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Structural Characterisation of Amorphous Solid Dispersions *via* Metropolis Matrix Factorisation of Pair Distribution Function Data

SUPPLEMENTARY INFORMATION

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Contents

1 Methods

Synthesis

Caffeine:povidone Mixtures

11 physical mixtures of powdered crystalline caffeine (Sigma-Aldrich) and amorphous povidone (Sigma-Aldrich) were prepared by mixing with caffeine mass fractions of 0%, 10%, ..., 100%. Samples were ground and loaded into 1 mm quartz capillaries prior to X-ray total scattering measurements.

Felodipine Amorphous Solid Dispersions

Amorphous felodipine was obtained by heating the drug (AstraZeneca, Macclesfield, United Kingdom) to 160 °C and, after melting, cooling back to room temperature. Amorphous felodipine and copovidone (BASF, Ludwigshafen, Germany) were pre-mixed for 20 min in a Turbula T2F mixer (Willy A. Bachofen AG Mashinefabrik). 0%, 15%, 20%, 30% and 50% drug-loaded amorphous solid dispersions (ASDs) of felodipine in copovidone were prepared using a co-rotating twin-screw extruder (Thermo Scientific HAAKE MiniLab II), which was manually fed with the physical mixture. The screw speed was set to 150 rpm and the temperature to 160 °C. The extrudates were then collected, cooled to room temperature and manually milled to fine powder.

X-ray Total Scattering

X-ray PDF measurements were performed using powder samples of all samples described in Section 1: 11 mixtures of caffeine and povidone with mass fractions of 0%, 10%,..., 100%; also felodipine, copovidone and felodipine:copovidone ASDs of varying active pharmaceutical ingredient API loading (0%, 15%, 20%, 30% and 50%). Samples were loaded in 1 mm quartz capillaries and mounted on a PANalytical Empyrean diffractometer equipped with a Mo X-ray tube ($\lambda = 0.71\,\text{Å}, Q_{\text{max}} = 17.7\,\text{Å}^{-1}$), Mo focussing mirror and GaliPIX3D detector. Divergence (1/2°), anti-scatter (1/4°) and Soller (0.02 rad) slits were used to adjust the incident beam profile; a programmable receiving slit, set to a height of 1 mm, was used for the diffracted beam. Total scattering data were collected over the angular range $2.75° < 2\theta < 140°$, yielding data with

useable $Q_{\text{max}} = 17\,\text{Å}^{-1}$. These data were corrected for background, Compton, and multiple scattering and beam attenuation by the sample container using the GudrunX package.[S1, S2] The normalised structure factor $F(Q)$ was converted to the PDF in the form of the $D(r)$ function as defined in Ref. S3. Experimental $F(Q)$ and $D(r)$ data for felodipine:copovidone ASDs are shown in Fig. S1 and Fig. S2 respectively; and $F(Q)$ and $D(r)$ caffeine:povidone mixtures are shown in Fig. S3 Fig. S4.

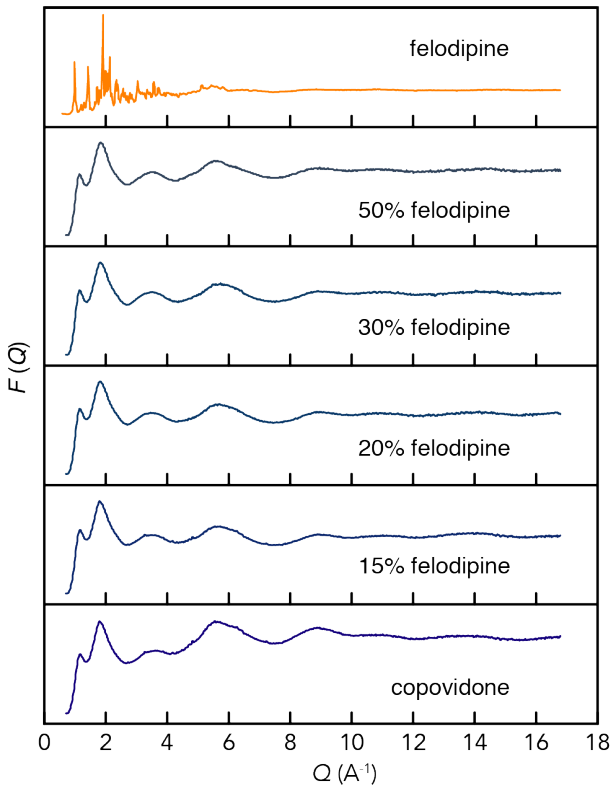

Figure S1: F(Q) of felodipine:copovidone ASDs. Felodipine loadings are 0%, 15%, 20%, 30%, 50% and 100%.

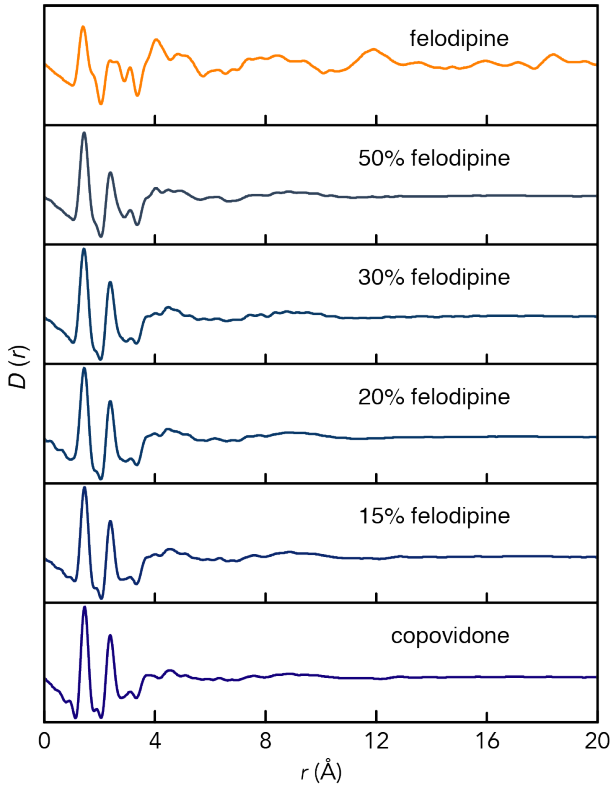

Figure S2: X-ray PDFs of felodipine:copovidone ASDs. Felodipine loadings are 0%, 15%, 20%, 30%, 50% and 100%.

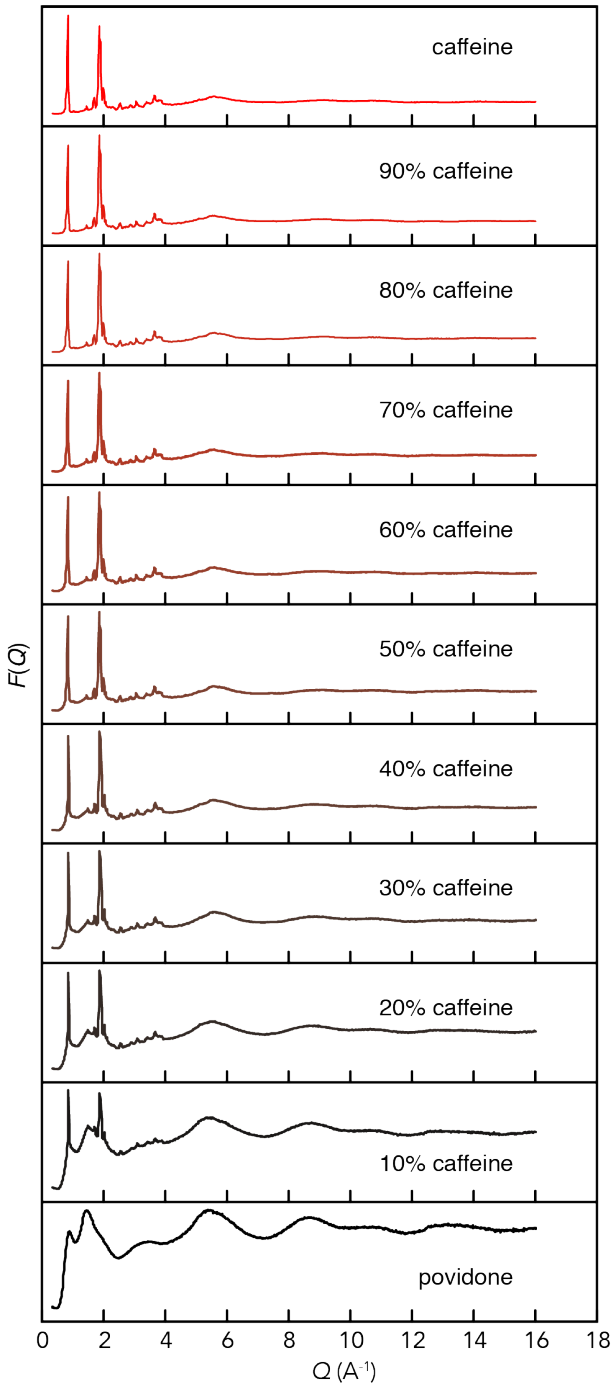

Figure S3: F(Q) of caffeine:povidone mixtures. Caffeine loadings range from 100% (red; top) to 0% (black; bottom).

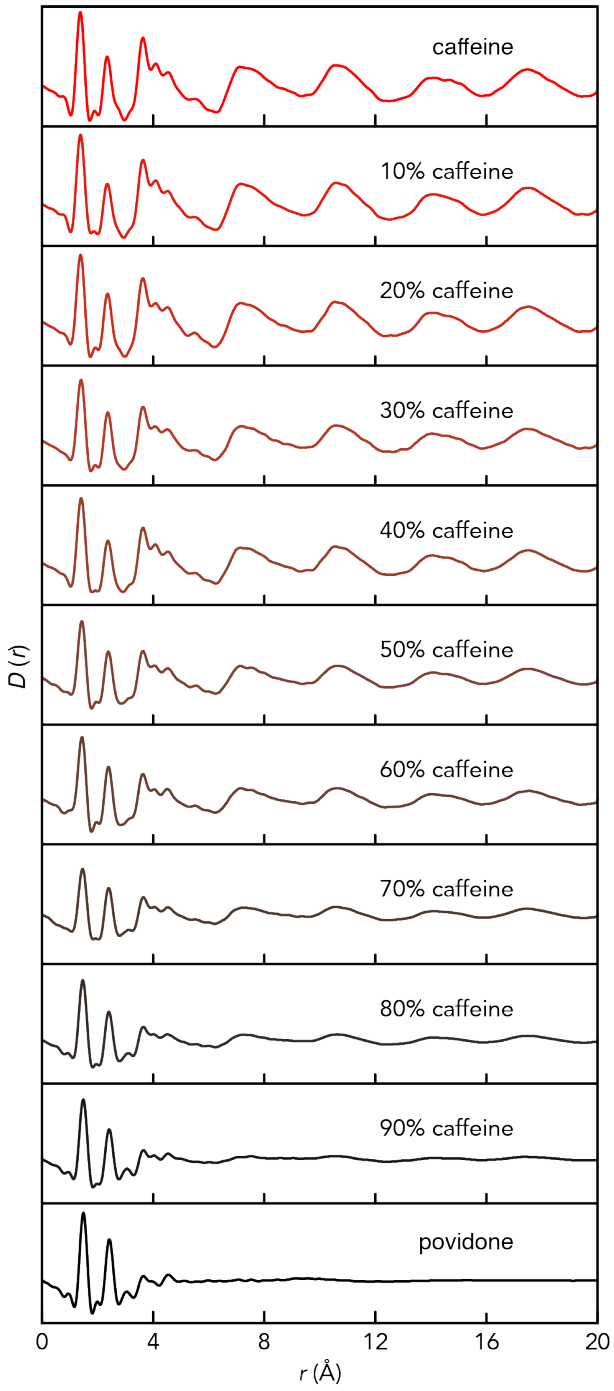

Figure S4: X-ray PDFs of caffeine:povidone mixtures. Caffeine loadings range from 100% (red; top) to 0% (black; bottom).

2 Metropolis Matrix Factorisation

Metropolis Matrix Factorisation (MMF), uses the Metropolis Monte Carlo (MC) algorithm[S4] to carry out non-negative matrix factorisation (NMF)[S5]. We find that MC obtains a robust solution to the NMF problem in a way that is not achievable using linear least-squares or related minimisation approaches. Ultimately, MMF aims to describe a collection of experimental datasets in terms of weighted linear combinations of fundamental components, and in doing so reduces the dimensionality and complexity of the data. In this study, the task for MMF was to identify the two fundamental components $G_i^*(r)$ ($i = 1, 2$ for caffeine; $i = 1, 2, 3$ for felodipine) and weights w_{ij} ($j = 1, 2, \ldots, 11$ for caffeine; $j = 1, 2, \ldots, 6$ for felodipine) so as to minimise $|\mathbf{G}^{\mathrm{calc}}(r) - \mathbf{G}^{\mathrm{exp}}(r)|^2$, where $G_j^{\mathrm{calc}}(r) = \sum_{i=1}^{2} w_{ij} G_i^*(r)$ are the elements of $\mathbf{G}^{\mathrm{calc}}(r)$. We applied the additional constraints that $G_i^*(r)$ is positive for all i and r, and that $\sum_{i=1}^{2} w_{ij} G_i^*(r) = 1$ for all j.

In the case of the caffeine–povidone system, the initial values of $G_i^*(r)$ and w_{ij} were assigned randomly, subject to these constraints. Each minimisation round involved random variations to these parameters, followed by calculation of the change in goodness-of-fit $\Delta|\mathbf{G}^{\mathrm{calc}}(r) - \mathbf{G}^{\mathrm{exp}}(r)|^2$ and subsequent acceptance or rejection according to the Monte Carlo criterion. Such rounds were repeated with increasingly stringent acceptance criteria (*i.e.* simulated annealing) until convergence was achieved.

For the felodipine–copovidone system, we followed essentially the same approach, except that we fixed $G_1^*(r)$ and $G_2^*(r)$ to be the PDFs of pure copovidone and crystalline felodipine, respectively, as we are interested in determining most accurately the PDF of amorphous API. This PDF, as given by $G_3^*(r)$, is also shown in Fig. 2(a) of the main publication. If the same approach is followed without fixing $G_1^*(r)$ and $G_2^*(r)$ (*i.e.* $G_i^*(r)$ ($i = 1, 2, 3$) are allowed to vary), we do not find a robust solution.

3 Molecular Dynamics

Molecular structures were extracted from the Cambridge Structural Database and the conformer used 'as is' without generating additional conformers. The structure was kept fully flexible during the molecular dynamics (MD) process.

The amorphous cell was built using Material Studio 2016 from Biovia, utilising the amorphous cell module. A total of 50 molecules of felodipine were used to build a cubic amorphous cell with dimensions close to 3.6 nm $\times$ 3.6 nm $\times$ 3.6 nm and a target density of 1.0 g cm^{-3}. In total, three configurations (amorphous cells) were used and the predicted glass transition temperature (T_g) averaged across the three amorphous cells.

These cells were then relaxed using the Forcite module for 12.5 ps under isobaric/isothermal conditions (NPT ensemble, COMPASS II forcefield, Berenden barostat) at a temperature $\sim$100 K above the experimental T_g (420K for felodipine). The resulting configurations were then used as starting ensembles for a cooling profile where the temperature was decreased in 10 K steps until a temperature $\sim$120K below the experimental T_g (200K for felodipine). At each temperature an NPT MD run was carried out for 50 ps and the specific density was sampled and averaged over the last 30 ps. A plot of specific density versus temperature shows a change in gradient at the T_g.

4 PDF Calculations

PDFs were calculated for crystalline felodipine and the felodipine melt using the PDFgui software.[S6] The crystalline model used was felodipine form 1 (DONTIJ),[S7] obtained from the Cambridge Structural Database; the felodipine melt was obtain from MD simulations. PDFgui parameters Temperature, Q_{max} and Q_{damp} were fixed to agree with experimental values, with values of 300.0 K, 17.0 Å^{-1} and 0.05 Å^{-1}, respectively. A scale factor, Q_{broad}, and isotropic atomic displacement parameters were then refined for both structures.

5 References

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