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“Particle Informatics”: Advancing our understanding of particle properties through digital design

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Abstract

We introduce a combination of existing and novel approaches to the assessment and prediction of particle properties intrinsic to the formulation and manufacture of pharmaceuticals. Naturally following on from established solid form informatics methods, we return to the drug lamotrigine, re-evaluating its context in the Cambridge Structural Database (CSD). We then apply predictive digital design tools built around the CSD-System suite of software, including Synthonic Engineering methods which focus on intermolecular interaction energies, to analyse and understand important particle properties and their effects on several key stages of pharmaceutical manufacturing. We present a new, robust workflow that brings these approaches together to build on the knowledge gained from each step and explain how this knowledge can be combined to provide resolutions at decision points encountered during formulation design and manufacturing processes.

Introduction

The attrition rate in pharmaceutical development is notoriously high, with as few as one in ten thousand candidate active pharmaceutical ingredients (APIs) realised as a marketed drug product.[1] Many of these failures are associated with safety and efficacy problems, although a significant proportion of new drug applications fail due to manufacturing factors.[2,3]

The interest in how computational approaches can provide insight into pharmaceutical development and manufacturing has grown considerably over the last two decades, especially following high-profile product failures such as ritonavir[4] and rotigotine.[5] Various approaches have resulted in the routine use of multi-scale molecular and data-driven modelling of properties such as polymorph stability,[6–8] solubility[9,10] and crystal morphology.[11–14]

In 2011, to celebrate the addition of the 500,000th entry into the CSD,[15] the paper "One in half a million: a solid form informatics study of a pharmaceutical crystal structure" was published.[16] In that study, the 500,000th entry into the CSD, an antiepileptic drug known as lamotrigine,[17] was used to highlight the state of the art of the field of solid form informatics and to establish a solid form risk assessment protocol that is widely used within the pharmaceutical industry,[18–20] and extensively used by the CCDC's Crystal Form Consortium (CFC).[21]

Although a good understanding of solid form properties exists, partly due to the availability of tactile informatics tools, a molecular level understanding of the relationship between particle and surface properties and manufacturability is less developed. Molecular modelling of the intermolecular interactions, or "synthons", in the bulk and at the surface of a crystalline particle has led to the prediction of properties such as morphology,[22–25] surface energy,[26] and particle cohesivity/adhesivity.[27] The wider use of these methods in a tactile way[28] could lead to a deeper understanding of the molecular mechanisms which lead to problematic particulate properties, such as poor flowability, agglomeration and "fines" production, which can cause significant problems during drug product manufacture.

As we now approach the 1,000,000th entry in the CSD, we revisit the structure of lamotrigine to both reassess its solid form in the context of nearly one million crystal structures and to highlight the advances made in analyses that provide information on particulate properties, addressing the next stage of the pharmaceutical product design and manufacturing pipeline. These tools are now being integrated into experimental workflows that can enhance our understanding of particle attributes and mechanical properties, enabling the link between form, performance and manufacturability to be made clearer.

The Advanced Digital Design of Pharmaceutical Therapeutics (ADDoPT) project[29], a collaborative endeavour between pharmaceutical companies, solution providers and academia,

seeks to bring the concept of "digital design" to the formulation design and manufacturing stages of the pharmaceutical supply chain. Here, we present a combined effort between several ADDoPT partners to establish a comprehensive workflow that naturally follows on from solid form informatics in order to streamline processes and anticipate potential bottlenecks in delivering drugs faster.

Lamotrigine – A model drug?

The antiepileptic drug lamotrigine (often marketed as Lamictal) was first developed by Wellcome Laboratories[30] and now has relatively well understood physical properties. Lamotrigine falls into the category of Biopharmaceutical Classification System (BCS) Class-II,[31] meaning that it has low aqueous solubility but high permeability.[32] Lamotrigine exhibits a far greater solubility in non-aqueous solvents and its solubility is significantly improved in solvent mixtures.[33,34]

Chemically and structurally, it was established in the previous study that lamotrigine is a typical drug molecule.[16] Consequently, the application of knowledge derived from all the structures from the CSD provides a powerful framework for better understanding a given material's solid form. More recent work further exploring the chemical and crystallographic space inhabited by drugs and non-drugs in the CSD[35] shows that the values of several descriptors for lamotrigine are typical of a marketed small molecule drug, although the number of acceptors in the molecule is slightly higher than average (**Figure 1**). Repeating the solid form informatics calculations in the context of nearly 1,000,000 crystal structures shows that the anhydrous form of lamotrigine (CSD Refcode EFEMUX) has features that are characteristic of a stable solid form – a "usual" conformation, based on geometric distributions from the CSD,[36] is observed and the arrangement of intermolecular interactions in the crystal structure is as would be expected.

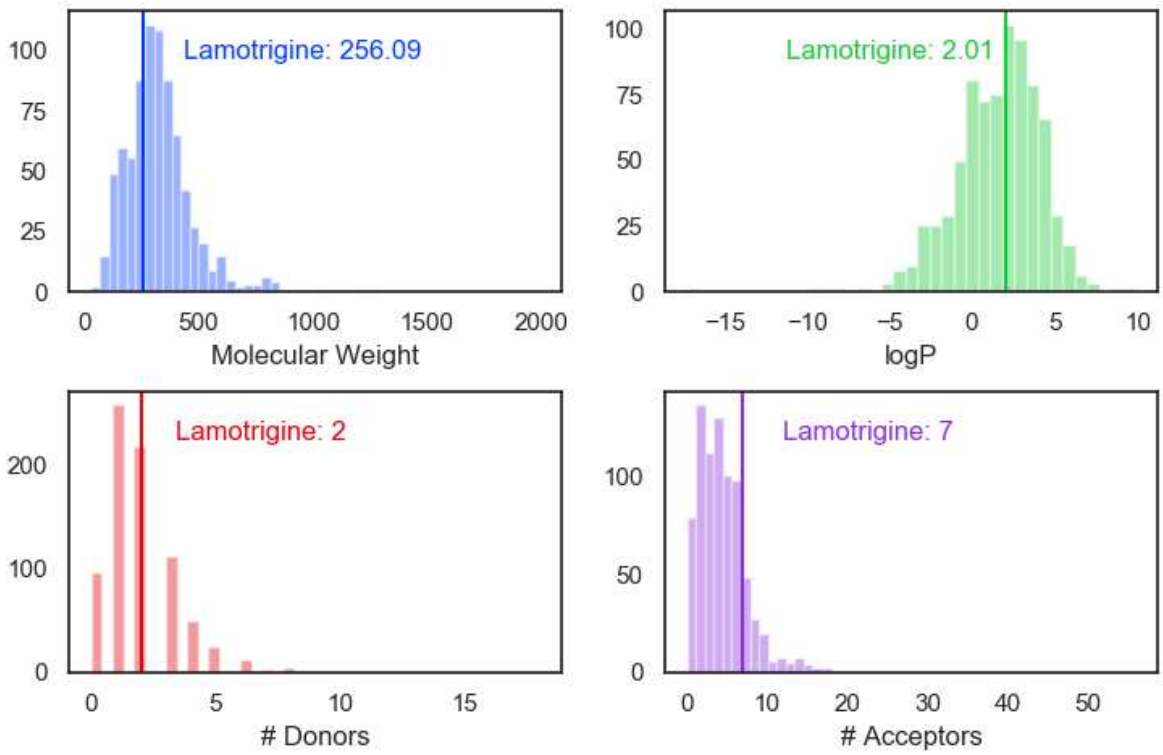

Figure 1. Comparison of selected molecular descriptors of lamotrigine relative to the distributions of approved drugs in the CSD Drug Subset.

While the solid form of lamotrigine is now well understood to be stable and efficacious, the behaviour of the particulate material during formulation and drug product manufacture is much further from the ideal. Through correspondence with GlaxoSmithKline and a thorough review of available literature, we have gained some insight into the manufacturing and formulation of the final product and acquired some understanding of the issues encountered therein. Formulations of lamotrigine are fairly typical, and generally consist of wet granulated lamotrigine in combination with lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.[37] Due to lamotrigine's low solubility in aqueous media, the API is typically micronized to 3-5 μm. Anhydrous lamotrigine is known to have poor flow properties, and is sometimes prone to "capping" upon tableting due to low compressibility of the API.[38]

Properties such as poor powder flow and poor compressibility seen for lamotrigine often pose a challenge in the production of a formulated medicine. When understood holistically, these properties can be used to assess the feasibility of different processing routes through the concept of the Manufacturing Classification System (MCS).[2,39] Identifying these factors through computational and informatics approaches in advance of manufacturing processes could cut the time and costs involved in bringing a drug product to market by reducing resource intensive experimental testing.[40] Additionally, by having a full description of both the solid form and particle form as a companion to experimental measurements, any potential problems might be rectified before they ever occur.

The "Particle Informatics" workflow

In this work we propose how novel and existing digital design tools can be organised into a workflow to better understand several stages in the formulation and manufacturing pipeline of small molecule pharmaceuticals.

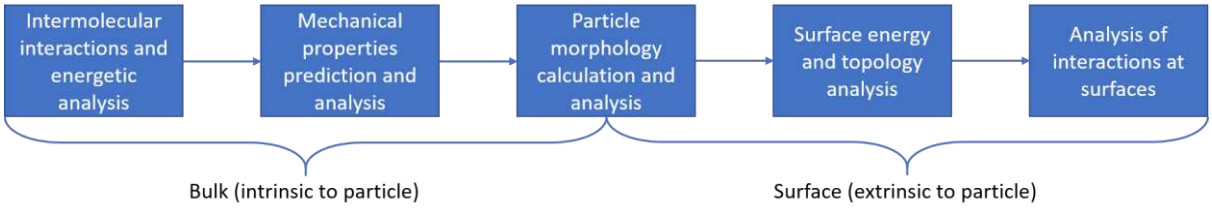

Figure 2. Steps involved in the proposed "Particle Informatics" workflow. The output from each step flows into the next to provide a full picture of the particle properties.

Taking each step of the workflow in turn, and comparing the insights gained with targeted experimental measurements, a thorough appreciation of the particle properties of a material can be gained. With this knowledge, key decisions made during pharmaceutical processes are better informed, avoiding potential bottlenecks during formulation design and manufacturing and enabling drugs to be delivered faster.

What follows is an explanation of each step in the "Particle Informatics" workflow using lamotrigine as an example drug product. The relevance, digital design tools used, and knowledge gained are outlined for each stage with each building on the last to provide a comprehensive understanding of particle properties and their contributions to pharmaceutical formulation and manufacturing processes.

Intermolecular interactions and energetic analysis

The solid-state properties of a material are inevitably dictated by the nature of the intermolecular interactions present. Gaining insight into the nature, chemistry and context of these interactions within the bulk of the particle (defining the intrinsic synthons) can shed key insight into how a solid might behave. Highly anisotropic interactions can have a marked effect on bulk properties, such as mechanical properties, but may also affect crystal growth morphology and surface behaviour. The orientation of these intermolecular interactions relative to the particle's surfaces (defining the extrinsic synthons) can also pose issues in formulation, particularly for highly anisotropic particles. Weak interactions normal to the long axis of a needle-like crystal, for instance, may result in breakage and the creation of "fines".

An assessment of the strength and directionality of the intermolecular interactions in a crystal structure can be made by performing a lattice energy calculation. Here, we have performed this using HABIT98[41,42] with the Dreiding forcefield.[43] This approach not only gives the individual intermolecular interaction energies and an estimate of the total lattice energy, but provides a breakdown of the energy into the contributing hydrogen bonding, van der Waals dispersion and electrostatic terms.

Compound	Molecular weight (g mol^{-1})	Calculated lattice energy (kcal mol^{-1})
acetanilide	135.2	-23.9

p-aminobenzoic acid	137.1	-24.5
paracetamol	151.2	-28.2
phenacetin	179.2	-29.1
ibuprofen	206.3	-28.9
mefenamic acid	241.3	-31.7
lamotrigine	**256.1**	**-32.3**
tolfenamic acid	261.7	-30.0
flufenamic acid	281.2	-28.5
niflumic acid	282.2	-31.1
diclofenac	296.1	-27.7
DPC-963	316.2	-29.0

Table 1. Comparison of calculated lattice energies and molecular weights for lamotrigine and some other small molecule pharmaceuticals

Table 1 shows that the lattice energy calculated for lamotrigine, relative to its molecular weight, compares favourably with the general trend of values calculated for other small molecule pharmaceuticals. The more negative lattice energy observed for lamotrigine may arise from its larger size relative to other small molecule drugs but may also indicate that it forms several strong interactions in the solid state. This is evidenced by observing how the lattice energy is partitioned over the functional groups of the molecule.

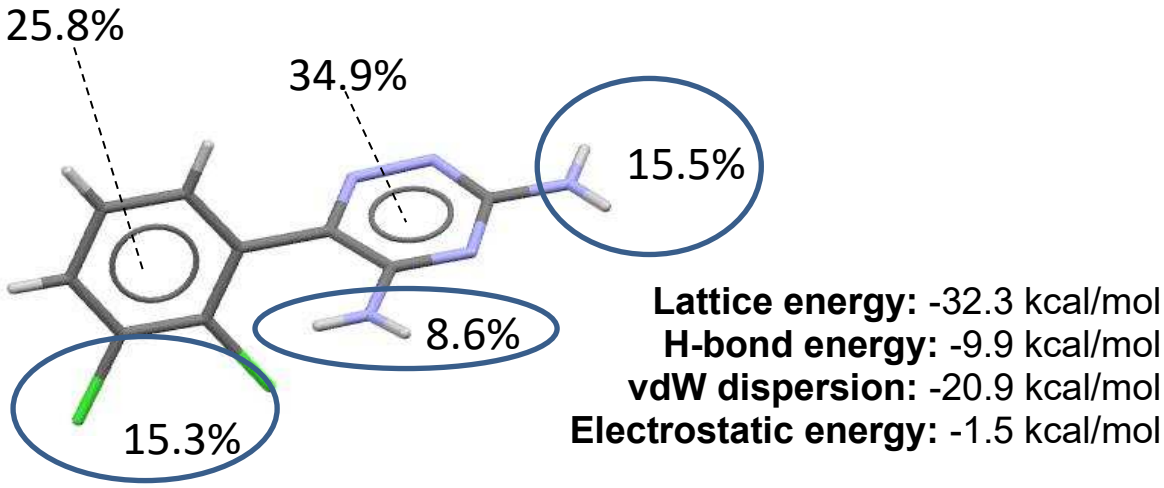

Figure 3. (Left) The percentage contributions to the total lattice energy of lamotrigine from each functional group. (Right) The calculated lattice energy of lamotrigine broken down into contributing terms.

Figure 3 Figure 3 indicates that, in terms of the atom-atom pairwise energy summation, the lattice energy is partitioned evenly between the moieties that comprise the molecule, with the more polar amine and chlorine groups making similar contributions to the lattice energy. The less polar ring moieties both make considerable contributions to the total lattice energy, with van der Waals interactions making up over 60% of the total energy.

The individual intermolecular interaction motifs, or "synthons", can be examined, and their relative energies and orientations can be used to understand the interactions in the crystal structure.

The most common source of anisotropy in a crystal structure comes from the dimensionality of any hydrogen bond networks present.[44,45] An automatic assignment of the hydrogen bond network dimensionality, based on the relative change in the dimensions of a bounding box surrounding the network as it expands,[46] can be used to assess the isotropy of these interactions. Anhydrous lamotrigine displays a 3-dimensional hydrogen bonding network, extending in all dimensions.

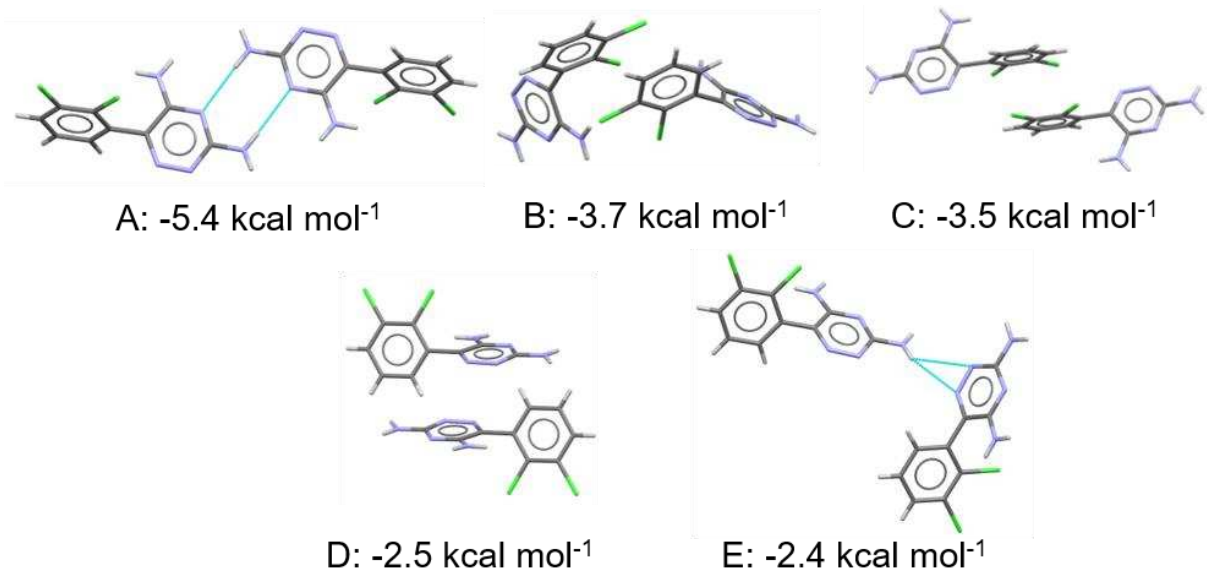

Figure 4. The strongest pairwise intermolecular synthons calculated from the bulk structure of lamotrigine and their energies. Hydrogen bonds are indicated by dashed lines.

As **Figure 4** shows, the strongest synthon (A) in the lamotrigine crystal structure is a dimeric hydrogen bonding interaction between one of the amine groups and one of the triazine nitrogen atoms. These dimers are subsequently linked through a weaker hydrogen bond between the same amine group and the remaining triazine nitrogen atoms (synthon E) to create sheets of lamotrigine molecules. Another hydrogen bond between the other amine group and one of the chlorine atoms (synthon B) bridges these sheets, creating the three-dimensional hydrogen bonding network.

Two important dispersion interactions are also present in the structure of lamotrigine. Synthon C is a stacking interaction that occurs between dichlorobenzene rings bridging the hydrogen bonded sheets made by synthons A and E. Synthon D arises due to a favourable "interlocking" of molecules, facilitated by the conformation that they adopt in the solid state, and sits within the hydrogen bonded sheets.

The relative strengths and orientations of the key synthons in lamotrigine indicates a broadly isotropic, three-dimensional arrangement of intermolecular interactions. Consequently, this suggests the likely formation of equant particle morphologies.

Mechanical properties prediction and analysis

The mechanical properties of individual pharmaceutical crystallites are strongly correlated with the overall formulation performance and processability.[47–49] In particular, the plasticity or compressibility of the API has been shown to have a marked effect on the quality of tablets, particularly those with high drug loading.[50,51] Materials with a low elastic recovery tend to produce stronger, more resilient tablets, and this behaviour is intrinsically linked to the arrangement of molecules in its structure and the orientation and strength of the forces between them.[52,53]

In crystals, the presence of a layered structure containing planes of molecules that are free to slide over each other has been consistently identified as a likely source of dislocation defect

formation in response to mechanical stress.[53,54] This, in turn, has been attributed to low elastic recovery and consequently improved tabletability. By scanning for the least interdigitated plane through a crystal structure, a prediction of the likely source of dislocation upon compression can be made.[46] When combined with additional descriptors, such as the spacing between planes or the dimensionality of any hydrogen bonding in the structure, the likely ease of dislocation, and consequently the likelihood of plastic deformation, can be assessed purely from the topological arrangement of molecules. An overarching structure for the prediction of mechanical properties has been summarised by Olusanmi *et al*.[55]

As discussed previously, lamotrigine is known to exhibit problems during tabletting – most notably low compressibility and "capping", the result of rapid elastic recovery upon removal of the tablet punch which leads to fracturing and lamination of the tablet. In the crystal structure of lamotrigine, the least interdigitated plane is identified as *hkl* = 2, 0, -2 with a separation of 0.86 Å (based on atom centroid-centroid distances).

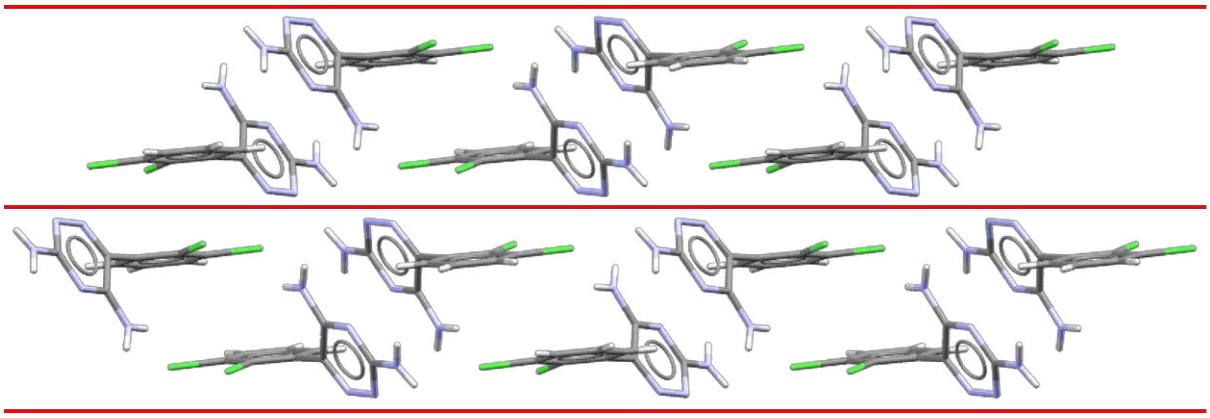

Figure 5. The (2, 0, -2) planes in the crystal structure of lamotrigine, identified as the least interdigitated.

While **Figure 5** shows that the (2, 0, -2) planes are not interdigitated, and therefore have the potential to slip, the analysis described above indicates that they are bridged by multiple strong

N-H…N hydrogen bonds (synthon A), as well as aromatic stacking interactions (synthon C) which will add rigidity across the interface and reduce any slip propensity. Additionally, the relatively small *d*-spacing of 6.28 Å between planes is indicative of low plasticity. These two descriptors combined indicate that lamotrigine is at best moderately plastic, however when combined with a high lattice energy, 3-dimensional hydrogen bonding network and the isotropic nature of the remaining intermolecular interactions this assessment indicates that the material is unlikely to exhibit good plastic deformation under compression.

Combining this topological approach with a knowledge of the strength and orientation of intermolecular interactions in a crystal structure provides key insights into the bulk properties of a material. Through investigating these features as early as possible during pharmaceutical development, potential bottlenecks that may arise in processes that depend on these properties, such as tableting, can be identified and anticipated.

Particle morphology calculation and analysis

While the bulk powder of an API will never be composed of perfectly formed single crystals of uniform morphology, having an understanding of the dominant faces and potential aspect ratio of the crystals can provide a great deal of information about potential downstream particle behaviour, particularly in terms of flow, sticking and tabletability.[56,57] In the case of lamotrigine, the experimentally determined crystal morphology of the bulk solid is found to be prismatic (**Figure 6**, left). However, in the presence of 1.2% 2,3-dichlorobenzoic acid (an impurity resulting from the chemical synthesis), the crystallites are found to be far smaller, more anisotropic in shape and to form agglomerates (**Figure 6**, right).[38]

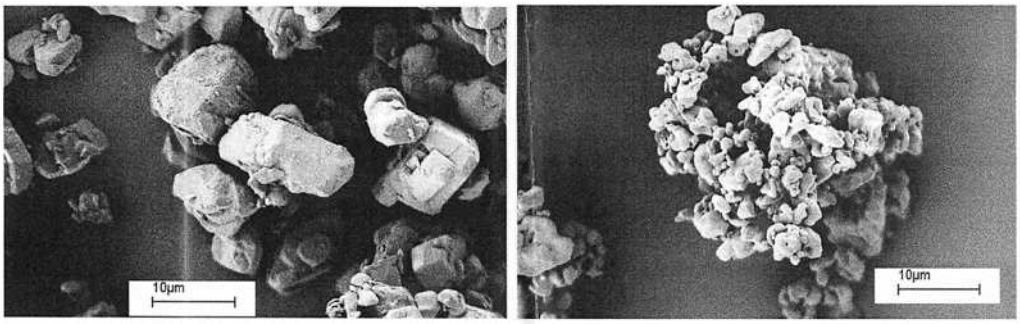

Figure 6. Experimental morphologies of lamotrigine without (left) and with (right) the presence of the impurity 2,3-dichlorobenzoic acid

An established means of predicting crystal morphologies is the energy of attachment method.[13] This uses some computational method to estimate the binding strength of molecules in different slices through a crystal structure, and equates the relative growth rate of a face to this strength of binding. Making use of the intermolecular interaction energies calculated above, we have used HABIT to predict the attachment energy crystal morphology of lamotrigine (**Figure 7**).

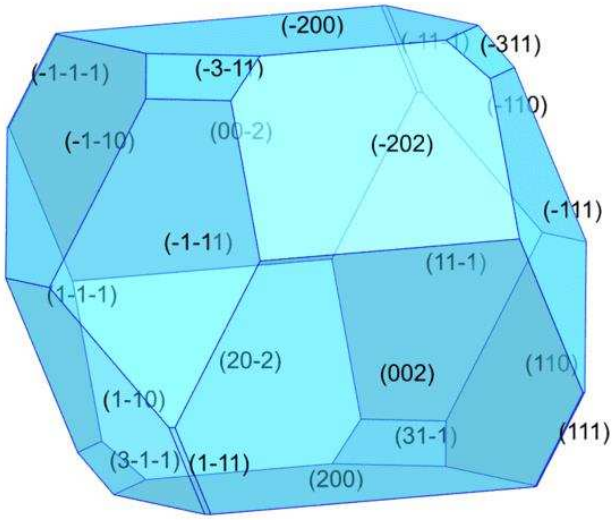

Figure 7. Attachment energy crystal morphology of lamotrigine calculated using the Dreiding forcefield.

The energy of attachment morphology of lamotrigine is found to be quite equant, consistent with the three-dimensional orientation of the synthons within the bulk structure described previously. This results in a prismatic crystal shape, which seems to qualitatively agree with the observed morphology of lamotrigine in the absence of an impurity. The external morphology is found to be dominated by the {200}, {002}, {110}, {11-1} and {20-2} faces.

Surface energy and topology analysis

Depending on the morphology, the surface energies, topologies and chemistry exposed on each crystal surface can vary enormously. Gaining an insight into this variation for a specific system is therefore a key factor in understanding the behaviour of a solid form during formulation, and assessing any risks posed by batch to batch variation. Furthermore, since each crystal surface will interact differently with air, moisture, tooling, solvents and excipients, for instance, understanding the nature of the dominant faces of a particle is critical in understanding the behaviour of the solid during manufacturing processes.

Face	Surface Energy (mJ m^{-2})	Anisotropy Factor (%)	Contributing Terms (%)		
			van der Waals	H-Bonding	Electrostatic
{200}	82.3	57	60	30	2
{110}	80.3	53	51	37	4
{11-1}	76.7	51	49	36	6
{20-2}	69.3	50	56	32	5
{002}	66.1	49	47	40	5
{31-1}	60.7	46	61	27	4
Total*	75.8				

Table 2. Individual surface energies and anisotropy factors for the attachment energy predicted morphology faces of lamotrigine. Also shown are the total particle surface energy, and the percentage contributions of different energy terms to the growth of these surface. *The total surface energy was calculated as the summation of the surface energy for each face multiplied by its fractional surface area.

The surface energies of the individual faces were obtained during the attachment energy calculation outlined above. For each surface, a single *d*-spacing of each face is cycled through in 0.1 *d*-spacing steps, and slice and attachment energies are calculated for the surface termination at each step. The termination with the lowest energy in each case provides the reported stable surface. For lamotrigine these surface energies have been normalised to their predicted relative surface areas in the crystal morphology (**Table 2**). The particle surface energy calculated for lamotrigine is higher than that of, for example, ibuprofen,[58] although this may be expected due to the greater lattice energy calculated for lamotrigine. In contrast to crystal morphologies with particularly large individual surfaces, such as plates or needles where the dominant face is likely to be very low in energy,[59] the equant shape of this crystal suggests that individual surfaces will have comparable surface energies.

The anisotropy factors (defined as the slice energy divided by the total lattice energy) calculated for the individual habit surfaces (**Table 2**) were found to be very similar, with the large {200} faces 57% satisfied and the small {31-1} faces 46% satisfied. These faces are also determined to have the greatest van der Waals contribution to their surface energy. This is again consistent with the isotropic shape of the crystal. The contributions of the different energy terms reveal that the {110}, {11-1} and {002} faces are found to have the greatest contribution from H-bonding interactions, consistent with the orientation of hydrogen bonds in the crystal structure. Both the {110} and {11-1} surfaces are major habit faces, indicating that lamotrigine crystals are likely to interact with more polar, hydrogen bonding species.

To further rationalise the particle properties, an understanding of the surface topology, and the chemistry presented on these surfaces, is required. The topology of a crystal surface is important, as rough faces typically have a lower barrier for surface adsorption than closely-packed smooth planes.[60] A knowledge of the position of certain functional groups relative to

topological features such as pockets and channels is also useful to enable the prediction of surface effects. Utilising the CSD Python API, we can generate a simple, standardised visualisation of the crystal surfaces present on a given morphology from which numerous topological and chemical features can be identified.

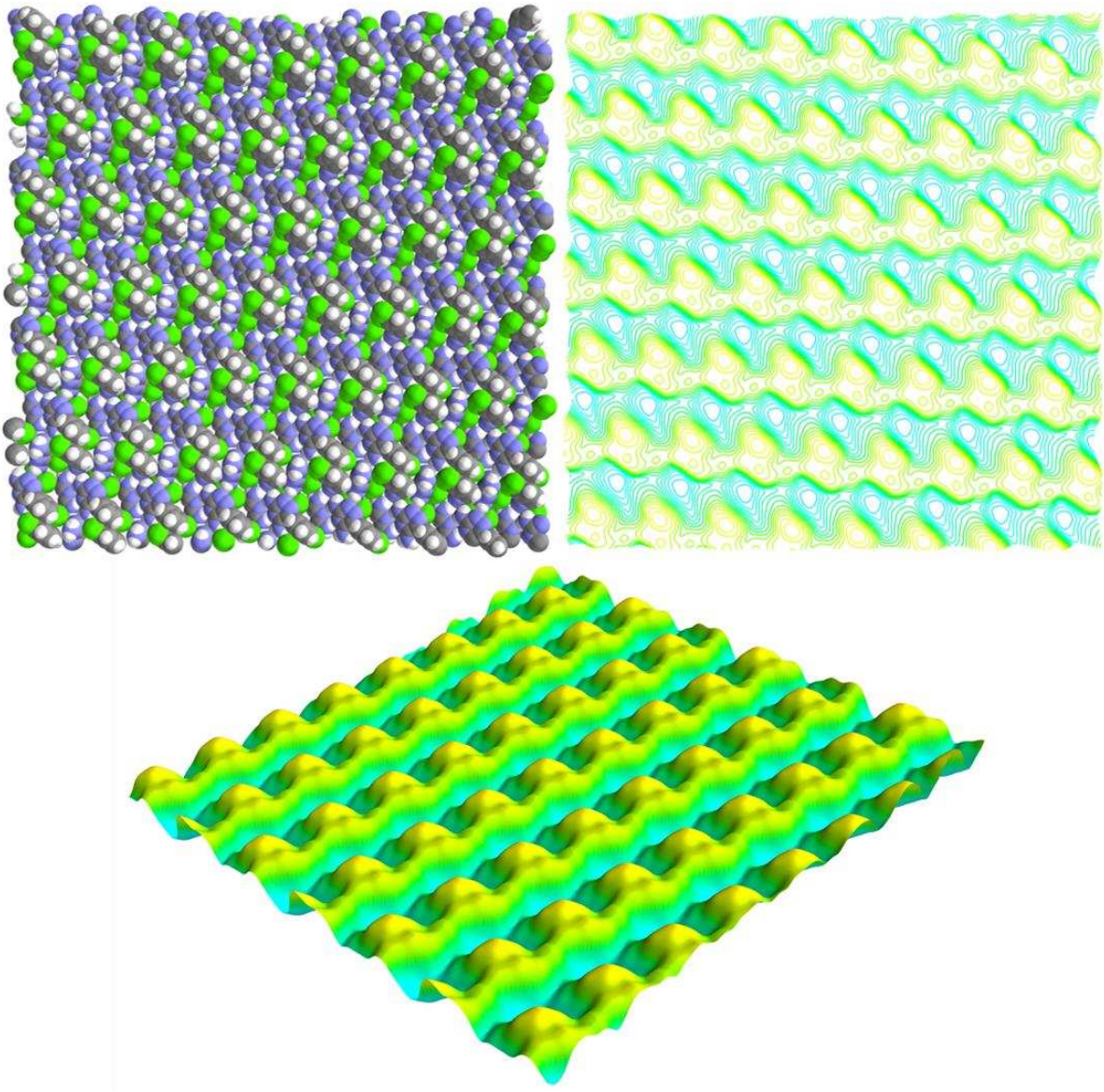

Figure 8. (Top left) The {1, 1, 0} face of lamotrigine displaying the chemistry of the surface. Nitrogen atoms are blue, chlorine atoms are green, carbon atoms are grey and hydrogen atoms are white. (Top right) The contour map of the corresponding van der Waals surface. Yellow

regions indicate displacement out of the plane of the page, and blue/green regions indicate displacement into the page. (Bottom) The topological van der Waals surface. All images show an 84 Å x 84 Å area.

Face	Donor Density	Acceptor Density	Aromatic Density	Roughness (Å)
{200}	1.74	3.48	13.6	3.23
{110}	1.90	2.50	10.3	6.53
{1-11}	1.10	2.90	9.6	3.50
{20-2}	1.20	3.50	16.4	2.60
{002}	1.20	3.09	15.6	1.97

Table 3. Surface descriptors for the major faces of lamotrigine. Donor and acceptor densities are given as atoms per unit area of the surface. The aromatic density is given by the number of aromatic bonds per unit area. Roughness is measured by the distance from the highest contour peak to the lowest valley along the Z-axis.

Figure 8 and **Table 3** show that the {110} face of lamotrigine contains several exposed amine groups, consistent with the relatively high hydrogen bonding contribution to the surface energy described above. While some chlorine atoms are exposed, the majority sit slightly further from the surface, as do the aromatic rings, consistent with the lower van der Waals contribution to the {110} face. **Table 3** also shows that the {110} faces are particularly rough, and the contour map (**Figure 8**, right) shows that peaks and valleys run across them. Figures relating to other major surfaces of lamotrigine are given in the Supplementary Material.

Combining surface energies along with an assessment of the topological and chemical nature of those surfaces allows for an assessment of their likely behaviour as particles, and an understanding of how they might interact with other particles and surfaces. For instance, the high-energy {110} face, with exposed functional groups and a relatively high roughness, is indicative of a surface that might readily interact with many other species during formulation and manufacturing.

Analysis of interactions at surfaces

With knowledge of the character of the likely exposed surfaces of particles, it is advantageous to be able to model how various solvents, excipients and impurities might interact with these surfaces during manufacturing processes. Utilising systematic search methods,[61] we have examined the adsorption of various relevant molecules to the major habit faces of lamotrigine.

Using the same computational methods outlined above for the calculation of morphologies and surface energies, the interactions of the solvents water and toluene, the excipients microcrystalline cellulose (MCC) and lactose monohydrate, the identified impurity 2,3-dichlorobenzoic acid, and of lamotrigine with itself, have been investigated.

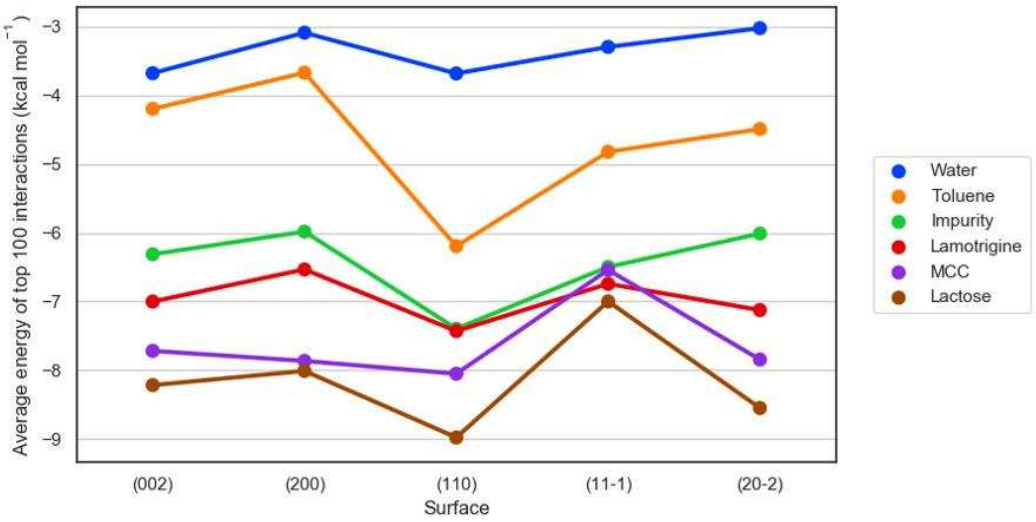

Figure 9. The average energy of the top 100 probe-surface interactions for the major facets of lamotrigine for water, toluene, dichlorobenzoic acid (impurity), lamotrigine, microcrystalline cellulose (MCC) and lactose monohydrate (Lactose). The MCC probe was modelled as a single repeat unit of the polymer and the lactose monohydrate probe as a single lactose molecule and a single water molecule.

Figure 9 shows the average energies of the top 100 interactions of the various probe molecules studied on each of the surfaces. The most favourable surfaces for interaction in all

cases are for the {110} form, consistent with observations made above regarding these faces' high energy and roughness. Water, toluene, and the impurity 2,3-dichlorobenzoic acid show similar interaction trends, indicating a relatively consistent level of reactivity for each lamotrigine face.

Comparing the interactions for lamotrigine with itself and 2,3-dichlorobenzoic acid, it is apparent that the impurity shows competitive interaction energies on several surfaces. Particularly in the case of the {110} faces, which show increased exposure of amine groups, a multi-component Hydrogen Bond Propensity calculation[62] indicates several competitive probable hydrogen bond interactions. As shown in **Figure 6**, lamotrigine crystals grown in the presence of even a modest amount of the 2,3-dichlorobenzoic acid impurity are much smaller and more irregular in shape than those grown in the absence of the impurity. This indicates that either the impurity depresses the cloud point and forces nucleation to occur at a much higher supersaturation, or that the impurity simply depresses crystal growth at key faces. The competing interactions of 2,3-dichlorobenzoic acid with lamotrigine are consistent with both effects.

It is interesting to note the relatively weak interactions of water with all major faces, consistent with the low aqueous solubility observed for lamotrigine. The interactions of the excipients (microcrystalline cellulose and lactose monohydrate) are found to be greater than those of the drug with itself. The low anisotropy factors of all the faces indicate that there are strong synthons broken at each surface, resulting in these surfaces being likely to form strong interactions with the surrounding environment in order to stabilise the surface exposed molecules. As mentioned above, lamotrigine is known to have poor flow properties and a tendency to agglomerate. Selecting these excipients, which bind well to the surfaces of the drug particles, will likely reduce this tendency to agglomerate and make the formulation more amenable to manufacturing processes.

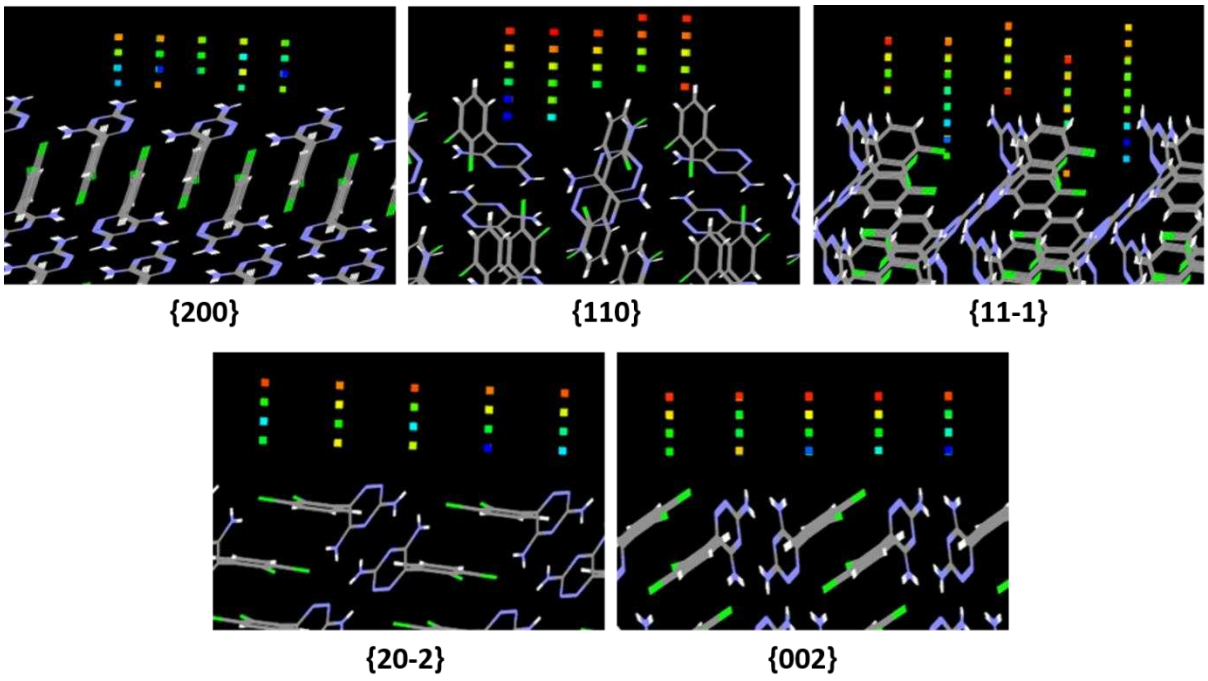

Figure 10. SystSearch interaction fields for the impurity dichlorobenzoic acid on the major surfaces of lamotrigine. Each point represents an individual interaction between a dichlorobenzoic acid molecule and the lamotrigine surface. The points are coloured depending on the strength of the interaction. Points coloured blue represent the sites of most favourable interactions while red points represent the least favourable interactions.

Figure 10 shows the interaction sites found for 2,3-dichlorobenzoic acid on the various major surfaces of lamotrigine. The depth and strength of the interaction points on the {110} and {11-1} surfaces, and to a lesser extent the {200} surfaces, highlights the important role of the roughness of these surfaces in creating favourable adsorption sites. Contrast this to the much smoother {20-2} and {002} surfaces, where favourable sites within the surface are not found.

By investigating the interactions of relevant molecules with the major particle surfaces of a material it is possible to gain a better understanding of how that material might interact with different media. When applied to lamotrigine, this approach enables rationalisation of the

drug's interactions with an impurity, its low aqueous solubility, and the choice of excipients during formulation.

Conclusions

This work has shown how use of digital design approaches can be used to provide a thorough analysis of a particle's properties. By combining this "Particle Informatics" workflow with key experimental measurements, a material's industrially important characteristics such as solubility, tabletability, flow, and crystal growth behaviour can be understood. The knowledge gained from this "Particle Informatics" approach can be used to resolve key formulation and manufacturing decisions and can anticipate potential bottlenecks in pharmaceutical processes.

Through a combination of computational and topological methods, we can better understand the particle properties of the drug lamotrigine. We have analysed its intrinsic intermolecular interactions, its mechanical properties, its morphology and its surface energy and chemistry, and used this information to rationalise several issues encountered during the formulation and manufacturing of this drug.

We hope that by application of the "Particle Informatics" workflow at the earliest possible stage of pharmaceutical development, issues such as those encountered for lamotrigine can be anticipated and avoided, enabling drugs to be delivered faster and more efficiently.

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Supporting Information

1. Visualisations and descriptors of major surfaces of lamotrigine
2. Molecular and crystallographic descriptors of lamotrigine compared to the CSD Drug Subset

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For Table of Contents Use Only

"Particle Informatics": Advancing our understanding of particle properties through digital design

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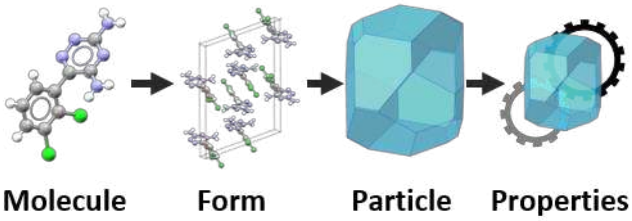

Synopsis

We introduce a combination of new and existing approaches to assess and predict particle properties intrinsic to the formulation and manufacture of pharmaceuticals. A novel workflow brings these approaches together to build on the knowledge gained from each step and explain how this knowledge can be combined to provide resolutions at decision points encountered during formulation design and manufacturing processes.