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Rajni M. Bhardwaj

Control and Prediction of Solid-State of Pharmaceuticals

Experimental and Computational Approaches

Doctoral Thesis accepted by
the University of Strathclyde, Scotland, UK

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2. **Rajni M. Bhardwaj**, Jean-bapiste Arlin and Alastair J. Florence. *Crystal structure of a mixed solvated form of amoxapine acetate.* Acta Cryst., 2015, E71, 139–141
3. **Rajni M. Bhardwaj**, Louise Price, Sarah L. Price, Susan M. Reutzel-Edens, Iain Oswald, Blair Johnston and Alastair J. Florence. *Exploring the Experimental and Computed Crystal Energy Landscape of Olanzapine.* Cryst. Growth Des., 2013, 13, 1602–1617.
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Other Publications

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9. Elanor Brammer, Fraser Mabbott, Laura Martinez-Marcos, **Rajni M. Bhardwaj** "*Continuous Manufacturing—A paradigm shift in the Pharmaceutical Industry*". UKICRS Newsletter 2014, 29–32.
10. Doris E. Braun, **Rajni M. Bhardwaj**, Jean-Baptiste Arlin, Alastair J. Florence, Volker Kahlenberg, Ulrich J. Griesser, Derek A. Tocher and Sarah L. Price. *Absorbing a Little Water: The Structural, Thermodynamic and Kinetic Relationship Between Pyrogallol and its Tetarto-hydrate. Cryst*. Growth Des., 2013, 13, 4071–4083.

11. Doris Braun, **Rajni M. Bhardwaj**, Alastair J. Florence, Derek A. Tocher and Sarah L Price. *The Complex Polymorphic System of Gallic Acid—Five Monohydrates, Three Anhydrates and Over 20Ssolvates.* Cryst. Growth Des., 2013, 13, 19–23.
12. **Rajni M. Bhardwaj**, Iain Oswald and Alastair J. Florence. *2,4-Diamino-6-methyl-1,3,5-triazine 1,4-butanediol Solvate.* Acta Cryst., 2012, E68, o3377.
13. Jean-Baptiste Arlin, **Rajni M. Bhardwaj**, Andrea Johnston, Gary J. Miller, Julie Bardin, Fiona MacDougall, Philippe Fernandes, Kenneth Shankland, Bill David and Alastair J. Florence. *Structure and Stability of Two Polymorphs of Creatine and its Monohydrate.* CrystEngComm, 2014, 16, 8197–8204.

Supervisor's Foreword

Crystallisation is an important process for purification and isolation of active pharmaceuticals and other chemicals, yet the critical factors that dictate the outcome for a given molecule under any given set of process conditions often remain unclear. Hence the identification and selection of potential crystalline forms during the development of new products still largely relies on empirical relationships and user experience to select initial experimental conditions and maximise the number of solid forms discovered. Whilst crystal structure prediction can be applied to increasingly complex molecular systems (flexible molecules; multi-component systems), it is still far from routine, and has the potential to inform experimental approaches by revealing the structural features and trends in feasible crystal packing arrangements. The work presented in this thesis seeks to develop improved experimental approaches for exploring physical form diversity in molecular systems and to exploit computational methods to provide a better understanding of the outcomes of such investigations as well as novel, computationally inexpensive, predictive capabilities. The work focuses on a structurally related series of molecules and provides insights into the differences that can result in crystallisation from small changes in molecular structure in such related systems.

Cost-effective, safe, rapid and sustainable methods for exploring solid-state diversity are of significant interest in academic research as well as industry. The development of a small-scale screening approach using manual multiwall plate preparation and Raman microscopy for effective salt, polymorph and solvate screening provides an effective means to generate structural diversity from only small amounts of material. The quality of this work has been recognised by the RSC "Duncan Bryant Prize" prize in 2012. The next experimental chapter shows the potential to build predictive capability based on the outcomes of such systematic experimental studies. At present we have no means of assessing 'crystallizability' of molecules-based molecular structure alone and so can be surprised by individual molecules' behaviour. The crystallizability prediction tool developed in this work emphasises the potential for multivariate statistical approaches combined with systematic experimentation to provide some useful predictive capability. In the

context of solid form discovery and preclinical development, if such approaches can be extended to cover a diverse range of molecules then there are considerable benefits in the early identification of problem compounds. The work on olanzapine solvates also highlights the potential to further extend the application of these tools to understand the crystal structure and molecular packing obtained from experimental tools and build a useful knowledge base that can inform future experiments for successful outcomes. The success of the work in this thesis has ensured that these approaches continue to be developed for application in other molecular systems. The detailed study on polymorphism and crystal packing in olanzapine is a showcase for the potential for combined crystal structure prediction, molecular modelling, packing analysis and intermolecular interactions to reveal the key features directing crystal structure. Crucially, this work also reveals key structure–property relationships enabling the rationalisation of the observed stability of solvated forms.

Overall, the work illustrates the potential for computationally assisted experimentation not just to provide more data, but also better information describing the factors that influence crystallisation and crystal structure. Moreover, it highlights the possibilities to improve the efficiency of early stage solid form discovery and selection. Whilst challenges remain for first principles prediction from molecular structure alone, there is still much more that can be achieved with existing tools. The work presented here continues to influence research in our group that seeks to extend the development and application of statistical models to assess completeness of physical form screens and enhance our understanding of crystal structure outcomes. It has also influenced our approach to training and skills development for researchers in this area to enable the increased use of multivariate analysis tools, molecular modelling and structure prediction alongside careful experimentation and analysis.

Glasgow, Scotland, UK
December 2015

Prof. Alastair J. Florence Ph.D

Abstract

This thesis illustrates techniques for discovery of solid-state forms and for probing the relationship between molecular structure and crystallisability. Also, the value of combined experimental and computational approaches to provide better understanding of the key factors underpinning the structural diversity in two groups each comprising of two structurally related pharmaceutical compounds is demonstrated.

An effective methodology of high throughput crystallisation and analysis for polymorph, solvate and salt screening using quartz 96/48 multi-well plate with an automated system for collecting high quality Raman spectra was developed and validated. Using this efficient technique, 10 novel salts of amoxapine, 3 novel physical forms of clozapine and 16 novel solid forms of olanzapine were obtained by utilising a total of only $\sim$640 mgs of API and $\sim$65 ml of solvents.

A statistical model with $\sim$70 % prediction accuracy was built for predicting the crystallisability of small organic molecules. This model is the first of its kind and provides an opportunity to identify problematic systems at early stages and allows early targeting for improvements.

Structurally related molecules within each group were found to have markedly different experimental solid-state diversity after comprehensive physical form screening using multiple crystallisation techniques selected to maximise the crystallisation search space. Crystal structure prediction studies have proved to be an important tool in rationalisation of the observed solid-state diversity. PIXEL calculations revealed that the largest contribution to crystal stabilisation comes from dispersion energy and enabled the identification of dominant intermolecular interactions in the crystal structures. Structural packing analysis using XPac and mercury enabled the structural relationship amongst all the crystal structures to be investigated. In the case of olanzapine solvates XPac analysis provides a rationale for desolvation products by highlighting the close relationships between the forms and desolvated 'end product'. Statistical modelling analysis revealed that the physicochemical properties of the solvents were directing the crystal packing in olanzapine solvates.

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Abbreviations

API	Active Pharmaceutical Ingredient
AXPN	Amoxapine
CBZ	Carbamazepine
CSD	Cambridge Structure Database
CSP	Crystal Structure Prediction
CT	Chlorothiazide
CZPN	Clozapine
DOE	Design of Experiment
E_C	Coulombic Energy
E_d	Dispersion Energy
E_p	Polarisation Energy
E_r	Repulsive Energy
E_{tot}	Total Lattice Energy
HCT	Hydrochlorothiazide
HTC	High Throughput Crystallisation
HTCAA	High Throughput Crystallisation and Analysis
LXPN	Loxapine
MWP	Multi-well Plate
OZPN	Olanzapine
PCA	Principal Component Analysis
QbD	Quality by Design
RF	Random Forests
RH	Relative Humidity
SC	Supramolecular Construct
SDPD	Structure Determination from Powder data
SXD	Single Crystal X-ray Diffraction
VT-XRPD	Variable Temperature X-ray Powder Diffraction
XRPD	X-ray Powder Diffraction