Olanzapine form IV: discovery of a new polymorphic form enabled by computed crystal energy landscapes

Sean Askin[†], Jeremy K. Cockcroft[‡], Louise S. Price[‡], Andrea D. Gonçalves[§], Min Zhao[#], Derek A. Tocher[‡], Gareth R. Williams[†], Simon Gaisford[†*] and Duncan Q.M. Craig[†*]

[†]UCL School of Pharmacy, 29-39 Brunswick Square, London, WC1N 1AX, U.K.

[‡]UCL Department of Chemistry, 20 Gordon Street, London, WC1H 0AJ, U.K.

[§]DPDD Drug Delivery, GlaxoSmithKline R&D, Gunnels Wood Road, Stevenage, SG1 2NY, U.K.

[#]School of Pharmacy, Queen's University Belfast, 97 Lisburn Road, Belfast, BT9 7BL, U.K.

ABSTRACT: Olanzapine is a polymorphic drug molecule that has been extensively studied, with over 60 structures reported in the Cambridge Structural Database. All anhydrous and solvated forms of olanzapine known to date contain the SC_0 dimer packing motif. In this study, a new screening approach was adopted involving heat-induced forced crystallization from a polymer-based molecular dispersion of olanzapine. Simultaneous differential scanning calorimetry-powder X-ray diffraction (DSC-PXRD) was used to heat the amorphous dispersion and to identify a novel physical form from diffraction and heat flow data. Comparison of the diffraction data with those from a computed crystal energy landscape allowed the crystal structure to be determined. The result was the discovery of a new polymorph, form IV, which does not use the SC_0 motif. Hence, while dimer formation is the dominant process that defines crystal packing for olanzapine formed from solution, it seems that molecularly dispersing the drug in a polymeric matrix permits crystallization of alternative motifs. Having identified form IV, it proved possible to scale up the synthesis and demonstrate its enhanced dissolution properties over form I.

INTRODUCTION

Polymorphism is the ability of a molecule to exist in more than one crystalline form and it is a significant issue for pharmaceuticals as changes in crystal structure can affect solubility, bioavailability and intellectual property rights.[1] The crystallization of olanzapine (Chart 1a), a former blockbuster antipsychotic drug licensed for the treatment of schizophrenia, has been intensely investigated. Three anhydrous polymorphic forms of olanzapine (forms I, II and III) have been characterized as well as many (>60) hydrates, solvates, co-crystals and salts.[2,3,12–18,4–11] The prolific solvate formation of olanzapine is attributed to the low packing efficiency of the drug molecules in the solid state.[15] It is noteworthy that while there are over 60 forms of olanzapine with full structural details on the Cambridge Structural Database (CSD), they all contain the same SC_0 dimer packing motif (Chart 1b), with the exception of some doubly ionized forms and one hydroquinone toluene co-crystal.[11,17]

Crystal structure prediction (CSP) is the process whereby thermodynamically competitive crystal structures are calculated based on quantum mechanical calculations. The output of CSP studies for small organic molecules such as olanzapine has led to the concept of computed crystal energy landscapes, sets of computer-generated structures that are thermodynamically plausible as potential polymorphs.[19] The theoretical structures are ranked by their calculated lattice energy, and the energy of the static lattice (at 0 K) is used as an approximation to the relative thermodynamic stability of the crystals.[20]

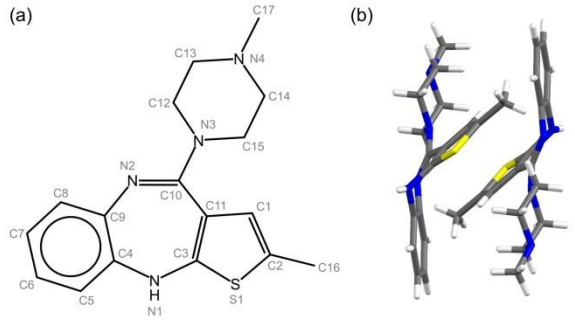

Chart 1 – (a) Chemical structure of olanzapine and (b) SC_0 centrosymmetric dimer packing motif present in almost all anhydrous and solvated crystalline forms of olanzapine.

One of the aims of CSP techniques, particularly in the pharmaceutical industry, is to identify thermodynamically feasible alternative crystal structures to aid in rational polymorph screening. Crystal energy landscapes can be used to establish structures that are likely to be sufficiently stable to form under laboratory conditions. A computed crystal energy landscape was generated for olanzapine in a previous study;[15] this investigation identified a number of alternative crystal packings that were thermodynamically competitive with the known anhydrous forms but which do not use the SC_0 dimer motif. These alternative structures have not been observed experimentally, despite extensive efforts to generate new polymorphic forms of olanzapine. In the polymorph screens performed, over 400 diverse crystallization conditions were used including many solution crystallizations, grinding, desolvation of solvates, crystallization from the vapour phase, melt quenching, recrystallisation from the amorphous form, spray drying and freeze drying.[15]

Despite all these experiments, only three anhydrous forms of olanzapine were produced, as well as numerous solvates, all using the SC_0 motif. Following this study, it was hypothesized that less conventional crystallization conditions may disrupt the SC_0 dimer motif or favor alternative crystal packings,[15] although to date no studies have established this possibility definitively.

A relatively unexplored crystallization method is to produce molecularly dispersed drug-polymer systems and promote crystallization of the drug by the application of heat. Differential scanning calorimetry (DSC) was previously used to investigate the crystallization of acetaminophen upon the heating of acetaminophen-hydroxypropylmethylcellulose (HPMC) dispersions.[21] The highly metastable form III appeared to crystallize from this system, which was attributed to Ostwald's rule of stages and the kinetic effects of the high viscosity polymer. However, the problem with using DSC to study crystallization is that structural information cannot be obtained from the heat flow data. To obtain crystal structures, X-ray diffraction data are required. Recently, a simultaneous DSC-PXRD analytical technique was developed and applied to study the same acetaminophen system; the results conclusively confirmed that form III crystallized from the molecularly dispersed state and was stabilized by the presence of the polymer molecules.[22]

Here, we used the DSC-PXRD approach to study crystallization of olanzapine dispersed in polyvinylpyrrolidone (PVP) and report the discovery of a new anhydrous olanzapine polymorph, form IV. Form IV does not contain the SC_0 dimer motif.

EXPERIMENTAL METHODS

Materials

Olanzapine ($C_{17}H_20N_4S$; M_w = 312.43 g/mol) was purchased from Myjoy Ltd, India. Polyvinylpyrrolidone (Kollidon® K90F and Kollidon® K17PF) was purchased from BASF, Germany. Dichloromethane and acetonitrile were of analytical grade and were obtained from Sigma-Aldrich, UK.

Production of amorphous olanzapine-PVP solid dispersion

An olanzapine-PVP (Kollidon® K90F) solid dispersion (70:30 w/w drug/polymer) was prepared using a spray drying method. A feed solution of 1.4% w/w olanzapine and 0.6% w/w PVP was prepared in dichloromethane. Spray drying was performed using a Buchi Mini B-290 spray dryer connected to a Buchi B-295 Inert Loop, forming a closed system. Nitrogen was used as the spray gas and processing was performed under an inert atmosphere (<6 % O_2) with an aspirator rate of 100%. A drying gas temperature of 60 °C was used with a feed solution pump rate of 5 mL min^{-1}. The solid particles formed were separated from the drying gas by a cyclone.

Simultaneous DSC-PXRD analysis

A simultaneous DSC-PXRD analytical platform, similar to that described by Clout *et al.*, was used to heat and crystallize the amorphous dispersion and concurrently capture heat flow and diffraction data.[23] A modified Q20 differential scanning calorimeter (TA Instruments, USA) was mounted on Beamline I12 at the Diamond Light Source (UK). The calorimeter was aligned so that the monochromated X-ray beam (diameter = 0.5 mm; λ = 0.23306 Å) passed directly through the entry and exit holes in the DSC cell and the aluminum sample pan before diffraction data were collected on a Thales Pixium RF4343 detector that was positioned 1.9 m behind the sample. The calorimeter was calibrated for temperature using an indium standard before the experiment. 30 mg of the olanzapine-PVP dispersion was filled into a Tzero aluminum DSC pan (TA Instruments, USA) and the sample was heated at a rate of 10 °C min^{-1} from 50 °C to 200 °C with a powder X-ray diffraction pattern collected every 6 seconds, which equated to every 1 °C on heating. The 2D PXRD data were processed to 1D diffraction patterns using DAWN Science Workbench software.[24]

Computed crystal energy landscape and crystal structure predictions

The computed crystal energy landscape used in this study was produced as part of a previous study and full access to the landscape and repository of predicted crystal structures was provided by the authors.[15] To identify the crystal structure of form IV a screen was performed using the Mercury software. Simulated PXRD patterns of the CSP-predicted structures were generated and compared to the observed PXRD pattern of olanzapine form IV.

Scale up of form IV crystallization and extraction from the polymer

An amorphous olanzapine-PVP (Kollidon® K17PF) dispersion (70:30 w/w ratio) was crystallized on a 300 mg scale under vacuum in an oven (140 °C, 1 h). Crystallizing under vacuum was essential to prevent oxidation of the material during the heating program, and the crystallization temperature and time were determined using a recently published quasi-isothermal modulated temperature DSC (QiMTDSC) protocol to ensure the process was complete.[25] The grade of PVP was changed to a lower molecular weight grade to facilitate the separation of the drug crystals from the polymer by centrifugation. The recrystallized material was allowed to cool and then was ground into a coarse powder with a pestle and mortar. To extract the drug crystals from the polymer, the material was suspended in distilled water (0.3 % w/v) by sonication (5 min) and stirred (200 RPM, 15 min) to dissolve the polymer (olanzapine has very low water solubility). The suspension formed was then centrifuged (8000 RPM, 30 min), and the pellet collected and re-suspended in distilled water by sonication before being centrifuged for a second time. The pellet of form IV crystals (100 mg) was then collected and dried (100 °C, 1 h).

Further characterization of form IV

The chemical purity of olanzapine form IV crystals was determined using a simple UV assay, whereby the crystals (3 mg) were dissolved in acetonitrile (10 mL) and the resultant solution was diluted 10-fold before analysis with a UV spectrometer (λ = 276 nm) to quantify the olanzapine concentration. Experiments were performed in triplicate and the mean average purity ± standard deviation was calculated.

Routine PXRD patterns for qualitative analysis were collected using a STADI-P (Stoe, Germany) diffractometer with $CuK\alpha_1$ radiation (λ = 1.5406 Å) in the 2θ scan range of 1° to 45° with a detector step of 0.5° at 10s per step in 23 min. . The sample was loaded into a capillary and measured in transmission mode.

DSC was performed on a Discovery series differential scanning calorimeter (TA Instruments, USA) at a heating rate of 10 °C min^{-1} from 0 to 200 °C. A cell constant and temperature calibration was performed before the experiment. 3-5 mg of sample

was filled into standard aluminum pans (TA instruments, USA) and measurements were performed in triplicate.

In vitro dissolution was performed using USP 2 apparatus in 900 mL of phosphate buffered saline (pH 6.8) at 37 °C, with a stir rate of 50 RPM. Olanzapine forms I and IV were sieved to a particle size fraction of <63 µm. In each experiment, 10 mg of olanzapine crystals was added to the dissolution vessel and 10 mL aliquots were taken for UV analysis (λ = 276 nm) at each time point to quantify the olanzapine concentration. 10 mL of fresh pre-warmed buffer was added to each vessel after aliquots were taken and experiments were performed in triplicate.

RESULTS AND DISCUSSION

Crystallization and identification of olanzapine form IV

The crystallization of olanzapine from an amorphous molecularly dispersed phase of olanzapine and PVP was investigated using a simultaneous DSC-XRD analytical platform. The bespoke apparatus allowed the drug-polymer dispersion to be heated in a highly controlled manner to promote crystallization of the drug from the amorphous state, whilst also capturing heat flow and XRD data, thereby allowing the phase changes that occurred to be to be characterized. The system was confirmed to be fully amorphous at 50 °C by PXRD analysis, followed by residual water loss from the PVP and olanzapine crystallization starting at approximately 110 °C as shown by the appearance of reflections in the PXRD contour plot (Figure 1).

The crystallization of olanzapine was slow and was therefore not recorded as a typical exothermic peak in the DSC trace; instead, endothermic water loss is followed by a gradual increase in the heat flow baseline. The increase started at approximately 110 °C and continued until the crystals melted, as indicated by the endotherm at 184 °C in the heat flow and the sudden loss of reflections in the PXRD plot. The intensity of the PXRD patterns recorded increased as the crystallization progressed until a maximum temperature of 170 °C, whereby it started to decrease as the crystals began to melt. The observed diffraction pattern was significantly different from the powder diffraction patterns of the known anhydrous forms of olanzapine (Figure 2), suggesting a new polymorphic form had been generated by crystallization from the molecularly dispersed state. Solvates were considered very unlikely as a possibility since crystallization was from a solvent-free system, and a mixed phase of anhydrous forms could also be ruled out as the phase melted cleanly over a narrow temperature range, which was observable in both the PXRD patterns and DSC heat flow (Figure 1). The heat flow data also supported the generation of a new polymorphic form of olanzapine as the melting point (T_m) of 184 °C recorded was not consistent with the T_m of forms I, II and III which are 196, 180 and 170 °C, respectively.[15]

The DSC-PXRD approach clearly allowed the presence of a new form to be identified. However, no single crystals were obtained for full single-crystal structure determination as the crystalline material formed was mixed with an amorphous polymer and melted *in situ* during the experiment. Without access to single crystal X-ray diffraction data of the new form, an alternative, and original, strategy was used to determine the structure from the available information. It was hypothesized that a model of the crystal structure of the newly observed polymorph (form IV) may have been generated as part of the previous CSP study on olanzapine, and that if the correct model could be identified then this may be used to confirm the form IV structure. The computed crystal energy landscape previously reported for olanzapine was provided by the authors, as was access to the repository of predicted crystal structures. A screen was performed using the Mercury software, by comparing the simulated PXRD patterns of the CSP-generated structures to the observed PXRD pattern of form IV.

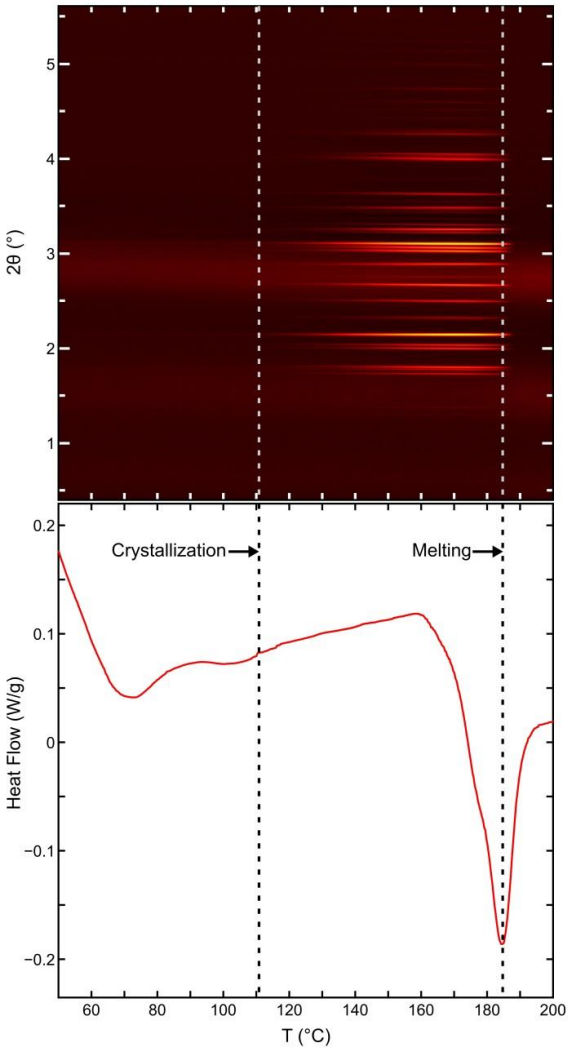

Figure 1 – Simultaneous DSC-PXRD analysis of the olanzapine-PVP system, showing a contour plot of the diffraction patterns (top) and DSC trace (bottom, exothermic events plotted up). Intensity of reflections are color-coded in the contour plot, with increased intensity of reflections shown by an increase in brightness.

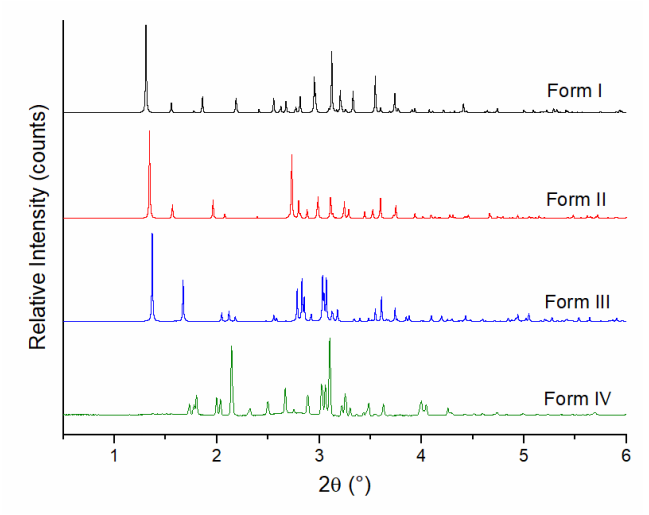

Figure 2 – Simulated powder X-ray diffraction patterns of the known olanzapine polymorphs compared with the experimentally observed diffraction pattern (baseline subtracted) of the new polymorph (form IV) in the olanzapine-PVP system. The form III pattern is based on the closest model predicted by CSP (structure A162) as a pure phase has not been obtained experimentally.[15] Simulated PXRD patterns were produced using Mercury software (λ = 0.23306 Å).

Initially only the five unobserved CSP structures that were more stable than form II and contained the SC_0 dimer were considered, but no resemblance was found between the experimental pattern and any of the hypothetical PXRD patterns. When the PXRD comparison was extended by working up the lattice energy ranking of all the CSP-generated unobserved structures, a very strong resemblance to the experimental PXRD pattern was immediately identified with the simulated PXRD pattern of the fourth lowest energy structure (denoted A1 in the original study).[15]

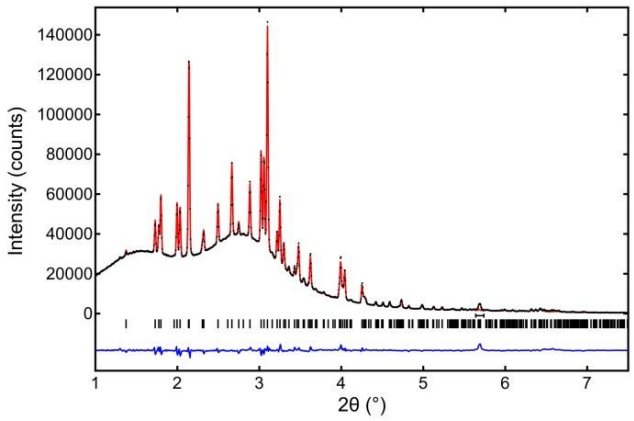

Figure 3 – Rietveld fit confirming the structure of olanzapine form IV is that of theoretical structure A1 (R_{wp} = 10.46%). Red line shows the calculated pattern of model A1, black dots the measured pattern of form IV and the blue line is the difference between the two. Amorphous halos present in the background are due to the presence of PVP, and the excluded Bragg peak at 5.7° is due to diffraction from the aluminum DSC pan. Diffraction data were recorded at 170 °C using synchrotron radiation (λ = 0.23306 Å).

The predicted PXRD pattern of model A1 was used to aid the manual indexing of the pattern of form IV, which allowed the lattice parameters to be calculated (Table 1). The calculated unit cell of model A1 was slightly different from that of the new form, so the unit cell parameters for form IV were substituted into the model of A1. A Rietveld refinement was performed on the model (Figure 3), with bond lengths restrained to an error of 0.1 Å and bond angles to an error of 1.0°, confirming that the crystal structure of model A1 and form IV were equivalent.

Table 1 – Lattice parameters of anhydrous olanzapine polymorphs

	Form I	Form II	Form IV
Space Group	P $2_1/c$	P $2_1/c$	P $2_1/c$
a (Å)	10.328(3)	9.8544(14)	8.6555(2)
b (Å)	14.524(3)	16.314(2)	15.4441(10)
c (Å)	10.500(3)	9.9754(12)	12.5558(9)
β (°)	100.606(14)	98.304(8)	95.284(4)
Volume **(Å³)**	1548.2(7)	1586.9(4)	1671.28(12)

The crystal structure of form IV does not contain the SC_0 dimer motif seen in the other anhydrous forms of olanzapine and the vast majority of its solvates. Instead, the packing involved ladder-like hydrogen bonding interactions between the olanzapine molecules, whereby each molecule is involved in two hydrogen bonds to two adjacent molecules between the piparizine N4 atom and protonated N1 atom (Figure 4**).** The crystal structure of olanzapine reported herein is not isostructural with any of the single component forms of structurally-related compounds with full coordinates in the CSD. The alternative packing exhibited in form IV was calculated to be thermodynamically competitive with the SC_0 dimer motif on the computed crystal energy landscape but could not be achieved experimentally by Bhardwaj *et al.* when crystallizing olanzapine using a variety of crystallization methods.[15] However, when the crystallization conditions were changed to crystallizing from an amorphous molecularly dispersed state with PVP, form IV crystallized as a pure phase. The calculated lattice energy of the models of forms I and IV were effectively the same within the error limits associated with these calculations (−135 and −136 kJ mol^{-1}, respectively),[26] and significantly lower than that of the metastable form II (−128 kJ mol^{-1}). This was particularly interesting as despite extensive efforts to identify olanzapine polymorphs the low energy structure of form IV has proved elusive, yet the higher energy forms II and III have been generated. The presence of PVP molecules in the amorphous state enabled the crystallization of this alternative low energy structure.

With the available data, the mechanism by which PVP molecules direct the crystallization pathway can only be speculated, but a reasonable explanation is as follows. It has previously been postulated that olanzapine may be present in the dimeric form in the pre-nucleation solution and amorphous state, and this therefore directs the crystallization pathway toward structures containing this packing motif.[15] Evidence of olanzapine

dimerization in solution has recently been communicated; clusters of olanzapine molecules (35 nm in diameter) have been observed in unsaturated aqueous solutions and are consistent with a model that predicts dimerization and subsequent aggregation of the structures.[27] The presence of PVP molecules in the amorphous molecular dispersion could be disrupting the formation of olanzapine dimers (which are stabilized by multiple weak C−H···π contacts) through the formation of hydrogen bonds between the polymer chains and drug molecules. Increased viscosity of the super-cooled liquid state, relative to the liquid state in solution crystallizations, is also likely to be playing a role, because olanzapine has been crystallized from many solvents to which it could be hydrogen bonded in solution and yet only forms containing the SC_0 dimer were obtained.[15] The formation of dimers may be kinetically inhibited in the high viscosity the PVP phase, thereby allowing growth of the alternative form IV structure.

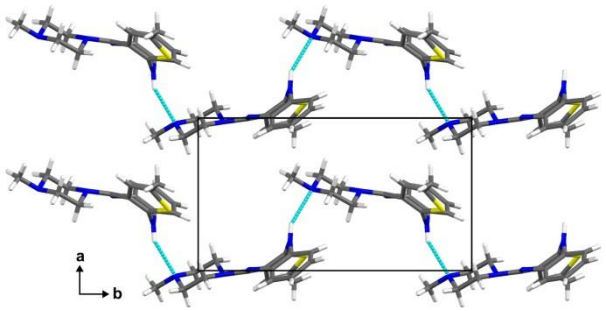

Figure 4 – Packing arrangement showing hydrogen bonding interactions between olanzapine molecules in form IV, as depicted in Mercury software.

Crystal structure prediction calculations and the interpretation of the resulting crystal energy landscapes are being developed as a useful tool in pharmaceutical solid form screening to identify possible polymorphic forms of drug molecules which could avert future issues such as product withdrawals due to unexpected polymorphic conversions (as famously experienced with ritonavir).[28,29] Effectively using such calculations to predict the polymorphs that can be found and help devise experiments to produce the first sample still requires more understanding of how different additives affect the kinetics of crystallization, however.[30] We have yet to identify how the use of specific polymers in a molecular dispersion may help target a CSP predicted polymorph, though progress is being made with other types of template design.[31] Nonetheless, this study adds to the growing number of examples of polymorphs that have been found after a CSP study has been published because of the development of more extensive polymorph screening methods.[32] The research presented demonstrates the potential power of computational crystal structure prediction methods to not only successfully predict structurally diverse polymorphs of a complex organic molecule such as olanzapine, but also facilitate determination of the crystal structure from PXRD data alone.

Extraction of form IV and further characterization

Olanzapine form IV was transiently generated in the simultaneous DSC-PXRD experiments, but the material formed was mixed with polymer. For this crystallization protocol to be a genuinely useful approach for polymorph generation it was important that the scale could be increased and the crystals formed could be separated from the polymer. A protocol was developed for the generation of 100 mg quantities of olanzapine form IV. Scale up could be achieved by crystallization at an elevated isothermal temperature under vacuum, and separation of the drug crystals and polymer could be accomplished by dissolution of the polymer in a selective solvent followed by collection of the insoluble crystals by centrifugation.

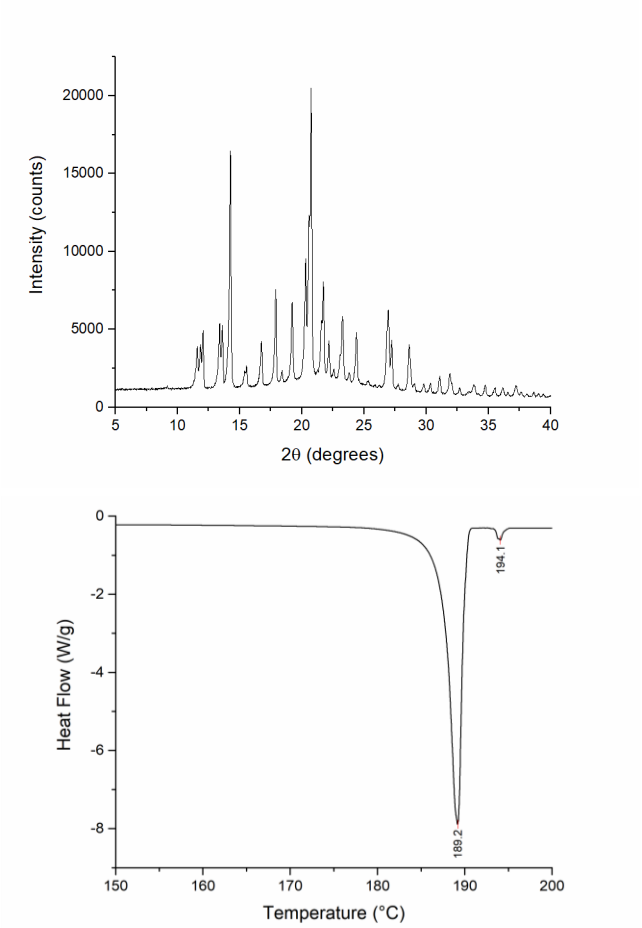

Figure 5 – Physical characterization of isolated olanzapine form IV crystals. PXRD pattern (top) and DSC thermogram (bottom). Exotherm direction is up in the DSC thermogram.

The physical and chemical purity of olanzapine form IV produced by this method were assessed. A UV assay determined the chemical purity to be 97.1 ± 1.1%, showing that the majority of the PVP had been removed during the dissolution and centrifugation process. The physical purity of the crystals was assessed using DSC and PXRD (Figure 5). The PXRD data confirmed that form IV remained the predominant form following the separation process, and no form I peaks were visible in the diffractogram. Given that the PXRD data was collected solely for the purpose of phase identification, a full Rietveld refinement fit to the quickly collected data set with a limited range of 2θ is considered inappropriate. In hindsight, it would have been desirable to collect Rietveld quality data but the capillary was disposed of at the end of the measurement.

The heat flow data showed two melting endotherms at 189 °C and 194 °C, indicating that a minor impurity was present. The predominant peak was the melting of form IV, which was found to have a T_m of 189.1 ± 0.1 °C and the minor peak was the melting of a small form I impurity. The Form IV T_m reported here is the true value as the T_m measured in Figure 1 was affected by the melting point depression effect of the miscible polymer.[33] The physical purity of form IV was calculated to be 99%, based on the enthalpy of the melting endotherms and the measured heat of fusion of pure form I of 129.5 ± 0.5 J/g. The heat of fusion of form IV was then calculated as 117.5 ± 1.0 J/g, corrected for the physical and chemical purity of the sample, lower than that of form I. This confirms that form I remains the thermodynamically stable form. Despite this, no conversion of Form IV to form I was noted by PXRD over a storage period of 4 weeks at room temperature.

The main pharmaceutical advantage of metastable polymorphs is a higher apparent solubility, resulting in improved dissolution rates and higher bioavailability. Olanzapine is a BCS class II drug, meaning that it has high permeability across the walls of the gastrointestinal tract but low aqueous solubility which can limit the absorbable dose.[34] The dissolution performance of forms I and IV were compared in vitro (Figure 6), and the dissolution rate of form IV was found to be far faster than form I, with dissolution of the former complete within 15 minutes compared to 90 minutes for the latter. The crystals of the two forms were sieved to ensure that a similar particle size was used for each form, and hence the difference in dissolution rate can be attributed solely to the physical form of the drug.

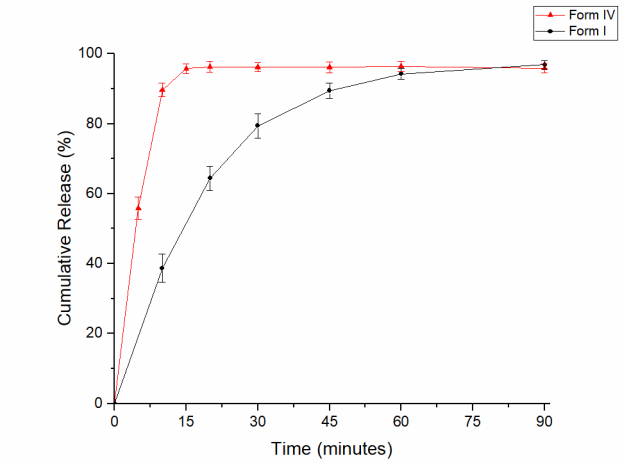

Figure 6 – In vitro dissolution performance of olanzapine forms I and IV assessed using USP 2 apparatus in PBS (pH 6.8) dissolution media. Mean ± SD (n = 3).

The alternative crystallization approach of heating an amorphous molecularly dispersed system of drug and polymer therefore facilitated the crystallization of a new olanzapine polymorph that has favorable dissolution properties compared with the thermodynamically stable form, and a separation protocol allows crystals of the new form to be isolated with reasonable chemical and physical purity. Crystallization from the pure amorphous state, generated by melt quenching or other processes, has long been used in polymorph screening in attempts to generate alternative crystal structures. The example of olanzapine form IV reported here suggests that the presence of additional excipients in the amorphous phase, such as polymers, can promote the crystallization of alternative structures that are difficult to obtain from other crystallization conditions. These observations are consistent with the work of Matzger on using polymer templating to control the physical form of APIs.[35–39] This has also led to the generation of previously unknown polymorphs, for instance of phenobarbital.[40] The isolation of olanzapine form IV in this study demonstrates that it is possible to obtain metastable forms with reasonable chemical and physical purity by heating amorphous solid dispersions of drug in polymer. Additionally, the simultaneous DSC-PXRD analytical platform used in this study provides a powerful tool for investigating polymorphism using this crystallization approach.

CONCLUSIONS

A new polymorph of olanzapine, form IV, has been identified and isolated. CSP correctly predicted the existence of form IV but prior to this work it had not been obtained experimentally because solution-based crystallization methods result in the formation of olanzapine dimers, which in turn lead to polymorphs based on the SC_0 motif. Crystallization from a solid amorphous phase allows crystallization of alternative structures, which is proposed to be by virtue of disfavoring dimer formation. DSC-PXRD was critical in establishing the presence of the new form.

SUPPORTING DATA

The CIF file for olanzapine phase IV obtained from the fit to the synchrotron PXRD data has been deposited at the Cambridge Crystallographic Data Centre with deposition number 1901216.

AUTHOR INFORMATION

Corresponding Authors

Professor Duncan Q. M. Craig
Email: duncan.craig@ucl.ac.uk Telephone: +44 20 7753 5819

Professor Simon Gaisford
Email: s.gaisford@ucl.ac.uk Telephone: +44 20 7753 5942

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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