_a + B$$ Linear calibration curve

↓

Refined scale factor for the LCM

Direct XRD methods:

- ❑ Single peak & Linear Calibration Method (LCM)
  - Calibration suite of samples needed
  - Amorphous contribution needs to be distinguishable from background
- ❑ PONKCS (**P**artial **O**r **N**o **K**nown **C**rystal **S**tructure) Method → the same we have seen for crystalline phases!
  - Empirical determination of ZMV constant for amorphous component(s)
  - Determination of PONKCS phases for each component, via incorporation of a crystalline Std in known %wt, but only ONCE! Careful: photon wavelength dependent!
- ❑ DoC (Degree of Crystallinity) Method
- ❑ Full Structure Method

➢ Partial Or No Known Crystal Structure (PONKCS) Method

Madsen & Scarlett, Powder Diffr. 21(4), 2006, 278-284;
Madsen, Scarlett & Kern, Z. Kristallogr.226 (2011) 944-955

→ implemented in Topas

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$$w_\alpha + w_{Std} = \sum_{i=1}^{2} w_i = 1$$

From the ratio:

$$\frac{w_\alpha}{w_{std}} = \frac{S_\alpha \cdot (ZMV)_\alpha}{S_{std} \cdot (ZMV)_{std}} \rightarrow$$

RECALL

$$\rightarrow (ZM)_\alpha = \frac{w_\alpha}{w_{std}} \cdot \frac{S_{std} \cdot (ZM)_{std} \cdot V_{std}}{S_\alpha \cdot (ZM)_\alpha \cdot V_\alpha}$$

Direct XRD methods:

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- ❑ DoC (Degree of Crystallinity) Method
  - Estimate of the total intensity scattered by crystalline and amorphous component(s)

$$DoC = \frac{Crystalline\ area}{Crystalline\ area + Amorphous\ Area} \rightarrow W_{amorphous} = 1 - DoC$$

- ❑ Full Structure Method

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- ❑ Full Structure Method
  - Identification of a structure model that adequately models positions and relative intensities of experimental pattern of amorphous

Direct XRD methods:

❑ Single peak & Linear Calibration Method (LCM)

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❑ Full Structure Method

- Identification of a structure model that adequately models positions and relative intensities of experimental pattern of amorphous

Indirect XRD methods:

❑ Internal Standard Method

- Crystalline components put on an absolute scale
- Amorphous contribution calculated by difference

$$Corrected(W_i) = W_{i,Rietveld}\frac{W_{Std,true}}{W_{Std,Rietveld}} \rightarrow$$

$$W_{unknown}=1.0-\sum_{k=1}^{n} Corrected(W_k)$$

$$\downarrow$$

$$W_{amorphous}=1.0-\sum_{k=1}^{n} Corrected(W_k)$$

❑ External Standard Method

★ $$w_\alpha = \frac{S_\alpha \cdot (ZMV)_\alpha \cdot \mu_m^*}{K}$$

μ_m^*: Mass absorption coefficient of the entire mixture

K: Normalization constant to put Wα on an absolute scale; K dependent on the instrument configuration

Thanks for your kind attention

EXTRA – NOT included in the PPXRD lecture

Factors influencing QPA

For a detailed and exhaustive discussion and references citation see:

- Madsen & Scarlett (***Ch. 11***, *Powder Diffraction – Theory and Practice*), **2009**
- Madsen, Scarlett, Riley & Raven (***Ch.10***, *Modern Diffraction Methods),* **2013**

Accurate QPA ⟷ Accurate integrated intensity (ca. 1-2% relative)

V. Factors influencing QPA and QPA accuracy

Sources of errors

Instrument related

- **Experimental geometry**:

BB (reflection) θ–2θ
BB fixed-θ
DS (transmission) capillary or thin layer

- **Counting errors** (random and sistematic)

Sample related

- **Particle statistics**
- **Preferential Orientation**
- **Absorption** and **microabsorption**
- Incorrect or insufficient **crystal structure** model
- Crystallite **size** and **strain** broadening

Operator related

- **Analyst choices** during QPA analysis affect the results → QPA Round Robin 1996-2002 (see Madsen & Scarlett)
- Dangerous side of **easy-to-use QPA software**
- Importance of setting up **QPA guidelines**

Accuracy & Precision associated to QPA

What sets QPA accuracy and precision?

What does a Rietveld (or Rietveld-like) refinement return?

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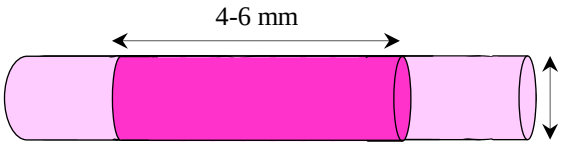
The accuracy in the I_{hkl} estimate is strongly influenced by N_{diffr} in a powder sample



$V \sim 3-5\ mm^3 \rightarrow N_{diff} \sim 3 \rightarrow \sigma_{PS} \sim 0.6$

Table 11.1 Relationship between crystallite diameter and the number diffracting (after Smith[24]).

Crystallite diameter (μm)	*40*	*10*	*1*
Crystallites (20 mm³)	5.97×10^5	3.82×10^7	3.82×10^{10}
Number diffracting N_{diffr}	12	760	38 000
σ_{PS}	0.289	0.036	0.005

From Madsen&Scarlett, Powder Diffraction-Theory and Practice, p. 309 reported from original work by D.K. Smith, Adv. X-Ray Anal. 1992, 35, 1-15; Elton & Salt, Powder Diffr., 1996, 11, 218-229.

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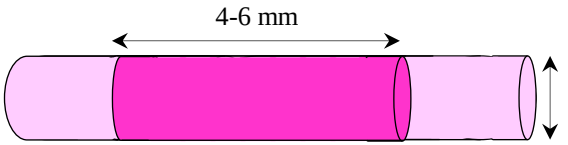

$V \sim 3-5\ mm^3 \rightarrow N_{diff} \sim 3 \rightarrow \sigma_{PS} \sim 0.6$

Remedies:

- Increase instrument beam divergence
- Sample spinning or oscillation
- Increase the powder volume analyzed or powder repacking
- Mechanical comminution (grinding, milling)

V. Factors influencing QPA and QPA accuracy

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DS geometry + capillary + 1D position sensitive detectors:

- intensity modulation due to inhomogeneus capillary packing
- inhomogeneus photon beam distribution

Remedies:

- Partial photon beam focusing
- Analysis of a large number of powder volumes

V. Factors influencing QPA and QPA accuracy

Sources of errors

Instrument related

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Operator related

- **Analyst choices** during QPA analysis affect the results → QPA Round Robin 1996-2002 (see Madsen & Scarlett)
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- Important of setting up **QPA guidelines**

- The need of absorption corrections should be minimized and corrections appropriate for the given experimental geometry applied

- **Microabsorption** (i.e. absorption contract) occurs when the phases in a mixture are characterized by different mass absorption μ* coefficients and/or different crystallite size → the %wt of the phase with higher μ* and/or larger crystallite size would be underestimated

Remedies:

- Choose an appropriate λ
- Reduce crystallite size

V. Factors influencing QPA and QPA accuracy

Sources of errors

Instrument related

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- Strong correlation between the **Rietveld scale factor** and the **Atomic Displacement Parameters** (ADP, B_{iso}, U_{iso}).

WARNING: very often .cif files in the crystallographic database DO NOT report such parameters → commercial programs use in such cases default values (i.e. 1 Å^2)

Be careful: most programs require as input B_{iso} (e.g. Topas, FullProf), often you find in literature and database U_{iso} → $B_{iso} = 8\pi^2 U_{iso}$