

Molecular Synthon Modelling of Inhalation Pharmaceuticals: A Digital Approach to Understanding and Engineering Particle Surface Interactions

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INTRODUCTION

The inter-particulate interactions between active pharmaceutical ingredients (API) and between APIs and co-formulated excipients play an important role in the performance of inhalation products. However, accurate experimental assessment of surface energy and hence inter-particulate interactions has proved to be especially difficult using available techniques. The purpose of this study was to develop a framework whereby molecular crystal structures are utilized as the starting point for molecular modelling approaches to study the crystal morphology, surface chemistry and surface energy of the inhalation drug compound terbutaline sulfate (TBS). The molecular modelling approaches were subsequently compared with experimentally-derived surface energy mapping, using finite dilution inverse gas chromatography surface energy analysis, both for validation purposes and to shed light on the fundamental assumptions of the IGC characterisation approach.

METHODS

Computational method

The computational analysis was carried out utilizing the Cambridge Crystallographic Data Centre (CCDC) Mercury [1], BIOVIA Materials Studio [2] and HABIT98 [3]. The calculated attachment energies were normalised to that of the slowest growing face, i.e. with the largest surface area to determine relative growth rates per surface, and through this, a prediction of the crystal habit was generated. The digital workflow summarized in Figure 1 gives an overview of the main features of the analysis.

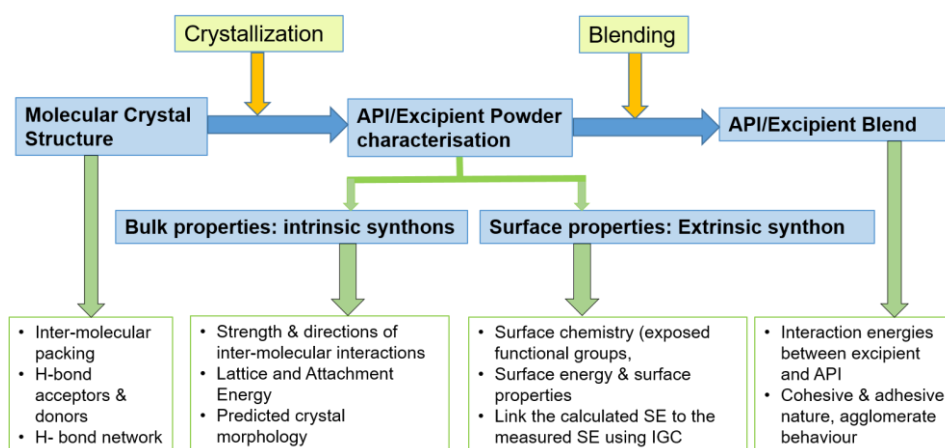


Figure 1: A digital workflow highlighting the methodology from crystallographic structure to particle properties for the prediction of formulation performance

Experimental method

TBS single crystals were prepared by cooling crystallisation as follows: 0.32 g of TBS (Sigma Aldrich; purity $\geq 98\%$) was added to a mixture of 70% water and 30% ethanol (% by mass) to make 1 g of solution. This was then heated to 70°C to ensure complete solute dissolution and then cooled to 5°C and left for 2-3 days until crystallization occurred. An Olympus BX51 microscope was used to characterize the shape of the resultant crystals for comparison to the *in-silico* predicted crystal morphology.

Surface energy (SE) analysis was conducted using a Surface Energy Analyser (iGC-SEA, Surface Measurement Systems Ltd, UK). Non-polar probes (n-decane, n-nonane, n-octane and n-heptane) and polar probes (chloroform, toluene, ethyl

acetate and acetone) were injected into the column at concentrations consistent with a range of surface coverages (between 0.5 up to 13% for all probes with the exception of n-decane that reached a maximum surface coverage of 4.5%). The dispersive (γ_d , non-polar) and acid-base (γ_{ab} , polar) components of the surface energy were calculated using the Dorris-Gray method and the Peak Centre of Mass Parameter. All measurements were made in triplicate for non-micronized terbutaline sulfate used as supplied by AstraZeneca using IGC.

RESULTS AND DISCUSSION

Table 1: List of crystal surfaces, calculated attachment energies, % crystal surface area, together with the predicted whole particle surface energy compared with those measured using IGC for TBS crystal.

Crystal surface (form)	Multiplicity	Surface Area A_{hkl} (%)	Slice Energy (kcal/mol)	Attachment Energy (kcal/mol)	Dispersive Surface Energy (mJ/m^2)	Total Surface Energy (mJ/m^2)
{010}	2	26.33	-133.7	-5.16	23.24	27.7
{100}	2	10.29	-128.2	-10.73	31.44	50.6
{001}	2	8.69	-121.7	-17.16	38.99	109.0
{1 $\bar{1}$ 0}	2	4.70	-127.8	-11.07	29.61	45.6
Calculated surface energy (weighting with % surface area)					28.27	48.2
Measured surface energy for surface coverage at 0.5% -13%					49.1 – 32.8	103.3 – 64.7

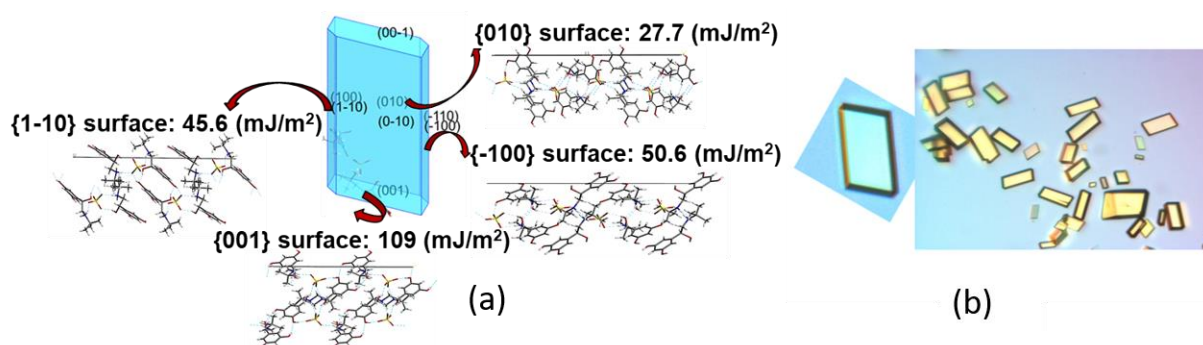


Figure 2: Predicted morphology showing a plate-like crystal morphology with the surface chemistry of {010}, {100}, {001} and {1 $\bar{1}$ 0} surfaces (a) and experimentally observed morphology of TBS single crystals (b).

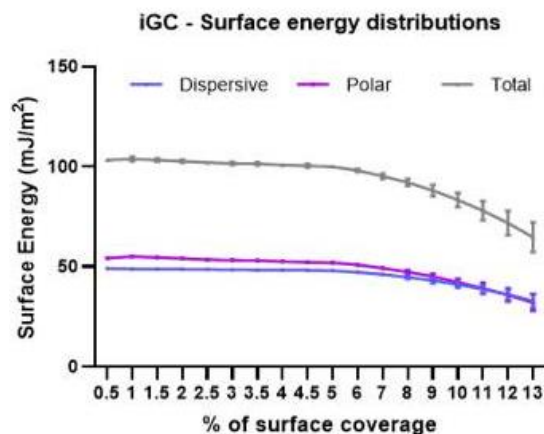


Figure 3: Measured dispersive and total surface energy of terbutaline sulfate.

The predicted morphology, shown in Figure 2 (a), based on the Attachment Energy model, shows a plate-like morphology with the $\{010\}$ being the dominant form, along with the smaller $\{100\}$, $\{001\}$ and $\{1\bar{1}0\}$ surfaces. The predicted morphology agrees well with the observed experimental crystal morphology grown in a mixture of 70% water and 30% ethanol at 5°C (see Figure 2 b).

The IGC data showed that the surface energy decreased with increasing surface coverage (see Figure 3). The calculated dispersive and total surface energy tended to correlate better at a higher surface coverage comparing to low surface coverage (0.5%), for example the measured dispersive surface energy 32.8 (mJ/m²) at the surface coverage 13%, and the calculated dispersive surface energy 28.27 (mJ/m²). The predicted surface energy showed significant differences between the surface energies of individual crystal surfaces (Table 1, columns 6 and 7). The surface energies of the $\{1\bar{1}0\}$ and $\{001\}$ forms were greatest whilst the surface energy of the $\{010\}$ is the lowest. This agrees well with the surface chemistry analysis which indicates that the $\{1\bar{1}0\}$ and $\{001\}$ forms have more polar and non-polar components exposed on the surfaces contributing to the dispersive and polar surface energy. Additionally, the calculation of the surface energy for the highest energy sites (the

{001} surfaces: 109 mJ/m²) correlated well with the experimental measurements at low surface coverage (103.3 mJ/m²), where the highest energy surface sites are probed (both from the crystallography and process-induced disorder).

CONCLUSIONS

This work demonstrates the utility of synthonic modelling approaches in understanding the surface properties of organic salt materials at the molecular scale. The ability to employ synthonic molecular modelling approaches for the salt terbutaline sulfate was validated through single crystal growth experiments and measured surface energy data using IGC. IGC tends to measure the highest energy surface sites, which corresponds well to the energy of the highest energy crystal face. The calculated dispersive and total surface energy tended to correlate better at a higher surface coverage comparing to low surface coverage (0.5%) in this study. The surface energy data measured using IGC was found to correlate well with the calculated surface energy of the most energetic crystal surface {001}, suggesting that this experimental technique tends to probe the higher energy surface sites. Further experimental measurement of surface energy by IGC is being employed in ongoing work to assess the face-specific heterogeneity of the surface energy distribution of TBS. The calculated surface energy analysis is very helpful for assessing and interpreting the measured IGC data, notably through its ability to both partition surface energies between the different morphological forms. The analysis has therefore shown the potential for a molecular modelling approach to study surface-surface contact forces when designing inhalation formulations.

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