Supplementary Material to

"Three Approaches to Total Quantitative Phase Analysis of Organic Mixtures using an External Standard"

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S1. Other Measurement Details

For organic samples Debye-Scherrer geometry is often preferred over Bragg-Brentano geometry due to (1) higher resolution and (2) more benign less asymmetric peak shape. When it comes to quantitative phase analysis two more aspects need to be considered namely (1) sampling and (2) particle statistics. In both cases Bragg-Brentano geometry is of some advantage as the diffracting volume is considerable larger and therefore the XRD-sample is more representative of the total sample and more crystallites are illuminated by the X-ray beam.

The study of Smith (D. K. Smith (2001) Powder Diffr. 16, 186-191) shows that a particle size of considerably less than 10 μm is desirable for obtaining good statistics (see Table S1).

Table S1: Particle distribution comparison for particles of various diameter, measured in Bragg-Brentano geometry assuming and a diffracting volume of 20 mm^3 (Smith, 2001) but additionally considering a packing density of 40%.

Size	40 μm	10 μm	4 μm	1 μm
Volume / particle	3.35×10^{-5}	5.54×10^{-7}	3.35×10^{-8}	5.54×10^{-10}
No. Crystallites total	2.39×10^{5}	1.53×10^{7}	2.39×10^{8}	1.53×10^{10}
No. Crystallites diffracting	5	304	2400	15200

As shown by SEM in our case ball-milling reduced the particle size to less than 5 μm. A typical image of a mixture sample is given in Figure 1. This particle size is in the acceptable range for providing good particle statistics for a reliable quantitative analysis.

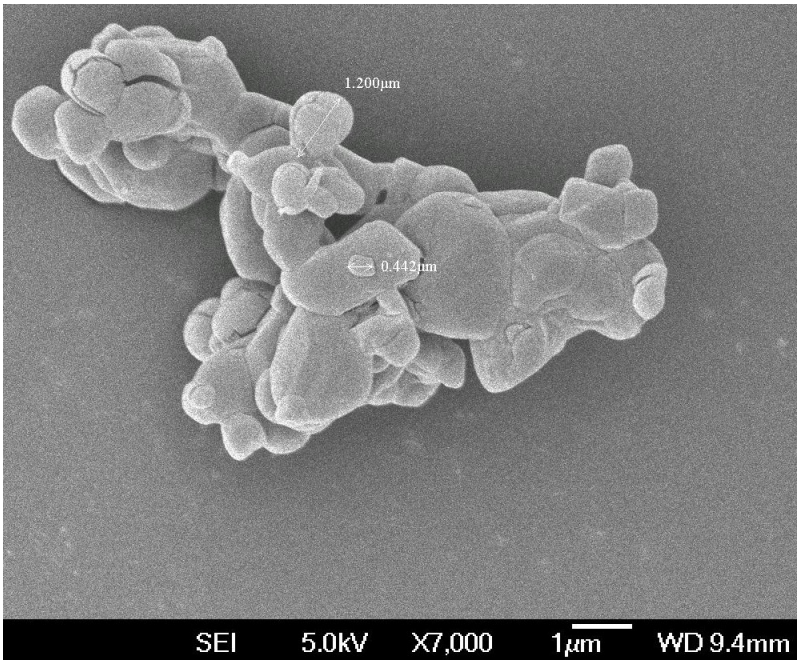

Figure S1: Typical SEM image of an agglomerate of particles in a sample of glycine, paracetamol and lactose.

S2. Further Numerical Details for Method B

$$\sum_{i=1}^{n} r_i W_{cki} = W_{ak} \quad for\ all\ mixtures, k = 1:m \quad \text{(where } m \text{ is number of mixtures)} \qquad (6)$$

A set of linear equations (Eq 6) can be written to account for the mass balance for the amorphous compositions of *n*-components in each mixture as Eq (S2.1).

$$\begin{aligned} r_1 W_{c11} + r_2 W_{c12} + \ldots + r_n W_{c1n} &= W_{a1} \\ r_1 W_{c21} + r_2 W_{c22} + \ldots + r_n W_{c2n} &= W_{a2} \\ &\vdots \\ r_1 W_{cm1} + r_2 W_{cm2} + \ldots + r_n W_{cmn} &= W_{am} \end{aligned} \qquad (S2.1)$$

The above equation system can be rewritten into a matrix form (Eq (S2.2)).

$$\begin{pmatrix} W_{c11} & W_{c12} & \cdots & W_{c1n} \\ W_{c21} & W_{c22} & \cdots & W_{c2n} \\ & \vdots & & \\ W_{cm1} & W_{cm2} & \cdots & W_{cmn} \end{pmatrix} \begin{pmatrix} r_1 \\ r_2 \\ \vdots \\ r_n \end{pmatrix} = \begin{pmatrix} W_{a1} \\ W_{a2} \\ \vdots \\ W_{am} \end{pmatrix} \qquad (S2.2)$$

For each mixture, Eq (5) is substituted into the right hand side of Eq (S2.2) and it results in Eq (S2.3):

$$\begin{pmatrix} W_{c11} & W_{c12} & \cdots & W_{c1n} \\ W_{c21} & W_{c22} & \cdots & W_{c2n} \\ & \vdots & & \\ W_{cm1} & W_{cm2} & \cdots & W_{cmn} \end{pmatrix} \begin{pmatrix} r_1 \\ r_2 \\ \vdots \\ r_n \end{pmatrix} = \begin{pmatrix} 1 - W_{c11} - W_{c12} \ldots - W_{c1n} \\ 1 - W_{c21} - W_{c22} \ldots - W_{c2n} \\ \vdots \\ 1 - W_{cm1} - W_{cm2} \ldots - W_{cmn} \end{pmatrix} \qquad (S2.3)$$

For *3*-component system, Eq (S2.3) becomes

$$\begin{pmatrix} W_{c11} & W_{c12} & W_{c13} \\ W_{c21} & W_{c22} & W_{c23} \\ & \vdots & \\ W_{cm1} & W_{cm2} & W_{cm3} \end{pmatrix} \begin{pmatrix} r_1 \\ r_2 \\ r_3 \end{pmatrix} = \begin{pmatrix} 1 - W_{c11} - W_{c12} - W_{c13} \\ 1 - W_{c21} - W_{c22} - W_{c23} \\ \vdots \\ 1 - W_{cm1} - W_{cm2} - W_{cm3} \end{pmatrix} \qquad (S2.4)$$

Subsequently, the ratio of amorphous to crystalline content r_1, r_2 and r_3 can be obtained by solving this set of linear equations Eq (S2.4).

Finally, the amorphous content W_{aki} of each component *i* for each mixture *k* can be determined (i.e. $W_{aki} = r_i \cdot W_{cki}$).

S3. Further Numerical Details for Method C

$$W_{cki} = \frac{S_{ki}(ZMV)_i \mu_{mix(k)}}{K} = \frac{S_{ki}(ZMV)_i \sum_{j=1}^{n} W_{ckj}(1+r_j)\mu_j}{K} \quad for\ all\ mixtures\ k = 1:m \qquad (8)$$

For *3*-component system, Eq (8) can be written for each mixture as

for Mixture 1 (*k*=1),

$$W_{c11}K = S_{11}(ZMV)_1[W_{c11}(1+r_1)\mu_1 + W_{c12}(1+r_2)\mu_2 + W_{c13}(1+r_3)\mu_3]$$
$$W_{c12}K = S_{12}(ZMV)_2[W_{c11}(1+r_1)\mu_1 + W_{c12}(1+r_2)\mu_2 + W_{c13}(1+r_3)\mu_3]$$
$$W_{c13}K = S_{13}(ZMV)_3[W_{c11}(1+r_1)\mu_1 + W_{c12}(1+r_2)\mu_2 + W_{c13}(1+r_3)\mu_3]$$
$$1 = W_{c11}(1+r_1) + W_{c12}(1+r_2) + W_{c13}(1+r_3)$$

for Mixture 2 (*k*=2),

$$W_{c21}K = S_{21}(ZMV)_1[W_{c21}(1+r_1)\mu_1 + W_{c22}(1+r_2)\mu_2 + W_{c13}(1+r_3)\mu_3]$$
$$W_{c22}K = S_{22}(ZMV)_2[W_{c21}(1+r_1)\mu_1 + W_{c22}(1+r_2)\mu_2 + W_{c13}(1+r_3)\mu_3]$$
$$W_{c23}K = S_{23}(ZMV)_3[W_{c21}(1+r_1)\mu_1 + W_{c22}(1+r_2)\mu_2 + W_{c13}(1+r_3)\mu_3]$$
$$1 = W_{c21}(1+r_1) + W_{c22}(1+r_2) + W_{c23}(1+r_3)$$

for Mixture *m* (*k*=*m*),

$$W_{cm1}K = S_{m1}(ZMV)_1[W_{cm1}(1+r_1)\mu_1 + W_{cm2}(1+r_2)\mu_2 + W_{cm3}(1+r_3)\mu_3]$$
$$W_{cm2}K = S_{m2}(ZMV)_2[W_{cm1}(1+r_1)\mu_1 + W_{cm2}(1+r_2)\mu_2 + W_{cm3}(1+r_3)\mu_3]$$
$$W_{cm3}K = S_{m3}(ZMV)_3[W_{cm1}(1+r_1)\mu_1 + W_{cm2}(1+r_2)\mu_2 + W_{cm3}(1+r_3)\mu_3]$$
$$1 = W_{cm1}(1+r_1) + W_{cm2}(1+r_2) + W_{cm3}(1+r_3)$$

In our 3-component system, all 10 mixtures are analyzed and this will provide a total of 40 equations with 33 unknowns (30 W_{cki} and 3 r_i). The system of equations is over-determined and optimization algorithms such as trust-region algorithm or Levenberg-Marquardt algorithm can be utilized to solve this set of non-linear equations.

S4. Refined Sample Parameters

Table S2: Refined sample parameters. Note: a constrained refinement was used where all patterns were refined simultaneously with identical values for each phase in all 10 patterns.

Substance	a(Å)	b(Å)	c(Å)	β(°)	$B_{overall}$	Size (nm)
α-Glycine	5.10413(6)	11.97339(7)	5.46149(4)	111.7357(8)	1.97(1)	273(2)
α-Lactose	4.81750(4)	21.5840(2)	7.7701(1)	105.9389(7)	1.70(2)	216(1)
Paracetamol(I)	12.8904(2)	9.38537(9)	7.10098(8)	115.6998(8)	2.07(2)	331(2)

S5. Comparison External vs Internal Standard

Sample No. 7 was spiked with 10.07 w% of diamond. The Rietveld refinement is shown in Figure S2. The results in comparison to the external standard approach are summarized in Table S3.

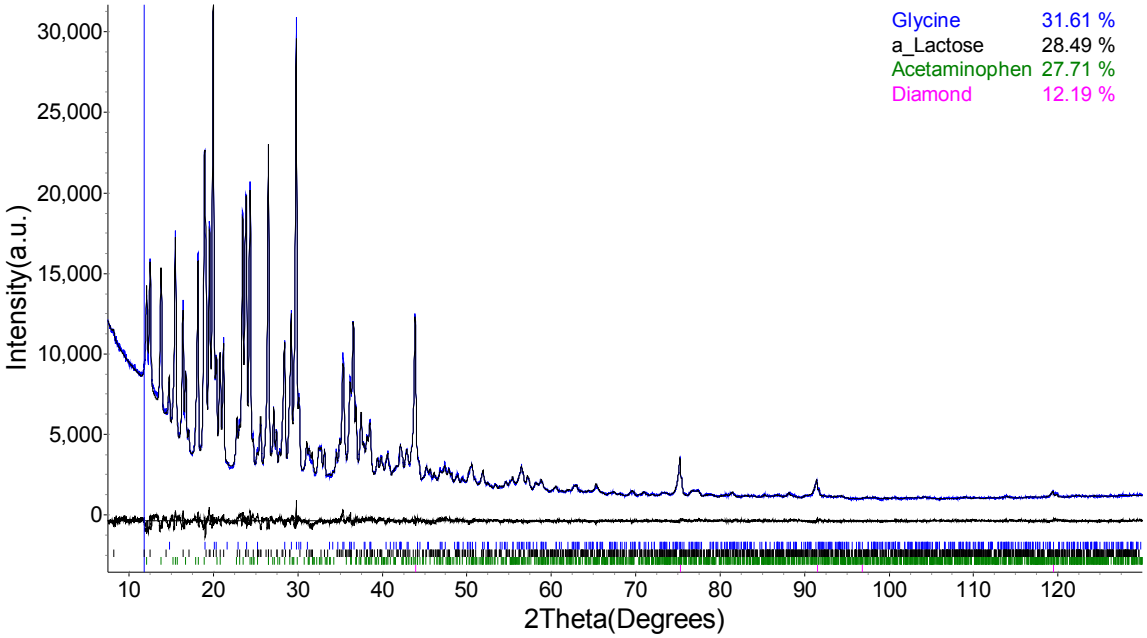

Figure S2: Rietveld refinement of mixture 7 with 10.07% diamond as internal standard.

Table S3: Comparison between the results for internal standard approach and the 3 external standard approaches (Methods A-C) for mixture 7. All crystalline components and the total amorphous content are given.

Method	α -Glycine (w%)	Paracetamol (I) (w%)	α-Lactose (w%)	Amorphous (w%)
Internal	29.05(9)	25.46(9)	26.18(8)	19.3(4)
External A	28.8(3)	26.1(3)	26.6(3)	18.5(7)
External B	28.4(3)	25.6(3)	26.1(3)	19.9(7)
External C	28.32(4)	25.61(3)	26.01(5)	20.1(5)

A good agreement between internal and three different external standard approaches (Methods A-C) is observed.